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### Trick or Treatment



**Dr. Clemens Decristoforo,**  
**Radiopharmacist**

\*\*\*\*\*@\*\*\*imed.ac.at

Radiopharmacist - Innsbruck  
Medical University

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**Access to powerful drugs for personalised medicine is hampered by EU legislation that is creating a radiopharmaceutical lottery, argues the EANM's Dr Clemens Decristoforo.**

Advances in drug developments and new insights into genetics and the diversity of diseases – in particular cancers – have generated a trend towards personalised medicine: using drugs and treatments ideally suited for an individual patient's need. Additionally, the high costs of drug development and of new drug treatments have stimulated both the pharmaceutical industry and regulators to look into ways to select the right drug for the individual patient.

Essential tools in the attempt to personalise medicine are so called 'imaging biomarkers', which specifically uncover the characteristics of diseased tissues and cells. One of the most successful technologies to utilise imaging biomarkers is Positron Emission Tomography (PET), whereby a radiolabelled compound (radiopharmaceutical) is injected and accumulates in cells based on certain specific properties, such as glucose metabolism, receptor expression, proliferation or oxygen supply. These properties are the basis for detecting diseased tissue, characterising its biological status, and selecting and monitoring treatment on a molecular basis with unprecedented sensitivity.

In recent years, PET has become an important tool both in patient diagnosis and for research in clinical trials. More than 100 different radiopharmaceuticals are used in clinical routine, not only for PET applications, and they are defined as medicinal products in the current European pharmaceutical legislation based on directive 2001/83.

PET radiopharmaceuticals contain a radionuclide with an extremely short half-life, such as fluorine-18 (F-18) with 110 min, C-11 with 20 minutes or Ga-68 with 68 minutes. This requires the radionuclide to be produced in a cyclotron, or so-called radionuclide generator, close to the application site and the patient. The radionuclide is transformed in a subsequent chemical process, incorporated to form the biologically active radiolabelled compound and formulated for administration to the patient. Due to their short shelf life, many of these radiopharmaceuticals are prepared 'in-house' – in the hospital or academic centres where they are used within minutes or hours of preparation. Highly specialised teams of radiopharmacists and chemists provide this service in many centres throughout Europe, and the number of applications is growing rapidly.

#### **The Effects of a Limited Market**

As radiopharmaceuticals are embedded in the European pharmaceutical framework, the standard way of making these drugs available is via marketing authorisation (MA). This is cost intensive and requires the submission of an extensive drug dossier to regulatory authorities, usually by a commercial manufacturer.

Even though a small number of PET radiopharmaceuticals have gained MA, a great number of established products are used outside the MA track, in particular those prepared at hospitals and academic centres. The number of applications at one production site is often very limited, typically serving only one hospital department, making the high-effort application for MA economically unviable. In some European countries, the application is possible based on a medical prescription for the individual patient (magistral preparation) while others deny this possibility within their national regulation.

The option to apply for a clinical trial application for the preparation and use of radiopharmaceuticals has been hampered by the EU Clinical

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Trials Directive. In particular, academia has great problems complying with the high efforts to conduct clinical trials. This leads to the current situation in which, in certain countries, patients may have access to certain radiopharmaceuticals, while in other nations they are denied the most recent developments in the field. A typical example of this is the use of peptides labelled with Ga- 68 in oncology for imaging special liver and gut tumours. In central Europe (including Germany) PET clinical use of Ga-68-radiopharmaceuticals are widely established, whereas in Western Europe (for example, Spain and France) only a handful of highly specialised units have managed to implement this technique.

#### **'Big Pharma' Standards for Small-Scale Preparation**

The second challenge to the use of radiopharmaceuticals is the way that these have to be prepared. Pharmaceutical manufacturing is standardised by Good Manufacturing Practices (GMP), which are defined in the European EUDRALEX. These standards are driven by the pharmaceutical industry with high production capacities and highly centralised, large-scale production sites.

Recent years have seen an ever-increasing pressure to comply with GMP standards, even in the small-scale production of radiopharmaceuticals. Hospitals and university centres have spent millions of euros installing dedicated clean rooms with the adequate radiation protection required for the handling of radioactive drugs.

Moreover, an ever greater number of highly specialised staff is required to prepare a decreasing number of products to comply with GMP requirements on documentation, monitoring processes and quality management. The implementation of GMP varies throughout Europe, depending not only on the particular national exemptions, but also on different ways of interpreting such a high specialisation by the pharmaceutical inspectors.

Despite the use of radioactivity, radiopharmaceuticals are very safe drugs. They normally contain only a microdose of the compound, usually in the range of micrograms or less, and adverse reactions are extremely rare. Additionally, they are used typically only once in a patient's lifetime and under highly controlled conditions within a clinical department.

Notwithstanding the importance of GMP regulations to ensure adequate safety and the quality and potency of medicinal products, it also has to be considered that their current application to the non-commercial production of radiopharmaceuticals, for in-house use, is imposing excessive hurdles on the everyday work of thousands of nuclear medicine practitioners across Europe. Furthermore, exercising a legislation framework designed for the industrial production and marketing of non-radioactive medicinal products over the whole radiopharmaceutical community is creating great difficulties for the development and research of the new products that patients are demanding.

#### **Towards Common Standards**

The current mandates of European and national legislation have led to the situation where the availability of radiopharmaceuticals and applied standards show an extreme variability throughout Europe. This is in striking contrast to the U.S., where the Food and Drug Administration guides both the commercial and small-scale preparation of radiopharmaceuticals. Specific European guidelines that harmonise and support the small-scale, local preparation and use of radiopharmaceuticals, together with a better understanding of this special field by regulatory bodies, would help to bring novel radiopharmaceuticals to the patients that need specific diagnosis and have the right for personalised medicines for optimal treatment.

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