

Summary

Session 6

14:00–16:00

Conclusions and recommendations per proposed action

Michael Lassmann

With input from the consortium

Conclusions and recommendations per proposed action

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

Questions to Panellists and Stakeholders

Panellists:

Please share the three most important topics to be discussed during the 2-day workshop on the SIMPLERAD project.

What is the greatest challenge in your view to providing access to high-quality and safe nuclear medicine and radiopharmaceuticals in the EU?

Which is the first priority with respect to implementation of EU legislation regarding this topic?

Stakeholders:

What is the greatest challenge in your view with regard to the remedies proposed?

Do you have additional suggestions on how to address this issue?

Ranking – Opinions of the Panellists

1. Insufficient linkage between EU pharmaceutical legislation/EMA guidance and BSSD
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Discussion during the workshop

- K. Herrmann: Some remedies recommended are overly complex
- Discussion of the distinction between dosimetry as a tool for generating evidence and to fulfill regulatory purposes vs. method benefitting patients in daily practice
- The need of better understanding and considering radiobiology
- Issues of health economics
- Networking of centers for generating robust dosimetry data

Discussion during the workshop

- Communication – Communication - Communication
- Need for a roadmap and a vision
- Comparing RN treatment to systemic treatment and EBRT: RN should be considered a field of its own
- Hospitalisation – yes/no – consider patient perspective
- Level of dosimetry required and resources to implement it

G. Simeonov:

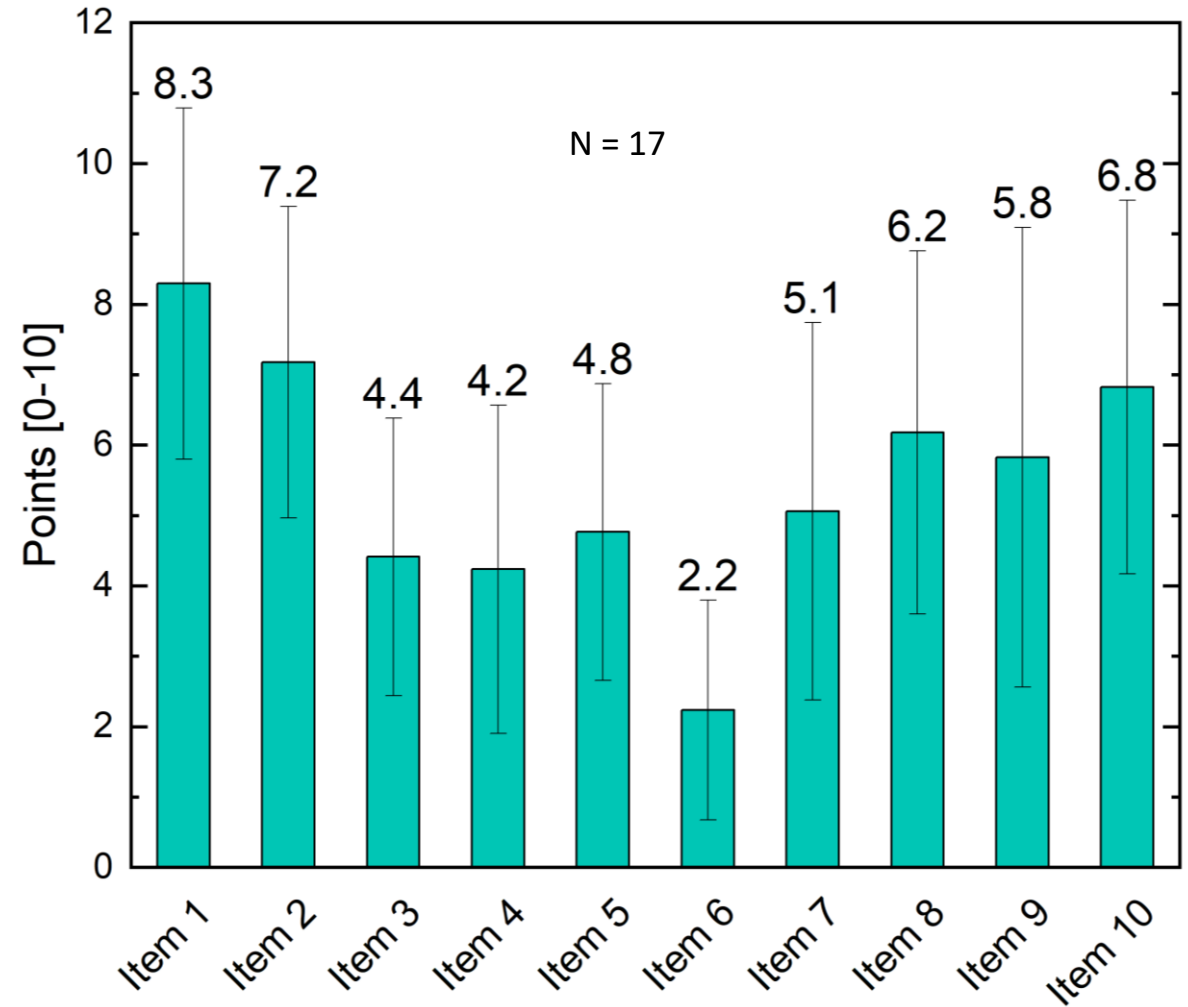
- Optimization principles is about maximising the benefit and we should put this into clinical practice
- Benefit of patients and treatment development

Discussion during the workshop

- There is a tipping point now for the success or failure of therapy
- Implementation of the next steps is needed
- More advanced centers vs. small centers for research, education and training
- Consider establishing registries for dose data

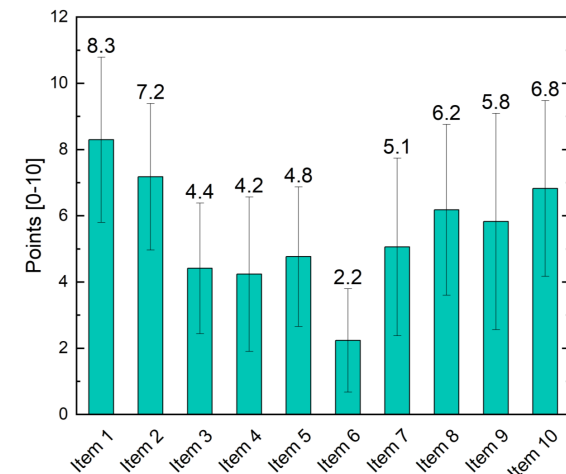
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Comments of the Stakeholders – Challenges

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

- The communication between appropriate stakeholders at the highest EU-level
- I think that a better coordination of the agencies should prevent this insufficient linkage.*
- the greatest challenge would be to have a forum – see also item 3*
- the task demands not only deep interdisciplinary expertise but also effective communication and consensus-building across various regulatory, clinical, and technical domains

* The implementation of the permanent expert working group on radiopharmaceuticals is very important and its recognition must be established for all agencies

Comments of the Stakeholders - Challenges

New pharmaceutical directive on the optimization of medical treatment with therapeutic radiopharmaceuticals

- For BSSD to always prevail, all unclarities how BSSD applies to radiopharmaceuticals need to be resolved.
- Indication in the new pharmaceutical directive on the optimization of medical treatment with therapeutic radiopharmaceuticals that another regulatory document, namely the BSSD, should take precedence
- A general priority of BSSD over pharma regulation is impossible to justify.

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

In the context of SAMIRA

- Lack of linkage between pharmaceutical legislation/EMA guidance documents and Euratom BSSD requirements considerably challenges development of new therapeutic radiopharmaceuticals
- The proposal for revision of Directive 2001/83 contains an important step towards recognising the concept of justification and optimisation also in the context of marketing authorisation of radiopharmaceuticals used for therapy. This, however, must be expressed unambiguously in the legal text, complemented by additions in annexes, guidance documents and CTIS and guided by professionals in the field of therapeutic radiopharmaceuticals.

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

In the context of SAMIRA

- Inclusion of radiopharmaceuticals in annex VII according to article 28 of the EC's proposal could open the possibility of adapted rules for radiopharmaceuticals in several other fields such as good manufacturing practice requirements, clinical trials, marketing authorisation procedures, requirements for qualified persons, etc.
- The current Directive 2001/83/EC does have a clear statement on the BSSD's requirements in both a recital and in an article of the legal text. Nevertheless, BSSD requirements are not fully recognised in all aspects, as this tender has demonstrated. The outcome of this suggested remedy might be limited
- Reform of the EU pharmaceutical legislation may not consider the BSSD or specifics of therapeutic radiopharmaceuticals

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

Consortium recommendations and SAMIRA actions

- SIMPLERAD has developed proposals on the interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine.
- Explicit proposals on the interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine were made:
 - "Implementing Dosimetry in Clinical Practice"
 - "Guidance Document on Treatment Planning and Verification for Selected Radiopharmaceuticals"
 - "EANM Guidance Document: Dosimetry for First-in-Human Studies and Early Phase Clinical Trials"
- It is strongly recommended that an integral effort is undertaken by the different directorate generals involved to implement these remedies on the national and European level.

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

Consortium recommendations and SAMIRA actions

- The proposed remedies, when taken up by the different stakeholders involved, will further enhance and improve the use of radiopharmaceutical therapies throughout Europe for the benefit of the patients. A coordinated joint action for networking and improving communication within the framework of the SAMIRA initiative, may be of great value and should be considered with high priority
- The weakness of the proposed actions is that no explicit proposals can be made on how to overcome the inequalities between the member states as this is beyond the scope of this tender
- A major threat to implementing the suggested remedies is the lack of linkage between the different authorities on a European level as well as on the national level within the member states

10. Differences between opinion of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance **Priority 3**

SIMPLERAD recommendations and SAMIRA actions

- Guidance and legislation on the implementation of dosimetry differ from expert opinion for certain therapies
- Competent authorities, national societies and experts should align guidance and requirements for the use of therapeutic radiopharmaceuticals
- Guidelines or guidance documents on applying dosimetry for radionuclide therapy
- Publication of results of SIMPLERAD WPs 1 and 2
- Translation of available European guidance to national level
- Collaboration between competent authorities and national societies
- Expert consultation for revision of new regulatory guidance documents

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

In the context of SAMIRA

- The need to harmonise the application process for clinical trials with radiopharmaceuticals regarding the radiation safety in dosimetry and dose finding is clear
- Variation in requirements across European member states risks Europe's role in global drug development and clinical trials
- Any modification of CTIS to allow data entry on radiation-safety related aspects will bring both pillars of relevant legislation closer together. Same applies for an obligation to incorporate radiation-safety related issues when applying for a clinical trial authorization
- Regulators who are competent for the enforcement of pharmaceutical legislation only will likely pay more attention to radiation-safety related issues when it comes to decision making on clinical trials or marketing authorisation applications. This could lead to a better alignment of pharmaceutical and radiation-protection legislation in the future

3. Lack of resources for dosimetry

SIMPLERAD recommendations and SAMIRA actions

- Implementation of the individual planning mandate stated in article 56.1 of the BSSD is hampered by a lack of resources, both in terms of educated staff and funding/reimbursement
- Coordinated actions among professional societies and national authorities would increase the availability of sufficient educated staff and funding

Personal remark: Also true for other disciplines!

9. Lack of specialist knowledge regarding EU pharmaceutical and medicine as well as BSSD related regulations **Priority 5**

In the context of SAMIRA

- More extensive specialist knowledge concerning nuclear medicine within various stakeholders regarding the EU pharmaceutical directive as well as BSSD-related regulations is needed
- Specialist training, harmonised legislation/guidance and close cooperation would strengthen regulatory frameworks
- Specialist training in both sets of relevant legislation bridges the knowledge gaps between pharmaceutical and radiation protection legislation. Improved cooperation between all stakeholders
- National regulators are at different levels of knowledge in one or even both sets of pharmaceutical and radiation protection legislation. Even if pharmaceutical and radiation protection authorities in a specific country collaborate, there can be conflicts in the interpretation of both sets of legislation as well as a lack of coordination between the different authorities

4. Differences regarding status of MPEs between member states

SIMPLERAD recommendations and SAMIRA actions

- Responsibilities and resources vary widely for medical physicists and MPEs across Europe
- Responsibilities should be harmonised, with staffing levels defined and enforced, and published guidance should be based on the current conditions in Europe
- Staffing levels should be defined and enforced
- Survey to map the roles and responsibilities for MPEs and medical physicists working with molecular radiotherapy
- A guidance document should be prepared on roles and responsibilities for MPEs and medical physicists working with molecular radiotherapy
- Staffing requirements for centres performing molecular radiotherapy should be defined and enforced
- Training of MPEs should be harmonised across Europe

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

In the context of SAMIRA

The process of setting release criteria and patient instructions is influenced by different criteria and decision levels which include the use of the concept of comforter and carers, the use of appropriate dose constraints for optimisation and the methodologies used in risk assessment studies.

- Harmonisation of patient release criteria and instructions cannot be accomplished if there is a lack of harmonisation of those specific criteria and decision levels
- Future EU programmes supporting the generation of scientific data can contribute to the harmonisation of risk assessment studies, and European guidance should advise on the medical exposure of comforters/carers and dose constraints

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

In the context of SAMIRA

The process of setting release criteria and patient instructions is influenced by different criteria and decision levels which include the use of the concept of comforter and carers, the use of appropriate dose constraints for optimisation and the methodologies used in risk assessment studies.

- Programmes present an opportunity to gather comprehensive dosimetric data, facilitating the establishment of harmonised patient release criteria. The proposal for European guidance documents offers the potential to create unified standards across member states. Collaboration with regulatory authorities and professional bodies will help ensure widespread adoption and implementation of harmonised guidance. Explanatory documentation can demystify concepts, providing clarity on the differentiation between limits and constraints

7. Differing guidance from professional societies for clinical practice

SIMPLERAD recommendations and SAMIRA actions

Different professional societies come to different, even contradictory guidance for the same disease/therapeutic modality on issues pertaining to the interaction between the pharmaceutical directive and BSSD as well as on interpretation of the BSSD in the clinical context.

- Publication of the results of WP1 and WP2 would highlight the need to harmonise guidance
- Contact by regulatory agencies with professional societies, reminding such societies of the legal precedence of the BSSD and asking such societies to ensure any guidance is compliant in this respect
- Generation of high-quality evidence on the need and benefit as well as optimal method of individual planning of various forms of radionuclide therapy using dosimetric methods
- Facilitation of interdisciplinary consensus discussion
- Interdisciplinary consensus discussion should integrate professional societies and EC

7. Differing guidance from professional societies for clinical practice

SIMPLERAD recommendations and SAMIRA actions

- Draft guidance on what pertains to individual dose planning to reinforce the precedence of BSSD in establishing treatment regimen
- Contact relevant professional clinical societies with the accompanying guidance document, requesting that societies adapt guidelines to conform to the BSSD
- Set up grant programmes for the generation of high-level clinical evidence on the benefit of individual planning of various forms of radionuclide therapy using dosimetric methods

6. Heterogeneity of management of radioactive waste across member states

In the context of SAMIRA

- Analysis and surveys concerning effluent release and waste management would illuminate conditions across the EU and different sectors.
- The acknowledgment that radioactive effluent discharge is a cross-sectoral challenge opens avenues for collaboration not only in therapeutic nuclear medicine but also in research laboratories and the nuclear industry
- Proposal for a working party to elaborate a specific guidance document on effluent release and waste management provides for medical radionuclides an opportunity for standardisation

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Conclusions and recommendations per proposed action

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2. Interpretation and implementation of the BSSD in diagnostic nuclear medicine
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5. Heterogeneity of dose constraints for MPEs among member states
6. Heterogeneity of management of MPEs across member states
7. Differing guidance from national authorities in clinical practice
8. Differing regulatory requirements between member states for drug development & clinical trials
9. Sufficient specialisation in diagnostic nuclear medicine within various stakeholders regarding EU legislation, diagnostic nuclear medicine as well as BSSD-related regulations
10. Differences in training of medical professionals concerning dosimetry and the necessity stipulated in the BSSD for training and guidance

To be followed more closely until the end of the project