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

**F. Alves**, V. H. Alves, A. Neves, S. J. do Carmo and A. J. Abrunhosa

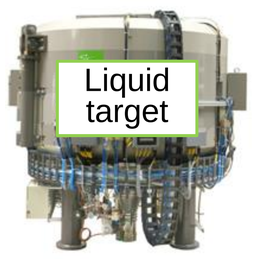
*ICNAS, University of Coimbra, Portugal*

## 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 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 [$^{68}$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].

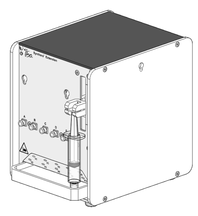
## Materials/Methods

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.




***IBA Cyclone®,18 MeV, 40 µA***
***$^{68}$Zn(p,n)$^{68}$Ga***
***EOB: End of Beam***

Purification



***[$^{68}$Ga]$^{68}GaCl_3$ (Gallium-Chloride)***

***EOP: End of Purification***

Labelling

***[$^{68}$Ga]-peptide***
***Peptides: DOTA-NOC, PSMA, etc.***
***EOS: End of Synthesis***

## Results

The existing $^{68}$Ga Eur. monograph is based on the commercially available Ge-68/Ga-68 generator. The limit for radionuclidic impurities is properly very low specifically for $^{68}$Ge impurity with a limit of 0.001%. There is no $^{68}$Ge 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,2n) reaction on $^{68}$Zn. $^{67}$Ga citrate has been approved as a human drug years ago and its monograph specifies a limit of 0.2% for $^{66}$Ga. Considering that both are isotopic impurities and share the same biodistribution as $^{68}$Ga, the limits of <0.2% for $^{67}$Ga and <2% for $^{67}$Ga for the cyclotron produced Ga-68 solution are considered adequate and can be met over its full shelf-life.

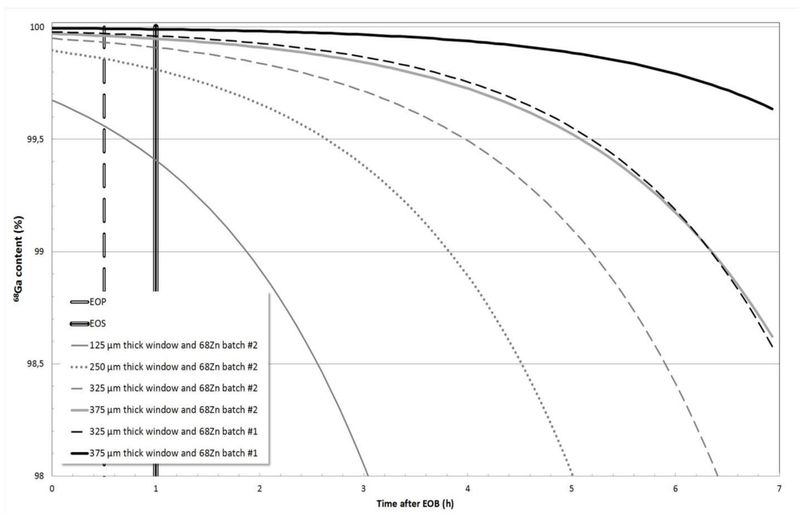



***Fig.1:Theoretical predictions of the purity of the $^{68}$Ga produced, as a function of time after EOB, for several target front windows of distinct thicknesses and two different batches of enriched $^{68}$Zn.***

| | | $^{68}$Ga | | $^{67}$Ga | | $^{66}$Ga | |
|---|---|---|---|---|---|---|---|
| | | Theo. | Exp. | Theo. | Exp. | Theo. | Exp. |
| **250 µm thick Niobium Window** | T0 (EOP) | 99,89 | 99,87 | 0,11 | 0,13 | 0,002 | 0,004 |
| | T1 | 99.79 | 99,76 | 0,20 | 0,23 | 0,003 | 0,008 |
| | T2 | 99,62 | 99,56 | 0,37 | 0,43 | 0,005 | 0,010 |
| | **T3** | 99,31 | **99,20** | 0,68 | 0,78 | 0,008 | 0,020 |
| | T4 | 98,74 | 98,54 | 1,25 | 1,42 | 0,014 | 0,040 |
| | T5 | 97,72 | 97,35 | 2,26 | 2,58 | 0,023 | 0,060 |
| **325 µm thick Niobium Window** | T0 (EOP) | 99,97 | 99,95 | 0,030 | 0,041 | 0,001 | 0,004 |
| | T1 | 99,94 | 99,92 | 0,055 | 0,075 | 0,002 | 0,008 |
| | T2 | 99,90 | 99,82 | 0,10 | 0,14 | 0,004 | 0,010 |
| | T3 | 99,81 | 99,68 | 0,18 | 0,25 | 0,006 | 0,022 |
| | **T4** | 99,65 | **99,42** | 0,34 | 0,46 | 0,010 | 0,040 |
| | T5 | 99,37 | 98,94 | 0,62 | 0,84 | 0,018 | 0,065 |

***Fig 2:Theoretical predictions and experimental measurements of the purity of the $^{68}$Ga produced with time from End-Of-Purification (EOP), for target foil thicknesses of 250 µm and 325 µm***

The purified $^{68}$Ga obtained was also used to label DOTA-peptides, HBEB-peptides and other for human use, using a commercial synthesis module and disposable cassettes. As an example, $^{68}$Ga-DOTANOC was obtained with 66.64±7.58 % DC in a 20 min process time, with very high radiochemical purity as shown by HPLC (Figure 3). The final product fulfils the specifications of the European Pharmacopeia (($^{68}$Ga) Edotreotide Injection (Eur. Ph. monograph 01/2013 2482) ) 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.

| Specification | Method | Acceptance criteria | Result |
|---|---|---|---|
| **pH** | Potentiometric | 4.0 to 8.0 | 4.80 ± 0.08 |
| **Radionuclidic purity** | Half-life determination | 62 to 74 minutes | 68.20 ± 0.28 |
| **Radiochemical purity** | HPLC & TLC | ≥ 91% | 98.77 ± 1.41 |
| **Residual HEPES** | TLC | ≤ 0.2mg/10mL | < 0.2 |
| **Zinc** | ABS UV/VIS | ≤ 5ppm | ≤ 5 |
| **Residual acetone** | GC-FID | ≤ 50mg/10mL | 0.77 ± 0.56 |

***Table I. Analytical HPLC of a final solution of 68Ga-DOTA-NOC (Rt: 2.5 min).***

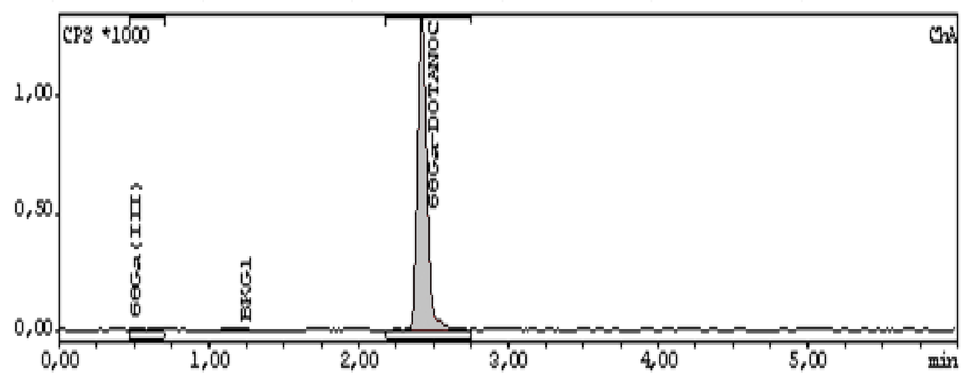



***Fig3. Analytical HPLC of a final solution of 68Ga-DOTA-NOC (Rt: 2.5 min).***

## Conclusion

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