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]$\text{GaCl}_3$ per elution and time between elutions. Moreover the $[^{68}$Ga]$\text{GaCl}_3$ 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]$\text{GaCl}_3$ European monograph were written based only on the commercially available $^{66}$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]$\text{GaCl}_3$ 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 ($^{66}$Ga half-life: 9.5h) mainly because of isotopic impurities in the zinc target and the competing (p,2n) reaction on $^{66}$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 $^{66}$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.