How fast will the U.S. market get access to ^{68}Ga?

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The nuclear medicine world is slowly preparing for the introduction of gallium-68-labeled (^{68}Ga) tracers.

The first ^{68}Ga-labeled molecules (^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC) obtained their marketing authorization in the course of 2016, but their use will become more obvious in connection with the associated therapeutic agent, ^{177}Lu-DOTATATE (marketing expected in 2017). A series of new ^{68}Ga tracers, in particular for imaging metastasized prostate cancer, will soon enter late-stage clinical trials. The manufacturing world needs to prepare for these new products. Nowadays, ^{68}Ga-labeled tracers rely only on ^{68}Ge/^{68}Ga generators and synthesis automates. Both the source of ^{68}Ga and the preparation process are already challenged by new technologies while the market will have to adapt to the growing needs.

The use of gallium-68 as an alternative to fluorine-18 (^{18}F) in the development of new tracers for positron emission tomography (PET) took off mainly in Europe over recent years. Although in absence of tracers with marketing authorization, the routine use of ^{68}Ga tracers was therefore mainly adapted to the European way to get access to radiopharmaceuticals. Most of the nuclear physicians are not aware that the industry providing radiopharmaceuticals is structured in a completely different way in the U.S. compared to Europe.

In Europe, and most countries other than the U.S., each hospital has developed an access to a dedicated preparation room which is equipped with a hot cell that is generally operated by technologists under the control of the hospital pharmacy. This department is preparing the final doses from cold kits and generators, while only long half-life tracers and fluorinated tracers are delivered from central places. Such an infrastructure can, without difficulty, adapt to ^{68}Ge/^{68}Ga generators.

However, when considering the current use of ^{68}Ga, especially using synthesis automates, this local hospital radiopharmacy structure remains expensive as it requires a proportionally high number of dedicated experts (radiochemist, radiopharmacist), local investment as well as local handling authorizations which are still only accessible for a limited number of the hospitals (<25% in Europe). The recent introduction of cold kits, allowing the production of ^{68}Ga tracers as easily as with technetium-99m (^{99m}Tc), will definitely reduce the time of preparation and the overall cost for ^{68}Ga tracers. However the presently high price of generators makes this local product interesting only if all doses of gallium can be used daily in patients.

In the U.S. and a few other countries, the vast majority of customers rely on industrial radiopharmacies. This structure is more pragmatic as it concentrates both investment and experts on central sites. In theory, those sites should also show better profitability. These sites run several large ^{99m}Tc generators from which they produce individual tracer doses sometimes even as pre-filled syringes directly shipped to hospitals and clinics. They buy large amounts of other radionuclides from which they prepare final products.

When ^{18}F-FDG started playing an important role, these same centers became equipped with cyclotrons as their geographic distribution fit well with the customer density. Additional centers were created to fill the distribution gaps. Four major players control the largest areas with their networks, which are now adapted to radionuclides with the half-life of fluorine-18 (108 minutes). These centers are located in the most populated areas and, if required, can ship doses at up to six hours distribution distance. Trying to adapt such a network to a radionuclide with a shorter half-life (^{68}Ga has a half-life of only 68 minutes) will unfortunately limit accessibility to distant sites.

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In other words, the existing U.S. radiopharmacy network is not fully adapted to

^{68}Ga due to its shorter half-life, while in Europe, the market is not yet ready for buying ready-to-use tracers when such tracers can be prepared on-site from a generator with the existing staff and infrastructure.

that could be produced and distributed per batch, the price of cyclotron-produced ^{68}Ga could even be competitive with generator-produced ^{68}Ga when the price of ^{68}Ge will have dropped.

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Additionally introducing a new ^{68}Ga tracer on any market will need to account for new parameters, including:

- Very soon there will be new sources of germanium-68 (^{68}Ge) available, the parent isotope for gallium-68. This will increase competition among manufacturers, and sooner or later, directly impact the price of generators. It will favor individual generator implementation, but providing that the final authorized product is based on cold kits, otherwise it will become too costly in terms of local marketing authorizations. Cost of goods (CoGs) calculations have shown that single doses of ^{68}Ga could reach levels that tend to be almost competitive with generator-produced ^{99m}Tc, reducing the price of the PET modality to the price of the Single Photon Computed Tomography (SPECT) modality.
- A new way to directly produce very large amounts of pure gallium-68 (more than 50 times the capacity of a generator) based on standard cyclotrons (the same cyclotrons as the ones used to produce fluorine-18) will become available. This will favor centralized production, but also have the double advantage of being independent of the decay of ^{68}Ge which reduces over time the generator capacity, and being clean of ^{68}Ge as a potential contaminant. Depending upon the number of single doses

From the final customer side there should be no major changes or investment to be required. Providers will have to guarantee a smooth supply of the new ^{68}Ga-labeled tracers and generators or bulk ^{68}Ga. Using gallium-68 as PET tracers instead of fluorine-18 labeled tracers will not need new equipment. Software will have to be adapted to this tracer and new indication, which is actually the case for any new tracer brought on the market. All PET imaging centers equipped for fluorine-18 will be able to use the new ^{68}Ga tracers. This means that the installed PET customer base will remain the same.

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There is some small growth to expect in Europe in some smaller, underequipped countries, but in all countries only if new PET tracers for indications other than oncology (neurology or cardiology) become available for larger applications. The largest growth is only expected in not-yet-saturated areas such as Asian countries, including China, and South American countries as well as Russia. Availability of ^{68}Ga on the basis of generators will favor development in those countries.

For countries with a well-developed cyclotron installed base, such as the U.S., it would make sense to use this equipment to partially supply customers with ^{68}Ga through this channel. Almost any cyclotron able to produce ^{18}F could, in theory, be able to produce ^{68}Ga, providing some small investment. Like for cameras, the U.S. market has a large and underutilized installed base of cyclotrons: some 240 cyclotrons with energy below 25 MeV (mega-electron volts), able to be used for producing gallium-68, are in operation in the U.S. The density vs. cameras is even higher in the European Union with 210 installed cyclotrons. Only daily capacity production will define profitability while new local regulation hurdles may slow down the implementation.

So far, no radiopharmacy company has taken a decision to invest in one or the other technology, but such decisions need to be made soon. Both in Europe and the U.S., the structures will have to adapt. Eventually, the owners of the new proprietary ^{68}Ga tracers will force their own way of access to market on the basis of the most cost-effective solution. The first cost of goods evaluations have shown that centralized cyclotron production could fit with both markets, but a time frame of about two years will be needed for full implementation. Let us see how this market will develop, but in any case, ^{68}Ga tracers will become available very soon.

About the authors: Paul-Emmanuel Goethals and Dr. Richard Zimmermann are co-founders of MEDraysintell, providing first-rate strategic intelligence in nuclear medicine, proton therapy and brachytherapy. MEDraysintell offers the most comprehensive set of reports and directories, with over 1,900 pages of unrivaled intelligence covering some of the most exciting health care technologies using radiation for diagnosis and treatment.

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