Presentation of the outcome of comparative analysis of the legal bases in the United States, United Kingdom and EU

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Identification and analysis of relevant international frameworks - EU

The basic principles of the pharmaceutical legislation for the EU are laid down in the Community Code Directive (Directive 2001/83/EC) as amended, especially by Directive 2003/63/EC (Directive 2003/63/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use). The consolidated version of Directive 2001/83/EC contains a main part consisting of more than 130 articles plus three annexes.

Annex 1 describes the contents and format that have to be followed for the establishment of the marketing authorisation dossier whereas annex II and annex III are of formal content only (i.e., list of repealed directives and correlation table, respectively) and therefore are of no relevance to this analysis.

Recital (18) of Directive 2001/83/EC states that any rules regarding radiopharmaceuticals must take into account the provisions of the BSSD. This is further elaborated in Article 4(1) of the directive: “Nothing in this Directive shall in any way derogate from the Community rules for the radiation protection of persons undergoing medical examination or treatment”.

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Identification and analysis of relevant international frameworks - UK

The Department for Health and Social Care (DHSC) is the ministerial department responsible for radiological protection of those exposed to ionising radiation as part of their own medical diagnosis or treatment in England. DHSC is the sponsoring department for the Care Quality Commission (CQC) and Public Health England (PHE) since the UK health Security Agency and the Medicines and Healthcare Products Regulatory Agency (MHRA).

Protection of patients, individuals and carers and comforters for medical exposures are covered by the Ionising Radiation (Medical Exposure) Regulations 2017 (IR(ME)R) in Great Britain and the Ionising Radiation (Medical Exposure) Regulations (Northern Ireland) 2018 in Northern Ireland. The regulations implement EU Directive 2013/59/Euratom (BSSD) and have had no further amendments following the UK's exit from the EU.

More details will be provided by Louise Fraser, Scientific Adviser, ARSAC, Medical Exposures Group, UK Health Security Agency

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Identification and analysis of relevant international frameworks - USA

Two major agencies govern the process on a national level:

- Food and Drug Administration (FDA)
- Nuclear Regulatory Commission (NRC)

Information on the legal situation were obtained from FDA and AAPM contacts.

An interesting first observation for the US is NRC Regulations Title 10, Code of Federal Regulations Part 35 – Medical Use of Byproduct Material states in §35.7: “Nothing in this part relieves the licensee from complying with applicable FDA, other Federal, and State requirements governing radioactive drugs or devices”

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Identification and analysis of relevant international frameworks - USA

NRC:

In its regulations and guidelines concerning the medical use of byproduct material (part 35, https://www.nrc.gov/reading-rm/doc-collections/cfr/part035/index.html) the NRC provides provisions for the protection of human research subject (§35.6) and clarifies the role of the FDA (§35.7, “Nothing in this part relieves the licensee from complying with applicable FDA, other Federal, and State requirements governing radioactive drugs or devices”).

Furthermore, it sets requirements for determining and recording the activity of each dosage before medical use (§35.63).

A licensee may not use a dosage if the dosage does not fall within the prescribed dosage range or if the dosage differs from the prescribed dosage by more than 20 percent (§35.63).

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Identification and analysis of relevant international frameworks - USA

NRC:

The NRC also regulates the training requirements for authorised radiation safety officers, medical physicists, and pharmacists (§§35.50, 35.51, 35.55).

For physicians, §§35.390, 35.392, 35.394 describe in detail the training needed for the use of unsealed byproduct material.

For ^{131}I, a distinction is made between the use of less or more than 1.22 GBq ^{131}I. This is, most likely, related to the release criteria of individuals containing unsealed product material (§35.75), in which a limit of the effective dose of 5 mSv is set for the release of patients.

§35.315 describes the safety precautions needed in case of hospitalisation of patients.

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Identification and analysis of relevant international frameworks - USA

NRC:

The Advisory Committee on the Medical Uses of Isotopes (https://www.nrc.gov/about-nrc/regulatory/advisory/acmui.html) advises the NRC on policy and technical issues that arise in the regulation of the medical uses of radioactive material in diagnosis and therapy. One of its members represents the FDA.

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Identification and analysis of relevant international frameworks - USA

FDA:

In 2019 the FDA published a document on „Non-clinical studies and labelling recommendations for oncology therapeutic radiopharmaceuticals“.

This document contains detailed information on radiation-related toxicity and dose-finding study requirements as prerequisite for a first-in-human use. It covers the topics pharmacology, animal biodistribution and dosimetry, toxicology, first-in-human dose selection (including a proposal, how to extrapolate from animal data to human data), and labelling recommendations.

There is no comparable document issued by the EMA.

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Identification and analysis of relevant international frameworks - USA

FDA:

For treatment with ^{131}I, the FDA provides ranges of activities to be administered for the treatment of hyperthyroidism (148–370 MBq) and thyroid cancer (post-operative ablation 1850 MBq, otherwise 3700–5550 MBq). An individualization of the therapy is possible; however, dosimetry is not explicitly mentioned as a means to achieve that.

For the absorbed dose assessment, a generic thyroid uptake-dependent table of values based on International Commission on Radiological Protection (ICRP) publication 53 is provided.

Lutathera®, according to the FDA, is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours, including foregut, midgut, and hindgut neuroendocrine tumours in adults. The therapy is prescribed as an administration of 7.4 GBq every 8 weeks for a total of four administrations. Modifications are possible based on adverse reactions of the patient….

The prescribing information does not contain any information on an absorbed-dose based approach for modifying the treatment activity.

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Identification and analysis of relevant international frameworks - USA

FDA:

Pluvicto®: the recommended Pluvicto® dosage is 7.4 GBq intravenously every 6 weeks for up to 6 administrations, or until disease progression, or unacceptable toxicity. Modifications are possible based on adverse reactions of the patient.

Dosimetry data for Pluvicto® was collected in 29 patients in the VISION sub-study and are summarised in a table in the FDA prescribing information. As for Lutathera®, the prescribing information does not contain any information on an absorbed-dose based approach for modifying the treatment activity.

Regarding treatment with radioactive spheres, two products have premarket approval by the FDA in the US: TheraSpheres™ and Sir-Spheres®. For these products, dosimetry-based prescriptions are either requested (TheraSpheres™) or possible (SIR-Spheres®).

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Identification and analysis of relevant international frameworks - USA

FDA:

In 2011 the FDA published a “Guidance for industry nonclinical evaluation of late radiation toxicity of therapeutic radiopharmaceuticals”.

The objective of this guidance is to provide recommendations to industry for designing nonclinical late radiation toxicity studies to determine potential late radiation effects of therapeutic radiopharmaceutical agents. Because studies in humans would be unethical, the best means to gain insight into this issue is by conducting nonclinical late radiation toxicity studies. These studies will aid in identifying organs at risk and establish a margin of safety for late radiation toxicity.

These studies will help to minimise the risk of late-occurring radiation toxicities in clinical trials of therapeutic radiopharmaceuticals.

There is no comparable document issued by the EMA.

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Comparison of the different regulatory frameworks

In the European Union, and also in the UK which adopted most of the regulatory frameworks of the EU, the situation is complex.

There are two different directorates - generals, Directorate-General for Health and Food Safety (DG SANTE) and Directorate-General for Energy (DG ENER), which are responsible for the legal frameworks governing the use of therapeutic radiopharmaceuticals. DG SANTE regulates the pharmaceutical part through directive Directive 2001/83/EC, whereas DG Energy regulates the radiation protection part for the application of radiopharmaceuticals through the BSSD.

Both directives are not directly applicable in the member states but require transposition into national law.

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Comparison of the different regulatory frameworks

USA:

The leading agency for marketing approval of therapeutic radiopharmaceuticals is the FDA. In contrast to the situation in Europe, the situation differs from the EU, as the NRC regulations and guidelines concerning the medical use of byproduct material states in §35.7, “Nothing in this part relieves the licensee from complying with applicable FDA, other Federal, and State requirements governing radioactive drugs or devices.”

The licensing process for radiopharmaceuticals is formally and, sometimes, informally supported by FDA contacts to the NRC.

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Comparison of the different regulatory frameworks

EU:

In the EU, the pharma directive 2001/83/EC states explicitly in its 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 ionising radiation.”

As a consequence, the way radiation protection is considered in the legal framework of both, the US and the European Union, is different.

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Comparison of the different regulatory frameworks

Posologies for licensed radiopharmaceuticals do not differ considerably among the US, EU and UK. For most cases, fixed activities are recommended, except for sodium iodide ^{131}I, for which some modifications of the activity to administer are not excluded.

Regarding the situation of radiopharmaceutical development, there is no guidance in the EU regarding the preclinical phase up to the marketing authorisation stage. This situation is possibly going to change but differs from that currently in place in the USA.

For radiopharmaceuticals recently put on the market, the current practice is to recommend fixed activities (or based on weight, BSA, etc.) with no patient-specific adjustment of the posology.

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Cor eworks

EUROPEAN MEDICINES AGENCY

SmPC: structure and content

- 1. Name of the medicinal product
- 2. Qualitative and quantitative composition
- 3. Pharmaceutical form
- 4. Clinical particulars
  - 4.1 Therapeutic indications
  - 4.2 Posology and method of administration
  - 4.3 Contraindications
  - 4.4 Special warnings and precautions for use
  - 4.5 Interactions with other medicinal products and
  - 4.6 Fertility, pregnancy and lactation
  - 4.7 Effects on atility to drive and use machines
  - 4.8 Undesirable effects
  - 4.9 Overdose
- 5. Pharmacological properties
  - 5.1 Pharmacodynamic properties
  - 5.2 Pharmacokinetic properties
  - 5.3 Preclinical safety data
- 6. Pharmaceutical particulars
  - 6.1 List of excipients
  - 6.2 Incompatibilities
  - 6.3 Shelf life
  - 6.4 Special precautions for storage
  - 6.5 Nature and contents of container
  - 6.6 Special precautions for disposal and other handling of the product

3

4.4 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 effect.

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Comparison of the different regulatory frameworks

EU:

There are parallel and currently non-intersecting mechanisms that govern nuclear medicine therapy regulations when it comes to marketing authorisation (under the responsibility of EMA) and radiation safety and optimisation (under the responsibility of DG ENER). This allowed the co-existence of inconsistent regulations.

Recent marketing authorisations delivered by EMA do not include nor mention the legal requirements for radiation protection optimisation. This has propagated at national levels where regulation calling to radiotherapy optimisation and marketing authorisations based on standard activity administration may coexist.

In addition, in many countries, there is a lack of awareness of the BSSD requirements from the authorities regulating pharmaceuticals (see Session 3).

USA:

The situation is different as FDA and NRC relations are more formalised.

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