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EDITORIAL

The ^{68}Ge/^{68}Ga generator has high potential, but when can we use ^{68}Ga-labelled tracers in clinical routine?

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In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, the article by Antunes et al., entitled "Are radiogallium-labelled DOTA-conjugated somatostatin analogues superior to those labelled with other radiometals?", provides another example of the high potential of the ^{68}Ge/^{68}Ga generator for PET applications in nuclear medicine. The use of ^{68}Ge/^{68}Ga generators in nuclear medicine is very attractive for several reasons:

1. The 270-day half-life of the parent ^{68}Ge allows use of the generator for a long period, potentially up to 1 year or even longer.
2. The 68-min half-life of ^{68}Ga matches the pharmacokinetics of many peptides and other small molecules owing to rapid diffusion, localisation at the target and fast blood clearance.
3. The PET radionuclide ^{68}Ga is continuously available at a reasonable cost from a ^{68}Ge/^{68}Ga generator, including for centres without a cyclotron.
4. Besides the DOTA analogues of somatostatin [1–5], DOTA-derivatised analogues of several other interesting peptides have been developed, such as bombesin [6–10], substance P [11, 12], neurotensin [13] and CCK [14–16]. DOTA is an excellent ligand for binding of gallium; as a consequence, DOTA-peptides can be rapidly and efficiently labelled with ^{68}Ga at high specific activities [10, 17, 18], which implies that the mass of peptide to be administered can be very low [6, 19, 20]. This is of particular interest in the case of peptides with potential pharmacological side-effects, including substance P, bombesin and CCK.

In addition, labelling with ^{68}Ga is not restricted to DOTA-derivatised compounds. As long ago as the 1970s and 1980s, several ^{68}Ga-labelled tracers were reported, e.g. for haematological applications and for investigations of myocardial, liver and kidney function [21–29], but the lack of a reliable source of the radionuclide prohibited their further development. It can be expected that the commercial availability of ^{68}Ge/^{68}Ga generators will stimulate radiochemists and radiopharmacists to develop new ^{68}Ga-based radiopharmaceuticals for PET application; hence the number of potential ^{68}Ga tracers for clinical applications is very likely to expand in the near future.

On the other hand, despite these encouraging prospects and the favourable results of recent clinical studies using ^{68}Ga-labelled peptides, there is still quite a long way to go before ^{68}Ga-labelled compounds become standard radiopharmaceuticals for widespread use in daily nuclear medicine routine. The reason for this has to be sought mainly in the requirements imposed by pharmaceutical legislation. Thus far, no company has a marketing authorisation for a ^{68}Ge/^{68}Ga generator. Such a marketing authorisation is a strict requirement for a radionuclide generator from which is produced a daughter radionuclide that is to be obtained by elution and used in a radiopharmaceutical, as clearly stated by Directive 2001/83/EC of the European Parliament and of the European Council, art.

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6.2 (November 6, 2001) on the community code relating to medicinal products for human use. Among many other requirements, such as those relating to establishment of chemical, radiochemical and radionuclidic purity of the eluate, the granting of a marketing authorisation for a ^{68}Ge/^{68}Ga generator is dependent on the condition that it is manufactured under conditions of good manufacturing practice (GMP). Indeed, the eluate of such a generator is to be considered as an active substance used as a starting material for a medicinal product for human use. Article 46 (f) of European Directive 2001/83/EC and Article 50 (f) of Directive 2001/82/EC, as amended by Directives 2004/27/EC and 2004/28/EC respectively, place new obligations on manufacturing authorisation holders to use only active substances that have been manufactured in accordance with GMP for starting materials [30]. To the best of our knowledge, no such GMP-produced generator is yet available on the European market, although some companies seem to be exploring the idea. In this respect, a clear expression of interest from the nuclear medicine community may help to speed up decisions in companies' headquarters and the necessary extensive preparatory work.

Apart from the need for an authorised ^{68}Ga generator of "medicinal quality", the use of ^{68}Ga-labelled agents as radiopharmaceuticals is dependent on many conditions, rules and laws. The simplest and most straightforward way to permit the use of such tracers in an authorised way would be for a manufacturer of medicinal products to obtain a marketing authorisation for one or more labelling kits for the preparation of ^{68}Ga-labelled radiopharmaceuticals and to make these kits available on the market. As is the case for the development of any new diagnostic or therapeutic drug, this work would take many years and cost millions of euros, requiring the elaboration of a complete dossier, including optimisation of manufacturing and analytical methods, establishment of pharmacological and radiation safety and extensive clinical studies to demonstrate the real clinical value and profit. In the most optimistic view, it would take at least 5 years for an approved ^{68}Ga radiopharmaceutical or labelling kit to become commercially available.

As an alternative, and in view of the several promising literature reports on the clinical benefit of ^{68}Ga-labelled peptides for specific and sensitive diagnosis of some pathologies (see above), one could argue that a medical doctor might rely on his or her therapeutic (and diagnostic) freedom of choice, one of the main elements of the medical profession, and thus might exercise personal responsibility to use any (radioactive) compound that he or she judges useful for the welfare of the patient. This argument is valid and in principle allows much earlier use of interesting new medicinal products, especially in the case of tracers of which only nanomolar amounts have to be administered once or a few times, thus entailing minimal risks of toxicity or side-effects. In this case, however, each ^{68}Ga-labelled preparation would have to be considered as a magistral or officinal preparation, subject to the restrictions and requirements of such preparations. A magistral preparation/product is defined as any medicinal product, prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula). An officinal preparation/product is any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula) [31]. In view of the absence of pharmacopoeial monographs on ^{68}Ga-labelled compounds to date, the only possibility of using such tracers at present seems to be in the form of a magistral preparation under the responsibility of the prescribing physician.

In view of the above-described legal definitions, ^{68}Ga-labelled tracers used as magistral (or, in the future, officinal) preparations necessarily have to be made by or under the responsibility of a (radio)pharmacist and only may be used for the patient(s) served by the pharmacy in question. In addition, only starting materials produced under GMP conditions by approved manufacturers of pharmaceutical ingredients may be used [30]. This requires that the ligands for complexation of ^{68}Ga, such as DOTATOC, DOTANOC, DOTATATE and other gallium binding agents, must have a certificate of GMP production. Moreover, they must be certified to meet the (purity) requirements described in a pharmacopoeial monograph, or in the absence of such a monograph, a monograph of the manufacturer approved by pharmaceutical authorities. Finally, the pharmacist in charge of such a preparation has full responsibility for the quality of the final radiopharmaceutical and thus should be able to rely on well-defined specifications as described in a pharmacopoeial or otherwise approved monograph.

As already stated, there are not yet monographs in the European Pharmacopoeia (Ph. Eur.) on the eluate of ^{68}Ga generators, on ligands for complexation of ^{68}Ga or on final ^{68}Ga-labelled radiopharmaceuticals. This means that every manufacturer of ^{68}Ga generators or ^{68}Ga-binding ligands which are intended to be used in the preparation of a radiopharmaceutical and every (radio)pharmacist responsible for a final ^{68}Ga-labelled radiopharmaceutical has to develop and receive approval for his own monograph(s). Apart from the low efficiency of such dispersed efforts, there is the potential problem of non-uniform requirements for these products throughout Europe.

In view of this situation, the initiative has already been taken to ask the European Pharmacopoeia Commission to allow Ph. Eur. expert group 14 (group on radioactive

compounds) to start the development of Ph. Eur monographs on ^{68}Ga solutions for labelling (the eluate of a ^{68}Ga generator), on DOTATOC as a first ^{68}Ga-binding peptide and on ^{68}Ga-DOTATOC as a first ^{68}Ga radiopharmaceutical. The existence of such monographs would significantly facilitate the use of ^{68}Ga radiopharmaceuticals as a magistral or officinal preparation and also, over a longer time scale, the approval and granting of marketing authorisations for the starting materials and ^{68}Ga radiopharmaceuticals. The development of these monographs could take quite some time, depending on the consensus on and complexity of the required analytical methods for establishment of chemical, radiochemical, radionuclidic and microbiological purity. However, input from radiopharmacists and radiochemists already familiar with such preparations for clinical studies and willingness to share information on analytical procedures and safety determinations might significantly contribute to the efficiency of the process and speed it up.

New specific radiopharmaceuticals are cornerstones for the survival and strength of nuclear medicine, but their development and the possibility of their early use are compromised by a number of factors such as the complexity of pharmaceutical legislation and regulations, the lengthy process of obtaining a marketing authorisation and in some cases a limited return on investment. In the case of diagnostic radiopharmaceuticals, the principle of magistral or officinal preparations may be a solution that allows physicians and their patients more flexible and early access to valuable new tracers, evidently only on the condition of sufficient guarantees for the safety of the patient and the efficacy of the clinical investigations. This requires a common strategy, disciplined adherence to basic pharmaceutical rules and a joint effort by all professionals in the field, radiopharmacists, radiochemists and nuclear medicine physicians, to prove and guarantee the safety, efficacy and purity of such agents. Under such conditions, the further introduction of new ^{68}Ga-labelled and other radiopharmaceuticals is a realistic expectation and may constitute an important boost to our field.

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