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# EFOMP policy statement NO. 19: Dosimetry in nuclear medicine therapy – Molecular radiotherapy

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A B S T R A C T

The European Council Directive 2013/59/Euratom (BSS Directive) includes optimisation of treatment with radiotherapeutic procedures based on patient dosimetry and verification of the absorbed doses delivered. The present policy statement 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 and development of codes-of-practice; resourcing to support an infrastructure that permits routine patient dosimetry; research funding to support investigation into individualised treatments; inter-disciplinary training and education programmes; and support for investigator led clinical trials. Close collaborations between the medical physicist and responsible practitioner are encouraged to develop a similar pathway as is routine for external beam radiotherapy and brachytherapy. EFOMP's policy is to promote the roles and responsibilities of medical physics throughout Europe in the development of molecular radiotherapy to ensure patient benefit. As the BSS directive is adopted throughout Europe, unprecedented opportunities arise to develop informed treatments that will mitigate the risks of under- or over-treatments.

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## 1. Introduction

Molecular radiotherapy[a] refers to the use of radioactive drugs or radioactive medical devices for medical treatment. First introduced in the 1930 s [1], the field is now rapidly expanding with many new agents for a growing number of indications [2].

Molecular radiotherapy may be administered orally or intravenously to deliver treatment systemically, as for conventional chemotherapy, or may be given intra-arterially or by loco-regional infusion. Examples include the treatment of benign and malignant thyroid disease with radioiodine, intra-arterial administrations of radioactive microspheres with $^{90}$Y or $^{166}$Ho for tumours and metastases in the liver, $^{177}$Lu PSMA ligands for the treatment of metastatic prostate cancer and $^{177}$Lu or $^{90}$Y peptide receptor radionuclide therapy for the treatment of metastatic neuroendocrine tumours. In all cases, the mechanism of treatment is with ionising radiation.

Patient benefit and regulatory compliance require that molecular radiotherapy should be considered as a radiotherapeutic procedure, based on the premise that the absorbed doses delivered to target tissues should be optimised while the absorbed doses delivered to non-target tissues should be minimised and within accepted constraints. Such an approach necessitates individualised treatment planning and verification, based on patient dosimetry.

The motto of EFOMP reads “Applying physics to healthcare for the benefit of patients, staff and public” [3]. Patient benefit and regulatory compliance have direct implications for the work and responsibilities of the Medical Physics Expert (MPE) that has clinical responsibility for measurements and imaging, dosimetry, and radiobiology. The interaction between the MPE and radiation protection expert, which may be one in the same person in personalised dosimetry settings, also brings the possibility of safer molecular radiotherapy from an occupational, public and environmental perspective [3]. This can result in more cost-effective treatments in e.g. outpatient settings which will meet regulatory requirements in a shorter time span.

## 2. Regulatory requirements

There are three main European directives that regulate the use of radiopharmaceuticals for therapeutic purposes.

### 2.1. The European Council Directive 2013/59/EURATOM of 5 December 2013

The European Council Directive 2013/59/EURATOM of 5 December 2013 “Laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation” (henceforth referred to in this policy statement as the Basic Safety Standards (BSS) directive) and was brought into force in national legislation and regulations in 2018 [4].

Within Chapter VII (Medical Exposures) it is stated:

Article 56

‘Optimisation

*1. For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.*’.

Within Chapter II (Definitions) Article 4 (81) the definition is explicitly given that ‘“radiotherapeutic” means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes.’.

This BSS directive follows recommendations given by the International Commission on Radiological Protection (ICRP), International Commission on Radiation Units and Measurements (ICRU) and the International Atomic Energy Agency (IAEA) relating to the fundamental principles of justification and optimisation for radiological protection including for therapeutic practice with radionuclides [5–8].

Specifically, ICRP report 140 states that:

‘*Individual absorbed dose estimates should be performed for treatment planning and for post administration verification of doses to tumours and normal tissues.*’.

### 2.2. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

To achieve marketing authorisation of medicinal products for human use in Europe, compliance must be demonstrated to the directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, of 6 November 2001 (referred to in this policy statement as the ‘Pharma directive’) [9]. This Pharma directive addresses radiopharmaceuticals and states that:

Pre-amble:

*‘(18) Any rules governing radiopharmaceuticals must take into account the provisions of Council Directive 84/466/Euratom of 3 September 1984*[b] *laying down basic measures for the radiation protection of persons undergoing medical examination or treatment ……’*.

Scope, 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 ionizing radiation.*’.

Annex I, Part 3, Introduction:

*‘4. For radiopharmaceuticals, it is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radiopharmaceuticals; in therapy, it is the wanted property. The evaluation of safety and efficacy of radiopharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognized system by a particular route of administration.*’.

### 2.3. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices

Radioactive microspheres are classified as medical devices. Requirements regarding the information supplied with the device are laid down in Annex I, Chapter II of Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices (referred to in this policy statement as the Medical Device Regulation, ‘MDR’) [10].

According to section 16, entitled ‘Protection against radiation’:

‘*(a) Devices shall be designed, manufactured and packaged in such a way that exposure of patients, users and other persons to radiation is reduced as far as possible, and in a manner that is compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for therapeutic and diagnostic purposes.*’.

According to section 16.4, entitled *‘Ionising radiation’* :

‘*(a) Devices intended to emit ionising radiation shall be designed and manufactured taking into account the requirements of the Directive 2013/59/Euratom laying down basic safety standards for protection against the*

[a] This therapy modality is referred to by different names, including for example: radiopharmaceutical therapy, radionuclide therapy, nuclear medicine therapy, radioligand therapy. Although selective internal radiotherapy is strictly not delivered by molecular pathways, this modality is also intended to be covered by the term within the scope of this policy statement.

[b] Council Directive 84/466/Euratom has since been superseded by the BSS Directive.

*dangers arising from exposure to ionising radiation.*'.

The Pharma directive and the MDR therefore mandate compliance with the BSS Directive that states that exposures of target and non-target volumes shall be individually planned and verified. Whilst the Pharma Directive does not explicitly specify whether dosimetry should be made on an individual or cohort level, or whether this choice depends on whether the radiopharmaceutical is used for diagnostic or therapeutic purposes, these separations are clearly specified in the BSS Directive.

## 3. Current status of molecular radiotherapy

Molecular radiotherapy has expanded rapidly in recent years, although there is an absence of detailed records throughout Europe of treatment procedures and outcomes. A review of clinicaltrials.gov has indicated a rapid growth in the number of and participation in clinical trials of new therapeutic radiopharmaceuticals [11]. A survey by the Internal Dosimetry User Group in the UK found that administrations have increased by a factor of 4 in the UK in the last 10 years [12].

At present, a range of treatment prescriptions are followed, often based on historical practice [13,14]. Recent marketing authorisation has continued a conventional prescription governed by fixed activities, often in multiples of 3700 MBq (100 mCi) [15,16].

The level of activity administered is a poor indicator of the radiation energy absorbed in different tissues and cannot predict effects of treatment. A parallel may be drawn to other radiotherapy modalities, in which the time or rate of radiation exposure have long been abandoned as sole treatment planning parameters. Therefore, the assessment of radiation effects and evaluation of probabilities of effectiveness and risks of toxicity based on the administered activities have a weak scientific foundation.

It is well established that fixed activity administrations to all patients deliver a wide range of absorbed doses to tissues-at-risk and to tumours [17–20], raising the risk of under- and over-treatments. The benefit of patient-specific dosimetry has been demonstrated in reports on relationships between the absorbed dose and toxicity of normal tissues or disease control [21–24].

For the development of new agents, cohort escalation studies designed with fixed-activity levels will result in variable absorbed doses within each escalation step. Such development should incorporate investigations of correlations between the absorbed doses delivered and treatment effects to improve risk-versus-benefit evaluation. The approval of new therapeutic radiopharmaceuticals with posology based on fixed activity levels but without inclusion of patient-specific dosimetry presents a major obstacle to patient-specific optimisation according to the BSS Directive.

In recent decades there have been significant methodological and technological advances in imaging and image processing, including hybrid imaging, image-based activity quantification, pharmacokinetic and pharmacodynamic modelling and formalisation of uncertainty analysis [7,17,25–29]. Substantial developments in the harmonisation of data acquisition and processing have supported clinical implementation and multi-centre clinical trials that have included patient dosimetry as a key element [23,24,26,30–36].

The feasibility of incorporating dosimetry in molecular radiotherapy procedures, either within clinical routine or in clinical trials, has been clearly demonstrated. For example, in many countries, dosimetry is frequently undertaken as part of the routine work-up for treatments with radioactive microspheres for tumours in the liver and with radioiodine for hyperthyroidism [14,27,29,37]. Several clinical trials have incorporated dosimetry, either for treatment guidance or as a primary area of investigation, for a range of treatments and indications. Examples include $^{131}$I-mIBG for neuroblastoma [38], peptide-receptor radionuclide therapy for neuroendocrine tumours [31,39–41], radioiodine treatment of hyperthyroidism [42] and differentiated thyroid cancer [36], and $^{90}$Y microspheres [23,24,43,44].

## 4. Challenges and opportunities

The implementation of radiation dosimetry into routine clinical practice faces a number of pressing challenges that, if addressed, will introduce unprecedented opportunities for cancer treatment.

I Collection of evidence to inform treatments

Few patients are treated with molecular radiotherapy in comparison with non-radioactive drug treatments or external beam radiotherapy. An understanding of treatment effectiveness and risks, and their dependence on patient-specific baseline characteristics and prognostic biomarkers, is hampered by limited data regarding the absorbed doses delivered and treatment outcomes. Coherent data collection, harmonisation and metrological standardisation of dosimetry results require close collaboration between the many disciplines involved with molecular radiotherapy [45–47].

Recommendations/EFOMP Policy:

1. European molecular radiotherapy networks must be supported and expanded to share experience, expertise and resources.
2. National and European databases are required to collect data on clinical factors, dosimetry and patient outcomes from multiple centres.
3. Codes-of practice for the validation and harmonisation of dosimetry results and patient outcomes for different treatments should continue to be developed and put into practice.

II. Service and research infrastructure

Further developments within molecular radiotherapy require resourcing for service and research infrastructure. This is particularly relevant to medical physics which suffers wide variations in staffing levels throughout Europe and minimal research funding. The capacity to perform patient imaging and dosimetry also varies widely across centres and countries.

Recommendations/EFOMP policy:

4. Imaging and patient dosimetry must be reimbursed as is the case for external beam radiotherapy.
5. Staffing requirements for centres offering molecular radiotherapy must be defined in compliance with the BSS directive [48–50].
6. Research should be supported through national and European programmes to investigate treatment planning strategies for individual therapeutic procedures.

III. Training and education

Training programmes in molecular radiotherapy, including patient imaging, dosimetry and radiobiology, vary widely throughout Europe and between disciplines. Awareness of the regulatory framework governing molecular radiotherapy should be promoted to ensure integration of dosimetry into routine clinical practice.

Recommendations/EFOMP policy:

7. Professional organisations should continue to provide joint guidelines to perform image-based dosimetry and guidance for resource requirements, for each treatment procedure.
8. Initiatives are required to promote engagement and knowledge transfer between the various disciplines, including medical physics and medical specialties, regulatory authorities and industry.

**Table 1**
Schematic, generic example of how roles and responsibilities in dosimetry-guided molecular radiotherapy can be shared.

| Step | Role and responsibility |
|---|---|
| i | The MD declares intention to treat and identifies the target tissues and tissues-at-risk. |
| ii | The MPE presents to the MD a range of activities to administer that are likely to yield a corresponding range of absorbed doses delivered to tissues-at-risk and/or target tissues. |
| iii | The MD decides whether treatment will be given. |
| iv | The MD specifies the maximum permissible absorbed doses to be delivered to tissues-at-risk and/or the aimed absorbed doses to be delivered to target tissues, taking account of relevant patient-specific parameters, clinical risk factors and treatment intent. The MPE gives advice on matters such as relevant tissues-at-risk and tolerance absorbed doses, as well as the absorbed doses that may be effective for treatment. |
| v | The MPE has responsibility for instruments and protocols used for measurement of the prescribed activity, patient dosimetry data (including e.g. quantitative imaging), data analyses and dosimetry calculations. |
| vi | Following administration, the MPE conducts the metrological monitoring of the biodistribution of the radiotherapeutic agent and verifies the absorbed doses delivered to target tissues and tissues-at-risk. The data on absorbed doses are recorded in the patient information system and should be traceable to (signed by) an individual MPE and MD. This information may then inform a further treatment cycle or retreatment. |

9. MPEs in training should gain experience in the implementation of dosimetry-guided treatments. Where necessary, training may be provided at remote centres.
10. Molecular radiotherapy is a highly multidisciplinary field. Programmes of education are therefore required to train all disciplines in relevant areas.

IV. Investigator-initiated clinical trials

Currently, many industry-developed radiotherapeutic drugs are introduced in the clinic without protocols for patient imaging or dosimetry. Collection of evidence to inform the development of personalised molecular radiotherapy must be complemented by investigator-initiated clinical trials, as is the case for external beam radiotherapy.

Recommendations/EFOMP policy:

11. Investigator-initiated multi-centre and multi-national clinical trials should be promoted to develop optimised treatments.
12. Networks for dosimetry expertise are required to enable sharing of know-how to support clinical trials. For example, image processing and dosimetry may be performed at remote sites with data collected according to specified protocols.
13. For industry- and investigator-initiated clinical trials, individual-patient dosimetry must be incorporated to enable risk-versus-benefit analyses within drug development. Results and evidence must be presented at the time of submission for drug marketing authorisation.
14. Health economics studies should be incorporated into clinical trials to investigate the costs of patient imaging and dosimetry relative to that of recently introduced commercial therapeutic radiopharmaceuticals and to other forms of radiotherapy.

## 5. Future implementation of molecular radiotherapy

Clinical implementation of molecular radiotherapy relies on shared roles and responsibilities between the MPE and the medical practitioner (MD). As for any radiotherapeutic modality the MPE should be responsible for treatment planning based on individualised patient dosimetry, metrological monitoring, and verification of the absorbed doses delivered, whilst the MD prescribes treatment according to the projected absorbed dose distribution, with account taken of patient specific information that may include baseline characteristics and treatment history (Table 1).

**Table 2**
Summary of Recommendations / EFOMP Policy

| | Recommendation / EFOMP Policy |
|---|---|
| 1 | European molecular radiotherapy networks must be supported and expanded to share experience, expertise and resources. |
| 2 | National and European databases are required to collect data on clinical factors, dosimetry and patient outcomes from multiple centres. |
| 3 | Codes-of practice for the validation and harmonisation of dosimetry results and patient outcomes for different treatments should continue to be developed and put into practice. |
| 4 | Imaging and patient dosimetry must be reimbursed as is the case for external beam radiotherapy. |
| 5 | Staffing requirements for centres offering molecular radiotherapy must be defined in compliance with the BSS directive. |
| 6 | Research should be supported through national and European programmes to investigate treatment planning strategies for individual therapeutic procedures. |
| 7 | Professional organisations should continue to provide joint guidelines to perform image-based dosimetry and guidance for resource requirements, for each treatment procedure. |
| 8 | Initiatives are required to promote engagement and knowledge transfer between the various disciplines, including medical physics and medical specialties, regulatory authorities and industry. |
| 9 | MPEs in training should gain experience in the implementation of dosimetry-guided treatments. Where necessary, training may be provided at remote centres. |
| 10 | Molecular radiotherapy is a highly multidisciplinary field. Programmes of education are therefore required to train all disciplines in relevant areas. |
| 11 | Investigator-initiated multi-centre and multi-national clinical trials should be promoted to develop optimised treatments. |
| 12 | Networks for dosimetry expertise are required to enable sharing of know-how to support clinical trials. For example, image processing and dosimetry may be performed at remote sites with data collected according to specified protocols. |
| 13 | For industry- and investigator-initiated clinical trials, individual-patient dosimetry must be incorporated to enable risk-versus-benefit analyses within drug development. Results and evidence must be presented at the time of submission for drug marketing authorisation. |
| 14 | Health economics studies should be incorporated into clinical trials to investigate the costs of patient imaging and dosimetry relative to that of recently introduced commercial therapeutic radiopharmaceuticals and to other forms of radiotherapy. |

## 6. Discussion

The field of molecular radiotherapy is expanding rapidly in terms of new agents either in development or in early phase trials, the number of clinical trials and the range of cancers treated. In recent years, molecular radiotherapy has become increasingly dominated by significant commercial investment. At a time that many alternative treatments are emerging, including targeted therapies, immune- and gene-therapies, the capacity to image the biodistribution and to calculate the radiation absorbed doses delivered on a patient-specific basis, as was pursued when molecular radiotherapy was introduced [51], is unrivalled and offers significant patient benefit.

There is mounting evidence of relationships between the absorbed doses delivered and outcomes. Individualised treatment planning will further develop as more data become available. These may serve as a foundation for treatment planning and patient stratification to mitigate the risks of treatments that are unlikely to be beneficial. Verification of the absorbed doses delivered may be performed readily for most treatments and, in cases of multiple fractions, may inform subsequent administrations.

Molecular radiotherapy cannot be regarded as a single treatment but as a range of modalities, dependent on how the treatment is administered and on the indication. Successful treatments are therefore dependent on a wide range of expertise that may include specialists in medical and clinical oncology, nuclear medicine, endocrinology, urology and interventional radiology. The role of the MPE is to advise on matters relating to radiation protection, image acquisition and

processing, radiobiology, and patient dosimetry. It is then the role of the responsible practitioner to prescribe treatment, tailored to the individual patient, as informed by these criteria.

A summary of the recommendations / EFOMP Policy is provided in Table 2.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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