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

Objectives:

Considering the ever expanding use of gallium-68 (^{68}Ga) based radiopharmaceuticals in clinical applications worldwide, there is a growing interest in producing this nuclide with 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 [^{68}Ga]$GaCl_3$ per elution and time between elutions. Moreover the [^{68}Ga]$GaCl_3$ from the generator presents a serious risk of contamination of the final preparation with the long-lived parent nuclide: ^{68}Ge (half-life 271 days).Considering these limitations we recently proposed a fully automated process for the production of ^{68}Ga-radiopharmaceuticals based on the cyclotron irradiation of a zinc-68(^{68}Zn) target solution via (p,n) reaction followed by subsequent purification and labeling [1].

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 current [^{68}Ga]$GaCl_3$ European monograph were written based only on the commercially available ^{68}Ge/^{68}Ga generator. The limit for radionuclidic impurities is appropriately very low with a specific mention of the ^{68}Ge impurity with a limit of 0.001%. There is no ^{68}Ge in the [^{68}Ga]$GaCl_3$ produced by the cyclotron method but other radionuclidic impurities arise from the process most notably gallium-67 (^{67}Ga-half-life 78h) and gallium-66 (^{67}Ga half-life: 9.5h) mainly because of isotopic impurities in the zinc target and the competing (p,2n) reaction on ^{68}Zn. The ^{67}Ga-citrate has been approved as medicinal drug for human many years ago and its monograph specifies a limit of 0.2% for ^{66}Ga. Considering that both are isotopic impurities and, therefore, share the same biodistribution as ^{68}Ga the limits of <0.2% for ^{66}Ga and <1% for ^{67}Ga for the cyclotron produced ^{68}Ga-solution may be considered appropriate and can be met over its entire shelf- life.

Conclusions

In summary, irradiation of liquid targets on a mid-energy cyclotron can readily produce a ^{68}Ga-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.

[1] Patent application: EP15170854