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EDITORIAL

# Radiopharmaceuticals are special, but is this recognized? The possible impact of the new Clinical Trials Regulation on the preparation of radiopharmaceuticals

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Dear Sir,

Nuclear medicine techniques are in the forefront of molecular imaging, thereby translating discoveries in molecular biology, genetics, pharmacology and many other disciplines into imaging diseases for the patient's benefit. A wide variety of radiopharmaceuticals for many different targets are available and many others are continually being developed for oncology, neurology, cardiology and other clinical settings. Over the past decade the major hurdle in translating this radiopharmaceutical development into the clinic has been an excessive and ever tightening regulatory framework for pharmaceuticals in general, which does not take into account the special nature of radiopharmaceuticals. In particular, novel radiopharmaceuticals are to a great extent developed at universities and hospitals and are prepared on a small scale in a non-industrial setting. This is due to their relatively short shelf life, which typically requires preparation on an extemporaneous basis for individual patients.

As radiopharmaceuticals are medicinal products according to Directive 2001/83 [1], radiopharmaceuticals used within clinical trials are regarded almost exclusively as investigational medicinal products (IMPs) [2]. With the release of the "Clinical Trials Regulation", i.e. Directive 2001/20 [3], the last decade was characterized by great regulatory changes [4], especially for the preparation of IMPs. In particular, the introduction of pharmaceutical Good Manufacturing Practice (GMP) as a requirement with subsequent release of specific guidelines (Annex 13, [5]), has shown its full impact in recent years in many European countries. The impact is manifold: GMP requires dedicated clean room facilities and as most radiopharmaceuticals have to be prepared aseptically, this requires the application of the highest clean room classifications. In many European countries millions of euros have been invested to build new or adapt old facilities to meet these standards. Additionally, GMP and the Clinical Trials Regulation also imposed the need for authorization and the

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requirement of a qualified person according to Directive 2001/83 being responsible for release of these radiopharmaceuticals [6]. Furthermore, GMP introduces the need for a highly sophisticated and extensive quality management framework, which, especially in terms of documentation requirements, consumes many personnel resources. For hospitals and universities preparing radiopharmaceuticals solely on a non-commercial, in-house basis, this is very difficult to follow. If very strictly implemented and controlled by regulatory authorities, full GMP requirements have slowed down and in many cases made it impossible to translate promising diagnostic molecular imaging concepts into the clinic.

The European Association of Nuclear Medicine (EANM) has set many initiatives to counteract this development [7] and to support its members in their developmental work. A number of guidelines have been written, including Good Radiopharmacy Practice (GRPP) documents [8], giving a practical approach for quality standards for the small-scale preparation of radiopharmaceuticals, and guidelines interpreting the existing guidelines for early clinical trials with radiopharmaceuticals [9]. In addition to these official documents, the EANM has commented on surveys by the European Medicines Agency (EMA) and the European Commission, in particular regarding clinical trials, as well as holding official meetings with EMA in London and the respective Directorates in Brussels.

It now seems that for the first time these initiatives have had a real impact at a regulatory level. On 27 May 2014 the new Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use was published in the *Official Journal of the European Union* [10]. It will repeal Directive 2001/20 and has been initiated by the phenomenon that since introduction of this Directive the number of clinical trials performed throughout Europe has significantly decreased. The new Clinical Trials Regulation will have a dramatic impact on how clinical trials will be performed in the near future. The fact that it is a regulation (that is immediately enforceable and does not need transposition to national legislation) is very relevant, as this will mean that all EU countries will have not a similar, but an identical regulation for clinical trials. This harmonization in the way clinical trials will be carried out in Europe should foster clinical research and consequently also biomedical translational and preclinical research.

The new Regulation is focused on patient safety and reasonable and proportionate risk assessment, simplifying all the approval procedures by replacing local ethics committees by a national application procedure and favouring multicentre transnational clinical trials.

Regarding radiopharmaceuticals, several important specific exceptions were introduced:

1. No need to hold an authorization for manufacture or import of radiopharmaceuticals used as diagnostic IMPs where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorized in the Member State concerned to carry out such process, and if the IMPs are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State (art. 61.5).
2. No need for GMP production of diagnostic radiopharmaceuticals used as IMPs and prepared and used in the conditions stated above (art. 63.2 in relation to 61.5).
3. Simplified labelling of radiopharmaceuticals used as IMPs (this refers to the label of the vial/syringe with the dose). Art. 68 in association with art. 66 and 67.

This is the first legal document to specifically exempt the small-scale preparation of radiopharmaceuticals from the full requirements of GMP and its full impact is difficult to judge at this moment. While the new Regulation will not come into force for 2 years, it remains open which requirements for radiopharmaceutical preparation will then have to be applied. It will be in the hands of the national authorities to regulate this, however, with the clear indication from the European Commission that full GMP should not apply.

In this context it seems important to mention that the small-scale, extemporaneous preparation of radiopharmaceuticals has been in the focus of two recent documents by different European regulatory bodies. One is a new Annex 3 on radiopharmaceuticals to the Pharmaceutical Inspection Co-operation Scheme (PIC/S) guideline for healthcare establishments [11] which has defined the standards especially applicable in the hospital pharmacy context. This new Annex 3 covers preparation of $^{99m}$Tc radiopharmaceuticals from kits and generators, but also positron emission tomography (PET) preparations such as those from $^{68}$Ge/$^{68}$Ga generators and deviates from conventional GMP, in particular in reducing requirements when the product is used within a short period of time based on risk assessment. The other document is from the European Directorate for the Quality of Medicines (EDQM), an organ of the Council of Europe that has released for public consultation the second version of a draft chapter for the European Pharmacopoeia on "Extemporaneous preparation of radiopharmaceutical preparations" [12]. It also defines quality standards and in particular implements a risk assessment approach, also giving guidance for the use of automated systems and cell labelling. It is currently open for comments and could be finalized by the end of 2014.

Both the PIC/S and EDQM documents indicate that regulatory bodies and authorities recognize the need for specific definitions of how radiopharmaceuticals should be prepared on a small scale, not for commercial purposes, on a prescription of a medical doctor for a specific investigation. Some questions remain open at the moment, such as: can these two documents be applied to investigational medicinal products? Which

documents should specifically be used, and which takes precedence when there are conflicting requirements? How should therapeutic radiopharmaceuticals be handled and prepared? If GMP does not apply to the small-scale preparation of investigational medicinal products, can GMP then be applied for the small-scale preparation outside a clinical trial? This last question is especially critical, as it would have no sense to apply a tougher regulation to small-scale in-house use production of radiopharmaceuticals than to the preparation of the very same products as IMPs for a clinical trial.

In any case the new Clinical Trials Regulation and other recently released documents have shown that, at least at the European level, the authorities have a rising awareness and recognition that radiopharmaceuticals are indeed a special group of drugs that require a specific framework to be safely prepared without disproportionate regulations hampering the development of novel diagnostic tools for the benefit of the patient. It's now time to, on a country by country basis, engage with the national competent authorities having in mind a similar approach.

It is important to recognize the role of EANM in achieving the changes stated above in relation to radiopharmaceuticals. It was of utmost importance that EANM contact with appropriate persons early in the process was able to influence the Commission when it drafted the very first proposal of this Regulation, followed up by an EANM delegation to Brussels during the consultation phase, reinforcing and expanding the exemption for diagnostic radiopharmaceuticals.

More work and concerted efforts are required to complete an appropriate regulatory framework that will allow us to develop novel radiopharmaceuticals, not being slowed down by inappropriate rules and guidelines. EANM is maintaining communication with relevant organizations such as EMA to achieve this aim. However, especially as our community is a very small one, it remains to everyone individually to work in this direction to be successful.

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