

Report on HERCA Multi-Stakeholder Workshop on the Justification of New Types or Classes of Practices In the Medical Field

(24 - 26 Oct. 2016, Montrouge, France)

Comments from Stakeholders

The justification of new types of practices is a concept introduced by ICRP and updated in 2007¹. The concept had been introduced in the Council Directive 97/43/Euratom and renewed in the Council Directive 2013/59/Euratom. In particular in the medical field – probably because of a real difficulty of applying this abstract concept in an operational way – the transposition of Art. 55.2 (a) Council Directive 2013/59/Euratom, referring to this, still poses some challenges to the MS.

In view of the MSW, the WGMA identified and explored potential approaches, which are discussed in the MS with respect to the transposition of Art. 55.2 (a) and other articles around it. From this work, relevant questions emerged which were discussed with relevant stakeholders at the MSW. To facilitate these discussions, five specific plenary sessions with case-studies referring to existing or planned regulatory practices in MS were scheduled at the MSW (see Appendix I: Plenary Sessions 1 - 5). The questions addressed included:

¹ ICRP 2007, The 2007 Recommendations of the International Commission on Radiological Protection, ICRP Publication 103

How can Health Technology Assessment (HTA)² contribute to the justification process of new types of practices (Plenary Session 1)?

- What are potential weak points of the HTA approach?
- How could these weak points be strengthened within HTA by Radiation Protection Authorities on a MS level / on an European level - by HERCA?

How can CE Marking contribute to the justification process of new types of practices (Plenary Session 2)?

- May CE marking according to the Medical Device Regulation serve as indication for justification of new types of practices due to the Council Directive 2013/59/Euratom?
- In this case, what is the potential impact of Art 78.2 Council Directive 2013/59/Euratom?
- How to handle new radiopharmaceuticals by this approach?

Does the regulator have to define a “Standard Medical practice List”, by which all ICRP level 2 justified types of practice are addressed, referring to the device, the radiopharmaceutical and the clinical indication and using a classification scheme of the different “types of medical practices” (Plenary Session 3)?

- How can this approach contribute to the justification process of new types of practices?
- What is the impact of granularity in this approach?
- What role may referral guidelines play in this approach?

Shall the regulator link the justification process of new types of practices to the authorization⁴ process (Plenary Session 4)?

² **Health technology assessment (HTA)** is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value (see: <http://www.eunetha.eu/about-us/faq#t287n73>).

The term “health technology” comprises a wide range of meanings, such as diagnostic and treatment methods, pharmaceuticals, rehabilitation and prevention methods, organisational and supportive systems within which health care is provided. The examples show that the scope of the term “health technology” extends far beyond the use of ionizing radiation in medicine. Furthermore, HTA organisations on a national and EU level usually perform assessments following their own list of priorities.

³ Art 78.2 Council Directive 2013/59/Euratom claims: *Member States shall ensure that any undertaking acquiring medical radiological equipment is provided with adequate information on the risk assessment for patients, and on the available elements of the clinical evaluation.*

⁴ The term "authorisation" means *the registration or licensing of a practice* (see: Art. 2.7 Council Directive 2013/59/Euratom). The term "licence" means *permission granted in a document by the competent authority to carry out a practice in accordance with specific conditions laid down in that document* (see: Art. 2.47 Council Directive 2013/59/Euratom). The term "registration" means *permission granted in a document by the competent authority, or granted by national legislation, through a simplified procedure, to carry out a practice in accordance with conditions laid down in national legislation or specified by a competent authority for this type or class of*

- How to ensure – by this approach – an adequate execution of Art. 55.2 (a) in a MS with respect to the claim that new types of practices involving medical exposure are justified in advance before being generally adopted?
- How to ensure – by this approach – a harmonized execution of Art. 55.2 (a) in a MS?

What further approaches exist in MS for the transposition of Art. 55.2 (a) Council Directive 2013/59/Euratom and other articles around it (Plenary Session 5)?

In a further plenary session, the interrelation between Art. 55.2 (a) Council Directive 2013/59/Euratom addressing new types of practices and Art. 55.2 (e) Council Directive 2013/59/Euratom addressing medical or biomedical research was discussed (see Appendix I: Plenary Session 6).

Based on Plenary Sessions 1 - 6, the HERCA-WGMA and the stakeholders participating in the workshop worked together to produce a set of conclusions, which summarizes the discussions in the plenary sessions and reflects some general considerations concerning the justification of new types of practices.

The following conclusions were agreed:

- A new type of practice is considered to be justified in general, when the practice is – in principle – appropriate to the application in medicine, taking into account benefit and risk.
- The key question is: what is a type of practice and in particular⁵, what is a new type of practice? Reflecting the term “type” reveals that some kind of categorization is needed, which implies some discussion on categorization and granularity issues. Furthermore, the distinction between a fundamentally new type of practice and the variation of a well-established type of practice could provide guidance and could lead to a graded approach. In line with this kind of reasoning, a rough granularity may be sufficient for the variation of a well-established device with an established clinical indication. However, it was also reflected that for a well-established device with a new clinical indication, such as any kind of population screening or individual health assessment, a fine granularity may be necessary. A fine granularity may also be necessary for a newly developed device, in particular if it also offers a new clinical indication.
- It is further important to understand that the intended approach to transpose Art. 55.2 (a) Council Directive 2013/59/Euratom needs to be flexible and simple enough to ensure appropriate benefit to the patient when considering technical progress, but also that the intended approach has to take into account the risk aspect.
- For a MS to transpose Art. 55.2 (a) Council Directive 2013/59/Euratom it is helpful to be aware of decisions and approaches in other MS.

practice (see: Art. 2.86 Council Directive 2013/59/Euratom). Further provisions are given by Art. 27 – 29 Council Directive 2013/59/Euratom.

A characteristic feature of this approach is that the justification process due to Art. 55.2 (a) is typically initiated by the undertaking when applying for a registration or licence for a new practice, is thus embedded in the registration or licensing process for this new practice, and does not refer to a new type of practice to be justified in advance before being generally adopted, but to a new practice to be permitted on a case-by-case basis.

⁵ See Chapter II.3

Commenté [CA1]: COCIR = We have discussed the draft and we believe it perfectly reports all the discussions and positions presented during the event. The workshop has been highly appreciated by COCIR Members and we would like to continue to keep up the discussion with HERCA on justification (and HTA) together with the other relevant points in the BSS.

- An important impact factor to be taken into account is the system of radiation protection implemented in a MS and its interrelation with the healthcare system in the MS. Reimbursement of practice and/or allocation of resources are important driving and sometimes obstructive forces in the healthcare system that could be helpful for radiation protection as well. Furthermore, if a type of practice is justified in general, it may not necessarily be established in healthcare (Health Authority) – e.g. due to financial limitations in the healthcare system.
- Concerns addressed in particular by Medical Associations and Manufacturers were:
 - Care should be taken that the transposition of Art. 55.2 (a) Council Directive 2013/59/Euratom does not unduly delay the adoption of new types of practices in a MS and thus, does not slow down progress in medicine.
 - Steps towards harmonization on the European level – as far as any possible – would be highly appreciated.
- CE marking cannot replace generic justification, but could be a source for information, in particular with respect to clinical evaluation and risk assessment, which could be helpful for the justification process on a generic level. Hereby, Art. 78.2 Council Directive 2013/59/Euratom addressing the information transfer from the legal system of Medical Devices Regulation to the legal system of Basic Safety Standards Directive is essential. COCIR / Manufacturers are willing to cooperate in this transfer of information.
- Approaches based on health technology assessment (HTA), a standard medical practice list, the authorization process, as well as other approaches discussed within the MSW, seem to be feasible with respect to the transposition of Art. 55.2 (a) Council Directive 2013/59/Euratom **in some but not all MS**. They all have their pros and cons. It is essential to take into account the characteristics of the individual MS. Finally, the involvement of relevant stakeholders is key in the process of generic justification of new types of practices to enhance credibility.
- Art. 55.2 (c) Council Directive 2013/59/Euratom addressing a type of practice that is not yet justified in general does not provide a shortcut to healthcare, bypassing the need for justification on a generic level. Instead, Art. 55.2 (c) is restricted to special circumstances with respect to an individual patient and requires a special individual justification. Similar approaches are used in *off-label* or *compassionate* use of drugs.
- Last, but not least, it was concluded that any system that is adopted by a MS has to work in practice.

Commenté [R.L.2]: In some countries it takes years before a general established practice is established in healthcare

Appendix I: Summary of Plenary Sessions 1 – 6 of the HERCA Multi-Stakeholder Workshop (24-26 October 2016)

In *Appendix I*, a summary of Plenary Sessions 1 – 6 of the MSW is provided:

Plenary Session 1: How can Health Technology Assessment (HTA) contribute to the justification process of new types of practices?

In an introductory presentation important information on the Health Technology Assessment (HTA) was provided. It was outlined that HTA is a systematic evaluation of available knowledge on safety and clinical effect of the method combined with an evaluation of cost-effectiveness as well as ethical, social, organizational and juridical aspects. HTA is a tool for decision-making in the introduction of new health technologies and practices with the main goal to ensure they are safe, cost-effective and associated with evidence-based clinical effect. HTA is also the tool for an evidence-based decision to phase-out practices that are no longer safe, clinically effective or cost-effective. This decision-making process has to be transparent, unbiased and based on proper stakeholder involvement.

HTA can contribute to the generic justification process by integrating the radiation detriment into already established procedures for HTA based decision-making. The main advantage with this approach is that radiation protection and the concept of generic justification is evaluated as an integrated part of the total HTA performed and not handled in a separate and isolated system. It is important to include experts with sufficient competence in radiation protection to ensure that the radiation detriment is properly addressed in these assessments. However, the integration of generic justification in HTA is not straightforward and may not be feasible in all countries.

Case-Study on Nordic Countries:

Some Nordic Member States have identified the implementation of generic justification into already established HTA systems as one possible approach to transpose Art. 55.2 (a) Council Directive 2013/59/Euratom into national legislation. A close cooperation between the national radiation protection authority and relevant national bodies, preferably competent HTA bodies, is required to succeed with the HTA approach. Integration of generic justification in HTA was outlined in a case-study from Norway. The Nordic radiation protection authorities have recently published a *Nordic Position Statement on Justification of New Types of Practices involving Medical Exposures*, which recommend the integration of generic justification into established methods for assessments of new health technologies. Further information on how HTA and similar methods can strengthen the generic justification process is given in this statement.⁶

Discussion:

In the discussion some concerns related to this approach were identified:

- The main concern was related to the time frame related to an HTA, and it was emphasized that the assessment must not delay the introduction of new methods or hinder innovations. In particular ESR uttered this concern and underlined, that HTA seems to be slow, complex, expensive and not cost-effective for diagnostic

⁶ <http://www.nrpa.no/dav/94777f951e.pdf>

imaging tests at least. In addition, the concern was raised that HTA organisations may prioritise drugs over equipment and application.

- Another concern was related to the possibilities of different conclusions in different countries. A harmonization among the European countries was welcomed among the manufacturer and medical professional societies.
- It was also mentioned that cost-effectiveness in healthcare is the main driving force for HTA, that radiation protection issues are not generally addressed in HTA, that HTA bodies normally have their own agenda for prioritizing HTA and that HTA are resource demanding.

Nevertheless, it was stressed, that HTA could – in particular - play a role in evaluating the cost-benefit-ratio with respect to screening projects, such as breast cancer screening, where additional aspects like finances, availability or regulatory aspects are essential.

It was further concluded that available resources to perform HTA may be a challenge for countries that want to adapt the HTA-approach. It is unrealistic for any country to have enough resources to perform comprehensive HTA assessments for all new health technologies, and the use of less resource demanding assessments like Mini-HTA and Rapid-HTA should be investigated. To make the best use of available resources in the long run, evaluation of evidence (safety and clinical effect) should preferably be carried out through European or international cooperation while the evaluation of the consequences associated with the decision to implement the method (cost-effectiveness and budget) should be made nationally. Most European countries have national or regional competent HTA bodies and most of them (but in daily routine by far not all) are member of the European HTA platform, EUnetHTA. This platform is responsible for European cooperation on HTA production and different tools for HTAs, including a core model for the production of HTAs, has been developed. A possible role of EUnetHTA and HERCA in solving issues related to resources and harmonizing of generic justification within the HTA-approach was raised.

Plenary Session 2: How can CE Marking contribute to the justification process of new types of practices?

In the introductory presentations of the session, the question was addressed, whether there is a possible conflict between Council Directive 2013/59/Euratom and Medical Device Directive / Regulation from a legal point of view. It was underlined, that in this case the Council Directive 2013/59/Euratom – being a *lex specialis* - could override the Medical Device Directive / Regulation, but no practical example is known at present.

Another point was the different terminology used in both legal systems. It was well accepted that the letter received from EC on 22.07.2016 was very useful to clarify this point. In particular, it was concluded that, even if the meaning of the terms “risk assessment” and “clinical evaluation” may not be fully consistent in both legal systems, the provision of this information collected under CE marking may be helpful for the justification of new types of practices. The challenge will be to make these data available easily and in a harmonised way for the justification of new types of practices.

Discussion:

The feedback from manufacturers was very supportive. CE marking can contribute to the generic justification process. Particularly, IEC and ISO standards requirements include quantitative information about radiation protection or risk management, and the MDD

Commenté [R.L.3]: That's right. HTA has very different implementations in MS and in some countries HTA is responsible for a delay of years between introduction of new types of practices and introduction into the healthcare. The time delay will be significant if the HTA process in each MS requires own national scientific studies for evidence before accepting a practice in HTA. A cross boarder acceptance of high ranked studies would be helpful to shorten a HTA process.

Guidance MEDDEV 2.7/1⁷ give detailed requirements on how to perform an appropriate clinical evaluation. COCIR outlines that information on risk assessment and clinical evaluation can be made available; nevertheless, manufacturers estimate that identifying relevant information may be difficult: *information is there but will need to be agreed*.

In this context, it was underlined by regulators and medical associations that for newly developed devices the display of dose parameters as well as instructions and phantoms for acceptance testing is often insufficient or missing. The question was raised, whether and to what extent quality assurance issues including quality control should be addressed before a newly developed device is authorized and new practices related to that device are justified in general. There was no controversy about the statement that quality assurance, generic justification and authorization needs strongly to be connected.

In summary, it was concluded that CE marking cannot replace generic justification. Nevertheless, it could be a source for information within the process of generic justification. Hereby, the transposition of Article 78 Council Directive 2013/59/Euratom, and particularly of Article 78.2 explicitly addressing information on "risk assessment" and "clinical evaluation" produced by the manufacturer within CE marking process, is pivotal. COCIR and the Manufacturers explicitly showed their willingness to cooperate in this transfer of information from the MD legal system to the RP legal system.

Plenary Session 3: Does the regulator have to define a "Standard Medical practice List", by which all ICRP level 2 justified types of practice are addressed, referring to the device, the radiopharmaceutical and the clinical indication and using a classification scheme of the different "types of medical practices"?

In this session the UK presented a case-study on the approach of using a "Standard Medical practice List".

Case-Study on UK:

In the case-study the UK regulations on justification of practices involving ionising radiation (2004) were presented. It should be noted, that these regulations apply to all practices of ionising radiation, medical as well as other types of practices. They provide a defined process with consultation, and address new practices, review of existing practices and determination of new practices.

Part of the regulation is a list of the existing practices which are already justified, and they are described through three components: purpose, classes or types of practice and the governmental department responsible for the justification. Within the medical field six purposes were identified, with associated classes or type of practice (shown in parenthesis):

- Diagnosis – medical (Radiography, fluoroscopy, CT, in-vivo nuclear medicine, in-vitro nuclear medicine)

⁷ GUIDELINES ON MEDICAL DEVICES, CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES UNDER DIRECTIVES 93/42/EEC and 90/385/EEC (June 2016), EUROPEAN COMMISSION

Commenté [MH4]: For our current use scenario, this list is more or less sufficient but is it planned to expand the list in the short term? (e.g. tomosynthesis, phase contrast imaging

- Treatment – medical (Interventional radiology, in-vivo nuclear medicine, teletherapy, brachytherapy, radiography and fluoroscopy (for planning purposes), CT, neutron activation)
- Occupational health screening (Radiography, in-vivo nuclear medicine)
- Health screening (Radiography, in-vivo nuclear medicine)
- Medical and biomedical research (Radiography, fluoroscopy, interventional radiology, CT, in-vivo nuclear medicine, in-vitro nuclear medicine, teletherapy, brachytherapy, neutron activation)
- Medico-legal procedures (Radiography, fluoroscopy, interventional radiography, CT, in-vivo nuclear medicine).

The UK Department of Health is the lead department for all of these.

Discussion:

It was commented from the EU commission representative that this approach is important, but further steps in the process are needed to ensure ICRP level 2 justification. It was elaborated from the UK representative, that this approach is not the only part of the justification process; it is complemented by HTA and other processes.

ESR was also critical about the approach and underlined that the clinical setting cannot be addressed in a fixed and rigid way, but needs to be looked at on a case-by-case basis. ESR further pointed out that this fine level of granularity will only be provided by referral guidelines, requiring a very specialised level of knowledge. This level of expertise might not be available at the radiation protection authority.

In contrast, EANM welcomed the simplicity of the approach and EFRS was in favour of this approach as well. They noted that referral guidelines are not level 2 justification. COCIR and the Manufacturers pointed to the advantages of a harmonised European approach.

In summary, it was noted that this type of process is driven mainly by radiation protections issues, and it is important to also consider clinical benefits as well as other types of risks, for instance overdiagnosis and overtreatment in the case of screening.

Plenary Session 4: Shall the regulator link the justification process of new types of practices to the authorization process?

In this session Luxembourg and the Nordic countries presented two case studies. Switzerland presented the potential problems and limitations related to linking the justification process of new types of practices to the authorisation process.

Case-Study on Luxembourg:

It was pointed out that Luxembourg is a small country with one straightforward public healthcare system. The justification process of new types of practices is linked to the authorisation process. The Ministry of health gives an authorisation for the installation and use of each and every radiological installation and radionuclide. The undertaking has to submit a demand for the new practice, which will allow for the establishment of the justification of the new practice. Specific regulations detail the information/documents to be submitted to the Ministry of Health.

Commenté [MHS]: According to ESR experts' opinion referral guidelines are level 2, as they apply to standard patients and standard clinical conditions (also in nuclear medicine)

The submitted file is forwarded to national and/or international experts for advice. If the beneficial effects of a new practice are not yet completely known the authorisation can be given for a defined period of time and under certain specified conditions.

Information to be provided by the undertaking include:

- description of the new practice,
- referral guidelines,
- radiation protection measures and security,
- written procedures,
- quality assurance program,
- quantification of no of acts to be done,
- quantification of the advantages for the patient and society,
- estimation of the risk for the professionals exposed, the patient and the patients entourage,
- names and signatures of the persons responsible for putting the into practice the new practice,
- proposal for a methodology for the evaluation of the benefits for the patients after 1 year.

If the authorisation of this new practice already exists in another EU country, documents recognising this practice for the EU country can be submitted.

In the authorisation of a new practice, conditions will be set concerning:

- education and training,
- QA,
- referral guidelines,
- others.

In order for this type of authorisation process to be able to function, Art. 78 Council Directive 2013/59/Euratom is very important.

Case-Study on Nordic Countries:

A new type of practice can either be related to an existing type of equipment or radionuclide, which can be difficult to identify, or can be related to a new type of equipment or radionuclide, which is easier to identify. Some examples of new practices which have been discussed in the Nordic Working Group on Medical Applications were presented. Based on the discussions, similar requirements have been introduced across the Nordic countries, adapted to the different legal structures in the individual countries.

Thus, in general, licenses are not required for ordinary dental applications, but for hand held dental equipment a license is required in several Nordic countries. As part of the application process to obtain this license, special reasons justifying the use of a hand held dental equipment instead of a mounted one have to be provided. Accepted reasons for this can be the use on elderly, disabled or psychiatric patients. The doses to the personnel must be assessed and monitored and extra documentation is required. Another example

is the radiopharmaceutical Xofigo (Ra-223). Before licenses were issued, it had to be approved for patient treatment by the national medicines agencies. In addition, a risk assessment regarding staff exposures was part of the licensing procedure.

Considerations from Switzerland on Problems and Limitations of the Approach:

In order to link the justification of new practices to the authorisation process, a list of medical practices considered to be justified in general needs to be established. The questions raised concerning this list are:

- In what detail or granularity should the list be formulated?
- Should it be static or dynamic?
- Who will be responsible for it:
 - holder of authorisation?
 - medical staff?

How to deal with new practices? When generic justification is to be considered, there are typically no clinical trials done yet and no sufficient evidence given. How to control these new practices is another issue raised. Possible solutions would be insurance control, health authority control and clinical audits. However the problems in all three cases are huge.

Discussion:

The first question discussed was:

- How to ensure – by this approach – an adequate execution of Art. 55.2(a) Council Directive 2013/59/Euratom in the MS with respect to the claim that new types of practices involving medical exposure are justified in advance before being generally adopted?

The case study of Luxembourg shows that it is possible for new types of practices to be justified in advance before being generally adopted. In this process all the stakeholders involved are made responsible for the new practice. The authorisation is given with strict conditions that have to be respected. However, it cannot be neglected that this process requires a lot of time and effort on behalf of the competent authority.

The next question discussed was:

- How to ensure – by this approach- a harmonised execution of Art.55.2 (a) in a MS?

In a small country such as Luxembourg where there is only one competent authority the execution of Art. 55.2 (a) can be harmonised. However, in a big country with a number of competent authorities it is more complicated. For this process to work, an excellent communication between competent authorities would have to be put into place. The competent authorities would have to collaborate together in the process of authorising a new practice.

Commenté [MH6]: The considerations of Switzerland are correct. The Luxembourg and Nordic case studies assume ideal scenarios in very small countries or a perfect and fast communication of all involved authorities. In most EU-MS we are far away from this.

Plenary Session 5: What further approaches exist in MS for the transposition of Art. 55.2 (a) Council Directive 2013/59/Euratom and other articles around it?

In this session, two approaches on how to implement the transposition of Art. 55.2 Council Directive 2013/59/Euratom were presented by France and the Czech Republic.

Case-Study on France:

The presentation proposed a complementary “approach” for the implementation of Article 55.2 (a) Council Directive 2013/59/Euratom. Hereby, in particular two questions were addressed:

- How to deal with the justification of new types of practices concerning both examinations (i.e. medical imaging) and treatments (i.e. therapy) - with or without a new technology?
- How to avoid administrative burden before the implementation of a new technology, in particular with respect to a new radiopharmaceutical?

The proposal is based – among others - on the following points :

- A “**watch**” should be organized on new technics and on new examinations or treatments. For this purpose, a **strong collaboration** between medical societies, expert bodies and regulators at national level would be necessary.
- The **key-stakeholders** from a radiation protection point of view (patient, occupational and public exposure) have to be identified as well as the needs in terms of research funding.
- The current text of the decree under preparation in France gives the possibility (depending on the stakes) to issue a **regulatory decision** to support the implementation of a new technic/examination/treatment, **during a transitory period**:
 - to collect data related to benefit/risk,
 - to state specific radiation protection rules, if needed.
- At the end of the transitory period, the evaluation of “justification” should be done by an **expert committee**.
- In parallel, the **updating of national guidelines** should be carried on.

Case-Study on Czech Republic:

The Czech approach considers that:

- when a type of practice is not – yet – justified in general according to Art. 55.2 (a), it has to be handled under the provisions of bio-medical research according to Art. 55.2 (e),
- in order to progress from the status of research according to Art. 55.2 (e) to the status of generally accepted type of practice according to Art. 55.2 (a), the research should be officially completed by a report agreed by the Ministry,
- the regulatory process has to be initiated, in particular for new types of practices, re-actively by e.g. undertakings - not within a notification / authorization process, but within the HTA process,

Commenté [MH7]: **⇐ important issue !!!**

- care should be given on the HTA process to ensure the full understanding and consideration given to the risks related to ionizing radiation by the HTA agencies; herby cooperation should be organised between RP competent authority and HTA agency and Ministry of Health,
- the justification process should be linked with the reimbursement process,
- CE Marking should be closely connected to the justification process of new types of practices.

Commenté [MH8]: not the case in most MS !!!

Commenté [MH9]: =< CE label must be mandatory before justification !!!

Discussion:

Following these presentations, the ESR's representative indicated that the proposed French approach seems feasible and transparent. Furthermore, it has been stressed that the involvement of stakeholders (experts/ scientific societies) is key in the process of generic justification to enhance credibility.

Plenary Session 6: Justification of New Types of Practices versus Biomedical Research?

In an introductory presentation, it was outlined that the *Principle of Justification* – as stated in Art 55.1 EU-BSS Directive for the medical field in general – requires that *medical exposures shall show a sufficient net benefit*. To evaluate this “*sufficient net benefit*”, an adequate benefit versus risk analysis is essential, which should be based on an adequate level of evidence. Thus, the *Principle of Justification* is closely linked to the level of evidence. In line with this kind of reasoning, it was then concluded that the adequate way from a new type of practice to the healthcare scenario requires an element of biomedical / clinical research. Otherwise, how else could the benefit versus risk analysis adequately be accomplished? But, there are shortcuts that directly lead to healthcare, without the detour on biomedical / clinical research. Based on these considerations, two questions were raised: (1) When a new type of practice is not – yet – justified in general according to Art. 55.2 (a), is it then to be handled under the provisions of bio-medical research according to Art. 55.2 (e)? and (2) How to progress from the status of research according to Art. 55.2 (e) to the status of a generally accepted new type of practice according to Art. 55.2 (a)?

In the second part of the introductory presentation, Art. 55.2 (c) Council Directive 2013/59/Euratom has been addressed. It claims that – if a type of practice involving medical exposure is not justified in general – a specific individual exposure of this type can be justified, where appropriate, in special circumstances, to be evaluated on a case-by-case basis and documented. The term “special circumstances” is closely related to the terms “off-label use of drugs” or “compassionate use of drugs”. Both cases refer to situations where a drug is provided to a patient – on humanitarian grounds – prior to a drug's receiving regulatory approval for a clinical indication. From this two further questions emerge: (3) How broad is the scope of application of Art. 55.2 (c)? and (4) Does Art. 55.2 (c) establish a further way to the healthcare scenario, i.e. to the individual application of medical exposures, which is not a shortcut, but a way consistent with the EU-BSS Directive?

Case-Study on France: New Radiopharmaceuticals

The case-study on France focused on the justification process for new radiopharmaceuticals, in particular the unsealed source therapy. The key-messages were:

- The process involves several institutions and agencies such as radiation protection authority (ASN), medical device / pharmaceutical authority (ANSM), ethics committees, healthcare authority, etc. Thus, exchange of data and information between institutions and agencies involved is essential.
- Occupational and public exposures have to be taken into account. But the direct impact on the justification process as well as on the licensing process has to be investigated.
- Proposal of new French system will enhance justification.

Case study on Switzerland: New Medical Devices

The case-study focused on the framework given in Switzerland for clinical research on new medical devices. The key-messages were

- Ethics committee judge benefit versus risk, but health authority and radiation protection authority are also involved in justification process.
- Regulation through Radiation Protection Act and Human Research Act.
- Estimated doses involved help define process – e.g. for effective doses < 5mSv radiation protection authority is not involved; for higher doses radiation protection authority is involved.
- In all clinical trials involving ionising radiation it is investigated whether the use of ionizing radiation is the primary purpose of the trial (i.e. primary use) or whether it is only used to assess important clinical parameters such as the regression of a tumor under a new therapy (i.e. adjunct use).
- Dose limits and constraints for special groups of volunteers (healthy, diseased) may be imposed relating to research, as well as claims concerning QA.

Discussion:

In their oral feedback, the medical associations and manufacturers focused in particular on the requirements imposed by Art. 55.2 (e) Council Directive 2013/59/Euratom on biomedical research and underlined that a graded approach is essential. Hereby, the primary purpose of the research is important: is the purpose of research to evaluate the impact of radiation itself or is it to monitor e.g. the impact of drugs by using radiation – among others – as a tool? Furthermore, doses should be considered relative to the inclusion criteria: are diseased volunteers (=patients) involved, who may benefit from the use of radiation, or normal healthy volunteers, who will not benefit from the use of radiation. The medical associations and manufacturers also stressed the need to bring ethical and radiation protection factors together, to ensure a comprehensive and well-balanced approach. Finally, they express their concerns that the development of better products may be inhibited when the transposition of Art. 55.2 (a) and (e) Council Directive 2013/59/Euratom into national legislations impose too many restrictions on the adoption of a new type of practice into healthcare.

One focus of the general discussion was Art. 55.2 (c) Council Directive 2013/59/Euratom addressing a type of practice that is not yet justified in general. There was a strong agreement that – in this case – Art. 55.2 (c) does not provide a shortcut to healthcare, bypassing the need for justification on a generic level. Instead, Art. 55.2 (c) is restricted to special circumstances with respect to an individual patient and requires a special individual justification. Explicitly, Art. 55.2 (c) does not cover the application of a new type

of practice to a group of patients. If this is the case, the application then has to be handled under the provisions of biomedical research according to Art. 55.2 (e) Council Directive 2013/59/Euratom.

Another focus was translation from research to generic justification for a new type of practice. It was agreed that an adequate process needs to be developed which properly links both spheres and which ensures a high level of transparency as well as communication – particularly with regard to data availability if it has direct impact on radiation protection issues. Hereby, both occupational and public exposures have to be considered and problems thrown up by research have to be reflected in later justification processes.