GMP Production of Gallium-68 from a Cyclotron
Using Liquid Targets: Regulatory Aspects

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Objectives

Considering the ever-expanding use of gallium-68 (68Ga) based radiopharmaceuticals in clinical applications worldwide, there is a growing interest in producing this nuclide in ways other than the traditional germanium-68/gallium-68 generator. Despite their widespread use and ease of operation, generators are limited in terms of their shelf-life, amount of [68Ga]GaCl₃ per elution and time between elutions. Moreover the [68Ga]GaCl₃ from the generator presents a serious risk of contamination of the final preparation with the long-lived parent nuclide, 68Ge (half-life 271 days). Considering these limitations we recently proposed a fully automated process for the production of 68Ga-radiopharmaceuticals based on the cyclotron irradiation of a zinc-68(67Zn) target solution via (p,n) reaction followed by subsequent purification and labeling [1].

Materials/Methods

The process is fully based on commercially available modules and, because it uses liquid targets and a standard mid-energy cyclotron, it can easily be integrated into the routine of a typical PET production facility. Nevertheless, in order for the process to be fully GMP-compliant, some regulatory aspects need to be addressed.

Results

The existing 68Ga Eur. monograph is based on the commercially available Ge-68/Ga-68 generator. The limit for radionuclides impurities is properly very low specifically for 68Ge impurity with a limit of 0.001%. There is no 68Ga in Ga-68 produced by cyclotron but other impurities arise from the process mostly Ga-67 and Ga-66 mainly because of isotopic impurities in the target and the competing (p,n) reaction on 67Zn. 67Ga citrate has been approved as a human drug years ago and its monograph specifies a limit of 0.2% for 67Ga. Considering that both are isotopic impurities and share the same biodistribution as 68Ga, the limits of <0.2% for 67Ga and <2% for 68Ga for the cyclotron produced Ga-68 solution are considered adequate and can be met over its full shelf-life.

The purified 68Ga obtained was also used to label DOTA-peptides, HBBE-peptides and other for human use, using a commercial synthesis module and disposable cassettes. As an example, 68Ga-DOTANOC was obtained with 66.6±4.7 % DC in a 20 min process time, with very high radiochemical purity as shown by HPLC (Figure 3). The final product fulfills the specifications of the European Pharmacopoeia (68Ga) Edetate Disodium Injection (Eur. Ph. monograph 01/2013 2485) where applicable as shown on Table 1. The final pH of the product is approximately 5, GC analysis showed no residual solvents apart from ethanol (<10% of final concentration) and sterility (by an independent laboratory) and apyrogenicity (gel-clot) tests were all negative.

Conclusion

In summary, irradiation of liquid targets on a mid-energy cyclotron can readily produce a 68Ga-solution that can be validated as a GMP process but monographs of the Pharmacopoeia should be adapted to include the specificities of the cyclotron process.


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