

# Maturation of a Key Resource – The Germanium-68/Gallium-68 Generator: Development and New Insights

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**Abstract:**  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generators have been investigated for almost fifty years, since the cyclotron-independent availability of positron emitting  $^{68}\text{Ga}$  via the  $^{68}\text{Ge}/^{68}\text{Ga}$  system had always attracted researches working in basic nuclear chemistry as well as radiopharmaceutical chemistry. However, it took decades and generations of research (and researchers) to finally reach a level of  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generator designs adequate to the modern requirements of radiometal labelling chemistry. Nevertheless, most of the existing commercial generator systems address aspects of  $^{68}\text{Ge}$  breakthrough and safe synthesis of  $^{68}\text{Ga}$  radiopharmaceuticals by adopting eluate post-processing technologies. Among the strategies to purify  $^{68}\text{Ga}$  eluates, the cation exchange based version is relevant in terms of purification efficiency. In addition, it offers more options towards further developments of  $^{68}\text{Ga}$  radiopharmaceuticals. Today, one may expect that the  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generator systems could contribute to the clinical impact of nuclear medicine diagnoses for PET similar to the established  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator system for SPECT. The exciting perspective for the  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generator system, in turn, asks for systematic chemical, radiochemical, technological and radiopharmaceutical efforts, to guarantee reliable, highly-efficient and medically approved  $^{68}\text{Ge}/^{68}\text{Ga}$  generator systems.

**Keywords:** Germanium-68, Gallium-68, Radionuclide generator, Post-processing, Positron emission, PET.

## INTRODUCTION

In 1960, a first  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generator was described by Gleason [1]. Although the radionuclide generator design was by far not adequate to our today's level of chemical, radiopharmaceutical and medical expectations, it perfectly met the needs of molecular imaging of this period.  $^{68}\text{Ga}$ -labeled tracers entered the field of functional diagnosis, in particular for brain imaging. In turn, increasing application of  $^{68}\text{Ga}$  tracers in nuclear medicine, but also the pioneering developments of the technology of PET itself, challenged radiochemistry relevant to  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generator concepts. Consequently, new approaches were described for improved  $^{68}\text{Ge}/^{68}\text{Ga}$  generators soon after 1960 [2, 3].

However, the impact of  $^{68}\text{Ga}$  imaging faded away in the late 1970s, due to mainly two reasons: the generator design itself appeared inadequate to the requirements of versatile syntheses of  $^{68}\text{Ga}$  radiopharmaceuticals, and the ones available through the existing technology had minor clinical relevance, in particular in view of the parallel and rapid developments of the new classes of  $^{99\text{m}}\text{Tc}$ - and  $^{18}\text{F}$ -labelled diagnostics. Nevertheless, numerous papers in the 1970's and 1980's described the use of inorganic matrices as well as organic resins, selectively adsorbing  $^{68}\text{Ge}$  and providing  $^{68}\text{Ga}$  desorptions within hydrochloric acid solutions of weak (0.1 – 1.0 N) or strong (> 1 N) concentrations, respectively.

A new type of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators became commercially available in the first years of the 21<sup>st</sup> century [4]. Gen-

erator eluates based on hydrochloric acid provided “cationic”  $^{68}\text{Ga}$  instead of “inert”  $^{68}\text{Ga}$ -complexes, opening new pathways of  $\text{Me}^{\text{III}}$ -based radiopharmaceutical chemistry. Again coincidentally, the  $^{68}\text{Ga}$  cation was introduced immediately into existing designs of MRI and SPECT imaging probes, namely DTPA- or DOTA-based derivatives. The impressive success of utilizing  $^{68}\text{Ga}$ -DOTA-octreotides and PET/CT instead of e.g.  $^{111}\text{In}$ -DTPA-octreoscan and SPECT paved the way towards clinical acceptance of this particular tracers for imaging neuroendocrine tumors, but also to the realization of the great potential of the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator for modern nuclear medicine in general.

The last decade has seen a  $^{68}\text{Ga}$  rush, cf. e.g. Roesch and Riss, 2010 [5]. Increasing applications of generator-based  $^{68}\text{Ga}$  radiopharmaceuticals (for diagnosis only and increasingly for treatment planning thanks to the inherent option as expressed by THERANOSTICS) [6] ask for further developments – towards the optimization of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators both from chemical and regulatory points of view. Dedicated chelators may be required to broaden the feasibility of  $^{68}\text{Ga}$  labelling of more sensitive targeting vectors and generator chemistry may be adopted to those chelators – or vice versa.

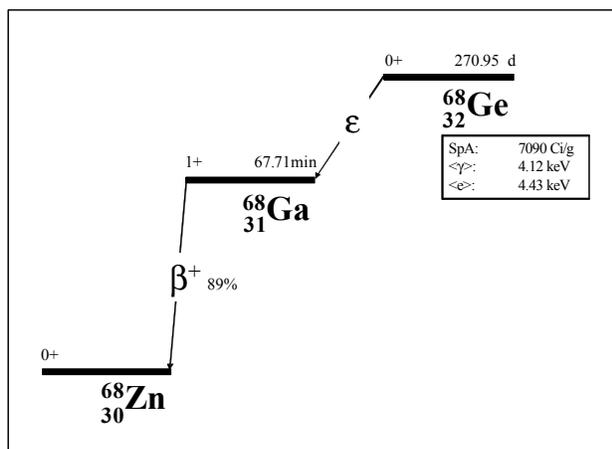
This review describes the development and the current status of the  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generator, as well as post-processing technologies available to direct the generators towards medical application.

## NUCLEAR CHARACTERISTICS

### $^{68}\text{Ge}$ Production

There are several nuclear reaction processes relevant for  $^{68}\text{Ge}$  productions. For a recent review cf. IAEA publication

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**Fig. (1).** Principal Decay Scheme of  $^{68}\text{Ge}$ . SpA = theoretical maximum specific activity;  $\langle\gamma\rangle$  = average electromagnetic radiation energy per disintegration;  $\langle e\rangle$  = average atomic electrons energy per disintegration [7,8,9].

series on parameters of radionuclide generator parent nuclides [11]. The commercially realized process today is the  $^{69}\text{Ga}(p, 2n)$  reaction on  $^{\text{nat}}\text{Ga}$  at about 23 MeV proton energy. Other options are the  $^{\text{nat}}\text{Ga}(p, xn)$  processes represented by  $^{69}\text{Ga}(p, 2n) + ^{71}\text{Ga}(p, 4n)$  reactions at higher proton energies, and  $^{66}\text{Zn}(\alpha, 2n)$ .

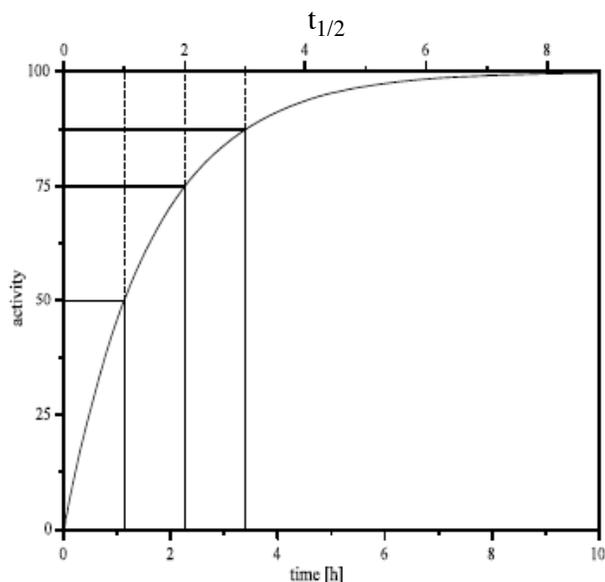
#### $^{68}\text{Ge}/^{68}\text{Ga}$ Parent / Daughter Pair

The parent radionuclide  $^{68}\text{Ge}$  decays via electron capture to  $^{68}\text{Ga}$ . The  $^{68}\text{Ge}$  half-life is 270.95 days.  $^{68}\text{Ge}$  itself does not emit significant photon radiation, Fig. (1).  $^{68}\text{Ga}$  is a positron emitter with 89% positron branching accompanied by low-abundant photon emission (1077 keV, 3.22%) [7, 8, 9]. It subsequently decays into stable  $^{68}\text{Zn}$  with a half-life of  $t_{1/2} = 67.71$  min.

#### $^{68}\text{Ge}/^{68}\text{Ga}$ Generator

Radionuclide generations are distinguished according to the half-lives of parent and daughter radionuclides [10]. Either the parent (1) is longer-lived, but not more than by a factor of about 100, i.e.  $t_{1/2,1} < 100 t_{1/2,2}$ , or the parent is much longer-lived than the daughter (2) ( $t_{1/2,1} \gg t_{1/2,2}$  i.e.  $\lambda_1 \ll \lambda_2$ ). The limiting case of radioactive equilibrium at  $\lambda_1 \ll \lambda_2$  is called *secular equilibrium*, i.e. the parent activity does not decrease measurably during many daughter half-lives. In the case of  $t_{1/2,1} \gg t_{1/2,2}$  the maximum activity of the daughter occurs at the time,  $t$ , which is calculated by  $t = \frac{1}{\lambda_2 - \lambda_1} \ln \frac{\lambda_2}{\lambda_1}$ . For the

$^{68}\text{Ge}/^{68}\text{Ga}$  system it gives  $t = 14.1$  h, representing the theoretical maximum of generated activity. However, practical separations are being performed much earlier. Following the growths of  $^{68}\text{Ga}$  activity on the generator column, 50% of the theoretical maximum is generated within one half-life. A period of three half-lives, which is about 3.4 hours, provides already 88% of the maximum value. Consequently, the generator may be eluted, for example, each 3.5 hours to give almost the complete (90%)  $^{68}\text{Ga}$  radioactivity. This perfectly allows 3 individual elutions per day. Interestingly, this period exactly reflects the handling regime of a batch of a  $^{68}\text{Ga}$ -



**Fig. (2).** Generation Kinetics of  $^{68}\text{Ga}$  on the Generator Column Following an Initial Elution. Upper x-axis: Number of Half-lives of  $^{68}\text{Ga}$ .

radiopharmaceutical for 2 to 4 patients per batch – at least for the imaging of e.g. neuroendocrine tumors using  $^{68}\text{Ga}$ -DOTA-conjugated octreotide derivatives. For this indication, clinically relevant images are obtained already within one hour post injection.

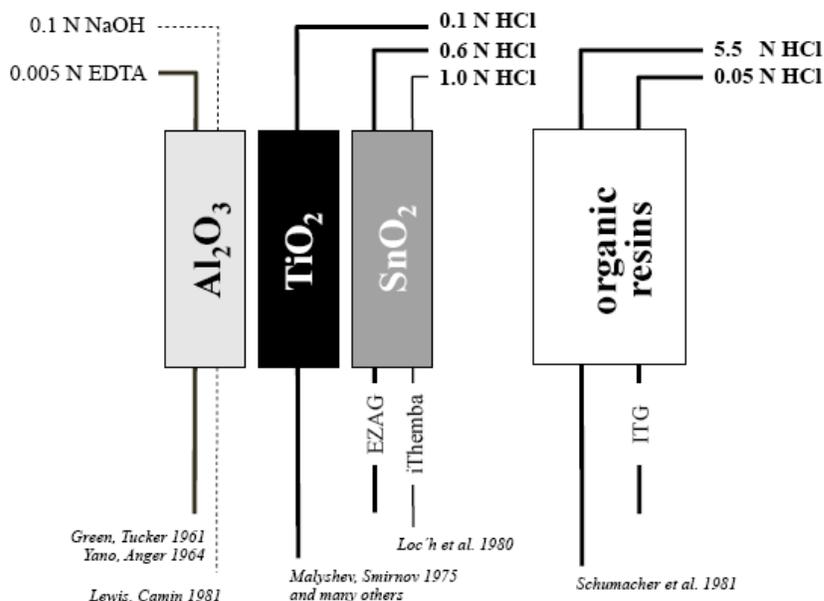
## GENERATOR CONCEPTS

Historically, all the first  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generators described were named “cows” whereof  $^{68}\text{Ga}$  was milked. The first paper by Gleason 1960 utilized liquid-liquid extraction chemistry [1]. The radiochemical concept was changed to solid phase-based ion exchange soon after (Greene and Tucker 1961 [2], Yano and Anger 1964 [3]). The titles of the three papers are in fact reflecting the priorities of the development: from chemistry towards medicine: “A positron cow”, “An improved gallium-68 cow”, and “A gallium-68 positron cow for medical use”. Liquid-liquid extraction later on was not considered anymore. Solid phase-based ion chromatography became the principal chemical direction. This chemistry is a versatile one and consequently the developments covered both organic and inorganic resins.

#### Liquid-liquid Extractions: The First Positron “Cow”

The first  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generator [1] utilized liquid-liquid extraction, and the whole processing was by far not revealing the real features of today's radionuclide generator systems.

Drawbacks of this generator chemistry have been the need of a second separation step, namely the transfer of  $^{68}\text{Ga}$  as acetylacetonate complex species into hydrochloric acid, a subsequent neutralization of  $^{68}\text{Ga}$  by NaOH and the addition of  $\text{Ga}^{\text{III}}$  carrier (thereby countering the concept of nca  $^{68}\text{Ga}$ ). Although an improved liquid-liquid extraction version was described in 1978 [12], the use of 8-hydroxy-quinoline / chloroform systems in liquid-liquid extractions did not qualify for a robust route to obtain  $^{68}\text{Ga}$ .



**Fig. (3).**  $^{68}\text{Ge}/^{68}\text{Ga}$  Radionuclide Generator Concepts Developed in the 1970ies and 1980ies and Commercial Types Available Today.

### Solid Phase Based Generator Designs Using Inorganic Resins

$\text{Al}_2\text{O}_3$ -based and EDTA-eluted generators: Because of the inherent disadvantages of the first liquid-liquid extraction-based generator, soon after, two improved generator concepts have been described utilizing solid phase-based ion chromatography [3]. These solid-phase chromatographic generators offered excellent radiochemical characteristics. Yano and Anger, 1964, [3] used an alumina column and EDTA (*edetate*) as eluent (10 mL 0.005 M EDTA). Compared to the liquid-liquid extraction this solid-based chromatography just needed the elution of the generator daughter - no further separation steps were required.  $^{68}\text{Ga}$  was repeatedly eluted in 95% yield without the need to introduce stable  $\text{Ga}^{\text{III}}$  as carrier. The eluate contained as less as  $1.4 \cdot 10^{-5}$  % of the parent  $^{68}\text{Ge}$ . Prior injections, 0.5 mL of 18% NaCl solution were added to the eluate.

This radionuclide generator basically was a synthesis unit of a relevant radiopharmaceutical,  $^{68}\text{Ga}$ -EDTA (named *veronate* these years). On one hand, this presented a very convenient approach towards nuclear medicine imaging of malfunctions of the human brain; on the other hand and despite of these new features of the generator and the great success of  $^{68}\text{Ga}$ -EDTA molecular imaging, in practice it was limited to the synthesis and use of  $^{68}\text{Ga}$ -EDTA exclusively. The transfer of  $^{68}\text{Ga}$  out of the thermodynamically very stable eluate species  $^{68}\text{Ga}$ -EDTA ( $\log K = 21.7$ , [13]) was not straightforward. Yano and Anger 1964 reported, that: “*attempts are being made ... to freed  $^{68}\text{Ga}$  ... from the EDTA complex*”. That procedure, however, was complex and by far not user friendly. The time required was given with 30 min, 10 mg Ga carrier should be added and the transfer yield was 60%.

$\text{Me}^{\text{IV}}\text{O}_2$ -based and mineral acid eluted generators: In order to be more flexible in terms of versatile synthesis of potential  $^{68}\text{Ga}$ -radiopharmaceuticals, improved generator concepts became mandatory. The generator eluate should be available either as rather weak complex species (e. g. citrate)

or as cation within a mineralic acid like HCl or  $\text{HNO}_3$ . (An approach to stay within the  $\text{Al}_2\text{O}_3$  solid phase, but to elute  $^{68}\text{Ga}$  with NaOH [14] appeared not useful.)

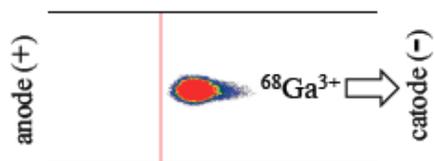
A number of papers in the 1970ies and 1980ies described the use of inorganic matrices, selectively adsorbing  $^{68}\text{Ge}$  and providing  $^{68}\text{Ga}$  desorptions within hydrochloric acid solutions of weak (0.1 – 1.0 N) or strong (> 1 N) concentrations, respectively. For this purpose,  $\text{Me}^{\text{IV}}\text{O}_2$ -type matrices (Me = Sn, Ti, Zr, Ce etc.) appeared to be adequate, effectively adsorbing  $^{68}\text{Ge}^{\text{IV}}$  [15-19], but also iron oxide [20], cf. Fig. (3). The concept to adsorb  $^{68}\text{Ge}^{\text{IV}}$  on / within  $\text{Me}^{\text{IV}}$  matrices was adopted around 2000 by Obninsk Cyclotron Ltd., Obninsk, Russian Federation, providing the first class of solid phase-based  $^{68}\text{Ge}/^{68}\text{Ga}$  generators eluted with diluted (0.1 N) HCl [4]. This system indicates the use of a “modified  $\text{TiO}_2$ ” matrix. Similar versions appeared later. Another commercial system (iThemba LABS, Somerset West, South Africa) today is utilizing a  $\text{SnO}_2$  matrix, needing however higher concentrations (0.6 – 1.0 N) of HCl [21, 22].

More recent scientific developments describe  $\text{Zr}^{\text{IV}}$  and  $\text{Ce}^{\text{IV}}$ -systems, classified as nano-composites [23, 24].

### Solid Phase Based Systems: Organic Resins

Simultaneously to the investigation of  $\text{Me}^{\text{IV}}$ -based resins, organic resins have been investigated between 1978 and 1981, e.g. [25 - 27] and further developed more recently [28].

$\text{Ge}^{\text{IV}}$  is known to form very stable complexes with phenolic groups [29]. Its adsorption on a 1,2,3-trihydroxybenzene (pyrogallol)-formaldehyde resin was utilized to elute  $^{68}\text{GaCl}_4^-$  in strong (4.5 N) hydrochloric acid [27]. Average yields of  $^{68}\text{Ga}$  of 75% during a period of almost one half-life of  $^{68}\text{Ge}$  were reported. The  $^{68}\text{Ge}$  breakthrough was < 0.5 ppm with no detectable radiolytic by-products. The pyrogallol-formaldehyde resin was found to be resistant to disintegration by radiation. Another organic macroporous styrene-divinylbenzene co-polymer containing N-methyl-glucamine



**Fig. (4).** Electrophoresis of a 0.1 N HCl  $^{68}\text{Ga}$  Generator Eluate (EZAG Obninsk generator) Demonstrating the Presence of „Cationic“  $^{68}\text{Ga}$ . (Parameters: 0.1 HCl, Whatman Paper Strip,  $l = 19$  cm,  $t = 5$  min, 191 V, 210 mA, 40 W).

groups was developed to provide  $^{68}\text{Ga}$  with a solution of a low-affinity gallium chelating ligand such as citric or phosphoric acid. The  $^{68}\text{Ge}$  breakthrough was less than 0.0004% of the  $^{68}\text{Ge}$  adsorbed on the resin [27]. Recent approaches utilize silica-based resins to produce commercial generators (ITG Garching, Germany) eluted with diluted hydrochloric acid [30], cf. also Fig. (3).

### COMMERCIAL “IONIC” GENERATORS

Generator eluates based on hydrochloric acid provide “cationic”  $^{68}\text{Ga}$ . Electrophoretic analysis clearly proves the presence of the cationic species, cf. Fig. (4) for 0.1 N HCl eluates.

Commercial generators distributed today are solid phase-based and use hydrochloric acid to elute the generated  $^{68}\text{Ga}$  – no matter what the type of the solid phase is – i.e. inorganic or organic. Due to the cationic speciation of the  $^{68}\text{Ga}$  in the eluates, all these generators are well designed for subsequent  $^{68}\text{Ga}$  labeling chemistry. The systems differ in particular in the concentration of the HCl needed to run the generator effectively, then in terms of  $^{68}\text{Ga}$  elution yields dropping with increasing usage frequency or shelf-life and also in terms of  $^{68}\text{Ge}$  breakthrough. Table 1 summarizes basic parameters of the generator performances indicated by the producers. Parameters may, however, depend on the practise of usage.

**Table 1. Performances of Commercial  $^{68}\text{Ge}/^{68}\text{Ga}$  Radionuclide Generators. Values are taken from Official Product Bulletins in the case of EZAG and ITG. For iThemba Generators, Data are Taken from [22]. Note that in this Case the “>100%” Initial  $^{68}\text{Ga}$  Yield are Achieved by Selling Generators of Higher Nominal  $^{68}\text{Ge}$  Load**

Company	Type	Colum Material	HCl (N)	$^{68}\text{Ga}$ Elution Yield (%)	$^{68}\text{Ge}$ Breakthrough (%)
EZAG, Berlin, Germany	Obninsk <sup>a</sup>	TiO <sub>2</sub>	0.1	initial ≈75 long term 60 <sup>b</sup>	initial 0.005 long term 60 <sup>c</sup>
	IGG100	TiO <sub>2</sub>	0.1	initial >65 long term >65 <sup>b</sup>	initial 0.001 long term 60 <sup>c</sup>
iThemba LABS, Somerset West, South Africa		SnO <sub>2</sub>	0.6	initial >100 <sup>f</sup> long term 75 <sup>c</sup>	initial <0.01 <sup>f,g</sup> long term n/a <sup>i</sup>
ITG Garching, Germany, ITG iQS® Ga-68 Fluidic Labeling Module		silica based <sup>h</sup>	0.05	initial >80 long term >80 <sup>d</sup>	initial <0.005 <sup>f</sup> long term n/a

<sup>a</sup> Provided by Cyclotron Co. Ltd., Obninsk, Russia

<sup>b</sup> After 200 elutions / <sup>c</sup> after 300 days / <sup>d</sup> throughout shelf-life of 4-6 months / <sup>e</sup> after 300 days or 1 year

<sup>f</sup> Generators are delivered with a nominal activity of  $^{68}\text{Ga}$  eluted initially

<sup>g</sup> Expressed as ratio of radioactivities of  $^{68}\text{Ge}/^{68}\text{Ga}$  in the eluate

<sup>h</sup> Values true for daily elutions only [22]

<sup>i</sup> 3,4,5-trihydroxy-benzoate

<sup>j</sup> No information available

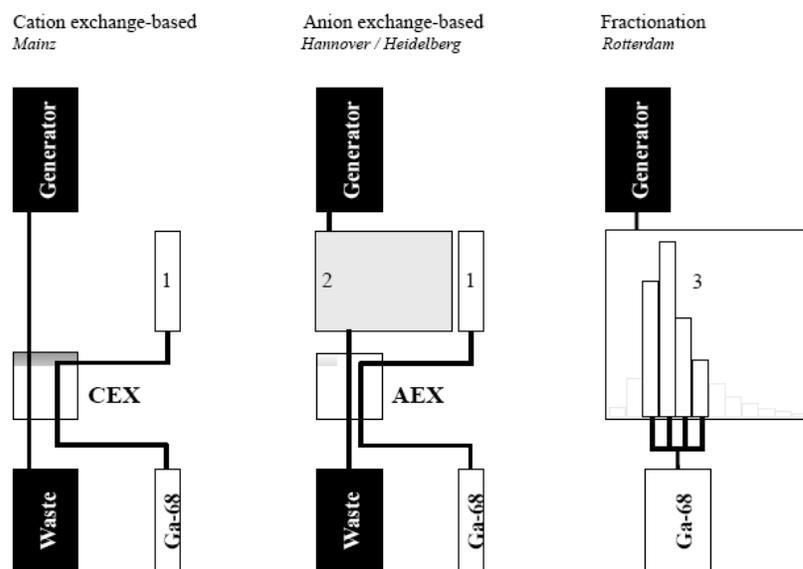
## POST-PROCESSING OF $^{68}\text{Ge}/^{68}\text{Ga}$ GENERATORS

### Different Strategies of Post-processing

For about one decade, the commercial “ionic” generators are entering clinical environments. Consequently, concerns on the adequate use, on radiation safety and legal requirements became more and more relevant. There are several facts which matter:

- While the long physical half-life of the generator parent should allow in principle usage of a generator for at least one year, the shelf-life of the generator does not necessarily parallel this long physical half-life. Decreasing qualities of the generator itself in terms of  $^{68}\text{Ga}$  elution yield, but mainly in terms of increasing breakthrough of  $^{68}\text{Ge}$  breakthrough indicate non-optimum performances.
- $^{68}\text{Ga}$  generator eluates are not perfectly pure chemically and radionuclidically. Non-radioactive metals such as  $^{68}\text{Zn}^{\text{II}}$ , generated on the generator by decay of  $^{68}\text{Ga}$ , cf. Fig. (1), and  $\text{Fe}^{\text{III}}$  as general chemical impurity, represent metals which can compete with  $^{68}\text{Ga}^{\text{III}}$  for coordinative labeling of radiopharmaceutical precursors.
- Commercial  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generators utilize hydrochloric acid solutions for  $^{68}\text{Ga}$  elution. The relatively high concentration of  $\text{H}^+$  do protonate functional groups of ligands needed for chelating  $^{68}\text{Ga}$  radiopharmaceuticals. Minimizing the  $\text{H}^+$  concentration and volume of eluted the  $^{68}\text{Ga}$  prior to labeling should facilitate syntheses yields.

In this context, several approaches have been developed to address one or more of these problems. For clinical application, generators are usually used in direct connection with one of the three post-eluate technologies mentioned. The methods are schematically illustrated in Fig. (5). Two proc-



**Fig. (5).** Overview on Post-processing Technologies for Commercial  $^{68}\text{Ge}/^{68}\text{Ga}$  Generators. [1 = solutions to Desorb  $^{68}\text{Ga}$  from AEX or CEX (Water or Acetone / HCl Mixtures, Respectively), 2 = Reservoir of HCl to obtain 5-6 N HCl Concentrations of  $^{68}\text{Ga}$  prior to AEX, 3 = simple Fractions of Eluate].

esses include chemical separation strategies and may be called “post-processing”, while a third technology uses simple fractionation of the eluate, i.e. isolating eluate fractions with highest  $^{68}\text{Ga}$  concentration. Another option, namely to process  $^{68}\text{Ga}$  eluates by solvent extraction via methyl ethyl ketone [37], was described as well but was not adopted to routine handling.

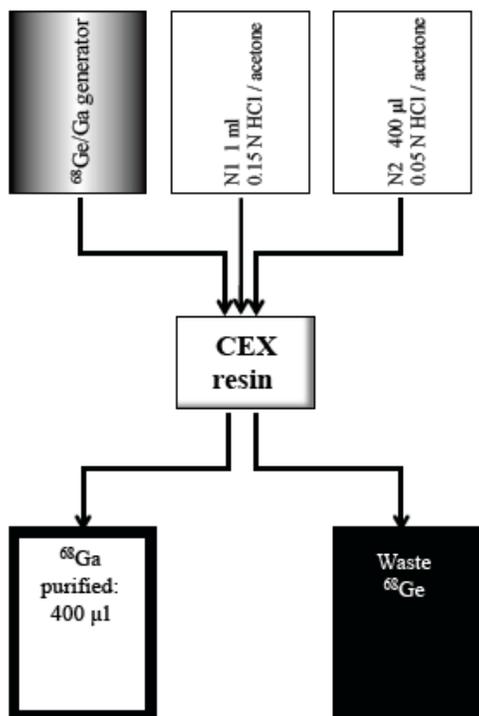
**Fractionation:** Fractionation basically uses the fraction of the generator eluate with the highest volume concentration  $A(^{68}\text{Ga})/\text{mL}$ . The fraction of the eluate containing e.g.  $\frac{2}{3}$  of the overall  $^{68}\text{Ga}$  activity (only) is collected usually online. The corresponding volume may vary for different generators, and is usually of about  $1.5 \pm 0.5$  ml. Subsequently, this fraction is transferred to a reactor with the labeling precursor in a buffered aqueous solvent. Obviously, there is no chemical strategy to remove disturbing metal impurities or  $^{68}\text{Ge}$  breakthrough. The idea is rather to minimize them according to the ratio of collected volume (e. g. 1.0 or 1.5 ml) to overall eluate volume (e. g. 10 ml) [36] on one hand and by preferred chelation of the precursor by  $^{68}\text{Ga}$  rather than  $^{68}\text{Ge}$  on the other hand.

**Anion exchange-based post processing:** Anion exchange-based post processing intends to trap  $^{68}\text{Ga}$  from the eluate on an anion exchange cartridge. This was introduced in the context of transferring 4.5 N HCl eluate as derived from organic resin-based generators [30] to more diluted solutions.  $\text{Ga}^{\text{III}}$  in 4-6 N HCl is adsorbed efficiently on strong anion exchange resins (AEX) such as e.g. AG 1, while some of the other metals are less bound.  $^{68}\text{Ga}$  is subsequently be desorbed by small volumes of water, saline or NaOH. This approach was adopted for the  $\text{TiO}_2$ -based  $^{68}\text{Ga}/^{68}\text{Ge}$  generators. Here, the 10 mL of 0.1 N HCl eluate is first added to a reservoir of relatively concentrated HCl to achieve an overall concentration of about 5 N. Next, this mixture is passed through the anion exchanger. The  $^{68}\text{Ga}$  is adsorbed almost quantitatively and subsequently washed off by small volumes of water [34]. It is supposed that the level of  $^{68}\text{Ge}$  in the processed

final fraction is reduced and the content of iron is minimized as well, which is questionable since it is well known that  $\text{Fe}^{\text{III}}$  desorbs under these elution conditions [38]. Also, anion exchange-based processing does not discriminate between  $\text{Ga}^{\text{III}}$  and  $\text{Zn}^{\text{II}}$ . Nevertheless, volume and  $\text{H}^+$  concentration are reduced significantly and subsequent labeling chemistry is achieved.

**Cation exchange-based post processing:** Online cation exchange adsorption of  $^{68}\text{Ga}$ , cf. Fig. (6), promises to address all mentioned problems before simultaneously. This is easily achieved by online passing the generator eluate (0.1 – 0.6 N HCl) through a small cation exchange resin (CEX). All the other cations are not adsorbed. This represents an on line purification effect [31 - 33]. In order to desorb  $^{68}\text{Ga}$  from the cation exchange resin, mixtures of mineralic acids with organic solvents work best. Initially, Bio-Rad AG 50W-X8 cation-exchanger < 400 mesh was identified to provide optimum parameters in terms of  $^{68}\text{Ga}$  adsorption and removal of metal impurities. Today, STRATA-X-C cartridges show similar performances.

The most efficient protocol uses mixtures of HCl with acetone, but HCl / ethanol mixtures qualify as well [33]. The CEX cartridge is typically washed by one mL of an HCl / acetone mixture (N1: 80% acetone / 0.15 N HCl). Subsequently,  $^{68}\text{Ga}$  is eluted in 400  $\mu\text{L}$  of a second mixture of acetone and 0.05 N HCl (N2: 98% acetone / 0.05 N HCl =  $2 \cdot 10^{-5}$  mol HCl) from the cation exchanger. The  $^{68}\text{Ga}$  recovery is as high as 98% within 3 minutes, including the usual period to eluate a generator. The additional removal of  $^{68}\text{Ge}$  reaches a decrease of four orders of magnitude, and the removal of metallic impurities including the inherent stable  $\text{Zn}^{\text{II}}$  is almost quantitative; removal of  $\text{Fe}^{\text{III}}$  is significant. Finally, the volume for subsequent labeling is just 400  $\mu\text{l}$  at low acid concentration – resulting in excellent yields of  $^{68}\text{Ga}$ -synthesis reactions. The chemical procedure is in part adopted by commercial modules combining generator elution, post-processing and radiopharmaceutical syntheses. The



**Fig. (6).** Successive Steps of Post-processing <sup>68</sup>Ge/<sup>68</sup>Ga Radionuclide Generator Eluates via Cation Exchangers [31]. <sup>68</sup>Ga is Trapped online by Passing the <sup>68</sup>Ge/<sup>68</sup>Ga Generator Effluent Through a 53 mg Cation Exchange (CEX) Resin AG 50W-X8, <400 mesh. Chemical Impurities such as Fe<sup>III</sup>, Zn<sup>II</sup>, Ti<sup>IV</sup>, but also a Significant Part of the <sup>68</sup>Ge Breakthrough are being Eluted from Cation Exchange Column into Waste Almost Completely.

resin is easily reconditioned by passing 1.0 mL of 4 N HCl and 1.0 mL water through the cartridge prior to a subsequent generator elution.

Table 2 reproduces the systematic data obtained from distributions of <sup>68</sup>Ga and relevant stable metallic impurities as well as <sup>68</sup>Ge [32]. The cation exchange resin may vary and products such as AG 50W-X8 (200 - 400 mesh) and AG 50W-X4 (200 - 400 mesh) provide similar parameters of <sup>68</sup>Ga yield if adopted carefully, cf. Table 3. Commercial

modules combining generator elution and cation exchange based post-processing utilize STRATA-X cartridges (phenomenex, Torrance, CA, USA).

The cation exchange-based post-processing minimizes volume and H<sup>+</sup> concentration online and reduces the amount of metallic impurities. This is relevant for the subsequent <sup>68</sup>Ga labeling chemistry. In particular, this procedure contains an important safety feature. It guarantees complete removal of any breakthrough of <sup>68</sup>Ge prior to radiopharmaceutical preparations. It thus guarantees safe use of the generator, which is upmost relevant for radiopharmaceuticals from the legal point of view.

**FURTHER FEATURES OF CATION EXCHANGE-BASED POST-PROCESSING**

The temporary trapping of highly purified <sup>68</sup>Ga on a small action exchange cartridge appears to be an ideal starting point for further options, cf. Fig. (7). The concept is, to

1. Stay with the on line cation exchange purification,
  2. Guarantee removal of most chemical impurities and <sup>68</sup>Ge breakthrough,
  3. Achieve high <sup>68</sup>Ga transfer from cation exchange resin and with the future options to:
    - (i) combine new and used <sup>68</sup>Ge/<sup>68</sup>Ga generators,
    - (ii) completely remove acetone by combining the cation-exchange step with a subsequent anion-exchange step,
    - (iii) transfer <sup>68</sup>Ga from aqueous into non-aqueous solvents,
    - (iv) instantaneously determine the level of <sup>68</sup>Ge breakthrough.
- i) Simultaneous use of several generators:

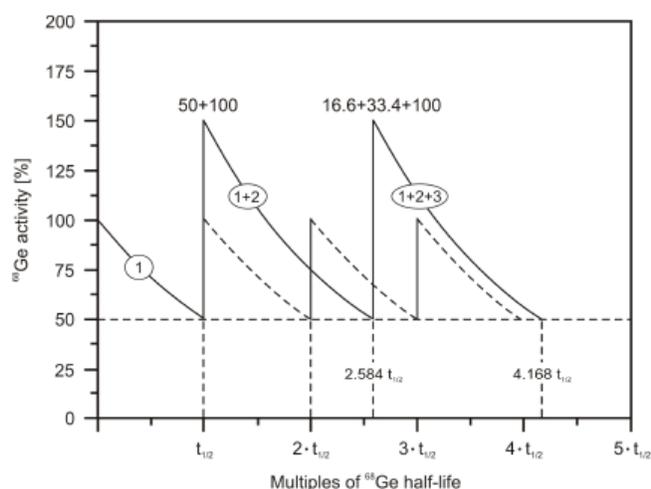
Due to the highly efficient purification and concentration performance of the post-processing protocol and due to the low hydrodynamic resistance of the generator system it is ready to connect several generators in a line [31]. In this setup the eluent is piped through the first generator which is connected to the eluent supply line of the next one. The second generator is directly connected to the micro-chromato-

**Table 2. Relative Distribution of <sup>68</sup>Ga<sup>III</sup>, <sup>68</sup>Ge<sup>IV</sup>, Zn<sup>II</sup>, Ti<sup>IV</sup>, Fe<sup>III</sup>, Mn<sup>II</sup> Within an Elution Sequence Using a Micro-Chromatographic Column (53 mg of Bio-Rad AG 50W-X8 resin <400 Mesh) in Hydrochloric Acid / Acetone Media [32]. While the Fractions of 0.1 N HCl, N1, 4 N HCl and Water all Reach the Waste Vial, the N2 Fraction Continues for <sup>68</sup>Ga Labeling**

Step	Eluent	Relative Distribution (%)						
		Vol. (mL)	Ga <sup>III</sup>	Ge <sup>IV</sup>	Zn <sup>II</sup>	Ti <sup>IV</sup>	Fe <sup>III</sup>	Mn <sup>II</sup>
Generator elution	0.10 N HCl	7.0	0.19	<b>98.14</b>	0.61	5.34	0.45	1.88
Purification	80% acetone/0.15 N HCl	5.0	0.58	1.83	<b>99.39</b>	2.68	<b>53.75</b>	0.32
<sup>68</sup> Ga <sup>III</sup> elution	98% acetone/0.05 N HCl	0.4	<b>98.50</b>	2·10 <sup>-2</sup>	5·10 <sup>-2</sup>	5·10 <sup>-2</sup>	43.54	10.87
Washing	4 N HCl	1.0	0.53	6·10 <sup>-3</sup>	<10 <sup>-3</sup>	<b>90.92</b>	2.01	<b>75.67</b>
Washing	H <sub>2</sub> O	1.0	0.20	5·10 <sup>-3</sup>	<10 <sup>-3</sup>	1.01	0.29	<b>11.26</b>

**Table 3. Comparison of  $^{68}\text{Ga}$  Distributions on the Fractions of the Elution Sequence for Various Cation Exchange Resins of Different Mesh and Amount. While the Fractions of 0.1 N HCl, N1, 4 N HCl and Water all Reach the Waste Vial, the N2 Fraction Continues for  $^{68}\text{Ga}$  Labeling. (N1 = 80% Acetone/0.15 N HCl, N2 = 98% Acetone/0.05 N HCl)**

Elution Sequence		Distribution of $^{68}\text{Ga}$ for Various Resins			
		AG 50W-X8	AG 50W-X8	AG 50W-X4	AG 50W-X4
	volume	<400 mesh	200-400 mesh		
	mL	53 mg	53 mg	53 mg	80 mg
0.1 N HCl	7.0	0.2	0.4	4.4	0.3
N1	1.0	1.4	0.5	3.6	3.7
N2	0.4	<b>97.8</b>	<b>60.6</b>	<b>90.9</b>	<b>94.8</b>
4 N HCl	1.0	0.4	20.6	0.9	1.0
Water	1.0	0.2	17.9	0.2	0.2



**Fig. (7).** Scheme of Extended  $^{68}\text{Ge}/^{68}\text{Ga}$  Radionuclide Generator Utilization by Successive Combination of a new Generator with one or two “old” Generators [31]:  $^{68}\text{Ge}$  – i.e. Maximum Elutable  $^{68}\text{Ga}$  activity as a Function of Elapsed Decay Time.

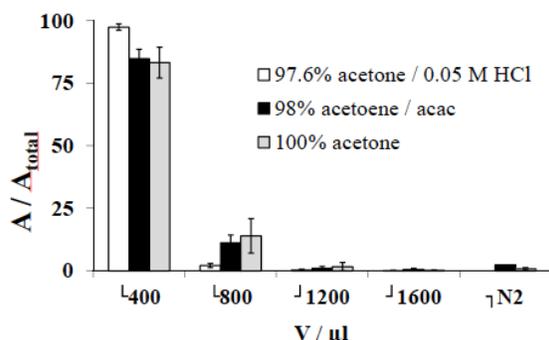
graphy CEX column. Alternatively, two generators can be eluted separately to one and the same cation exchange column, which subsequently is processed as described. This might be relevant in context of routine clinical use as it increases the efficacy of generator availability (Fig. 7).

The solid line (1) gives the decay of a first, initial generator, which drops from 100% to 50% within one half-life of  $^{68}\text{Ge}$ . These 50% are considered here to terminate the practical usage. If, after this first half-life of 270.95 days, a second “fresh” generator of the same initial activity is added to the first, used one, the total activity of  $^{68}\text{Ge}$  achieved is 150%. With this activity, another working period of  $1.584 \times t_{1/2}$  of  $^{68}\text{Ge}$  is created until the available activity again drops to 50% relative to a single fresh generator. Instead of 2 successive times of  $(1 + 1) t_{1/2}$  of  $^{68}\text{Ge}$  working periods, in this case  $2.584 \times t_{1/2}$  are achieved. This can be extended easily adding a third “fresh” generator to the two “old” ones. With this approach, a period of  $4.168 \times t_{1/2}$  is provided, instead of  $3.0 \times t_{1/2}$  thus saving more than one generator. Application of several generators in such a conjugation can thus be utilized to optimize the shelf-life of the generators and thereby reducing

costs. This methodology is now in routine use at several clinics.

**ii) Removal of acetone by combined cation and anion exchange-based post processing:** The radionuclide  $^{68}\text{Ga}$  is quantitatively desorbed from the resin with 0.4 mL of a 0.05 N HCl / 98% acetone solution (N2). Contents of the acetone in the reaction mixture are mostly uncritical. They are reduced easily down to non-detectable levels within labeling procedures at elevated temperature by evaporation. Acetone might be, however, avoided for direct *in vivo* applications or for radiolabeling reactions performed under high temperature or for chemical reactions asking for pure aqueous media exclusively. An improved column-based chemical strategy combines the CEX-advantages with anion exchange (AEX) processing. Direct pre-concentration of  $^{68}\text{Ga}$  from the original eluate and its purification is supposed to be performed on the cation exchanger according to the Mainz approach [31]. This  $^{68}\text{Ga}$  can be eluted with hydrochloric acid solutions of  $> 2$  N concentration and trapped again by a AEX column allowing for complete removal of acetone by a washing step. From the AEX,  $^{68}\text{Ga}$  is finally stripped off with a small volume of pure water. Instead of a typical anion exchanger, a novel extraction chromatographic resin based on tetraalkyl diglycolamides (DGA) appeared particularly useful [39]. With 98% efficiency for the cation exchange part, 92% and 98% yields were obtained for desorbing  $^{68}\text{Ga}$  from the classical anion exchange and TODGA column, respectively. The overall yield in the final 0.3–1.0 mL water fraction is  $87 \pm 5\%$  (for AG 400 1-X8) and 96% (for TODGA resin) related to the initial generator eluate [39].

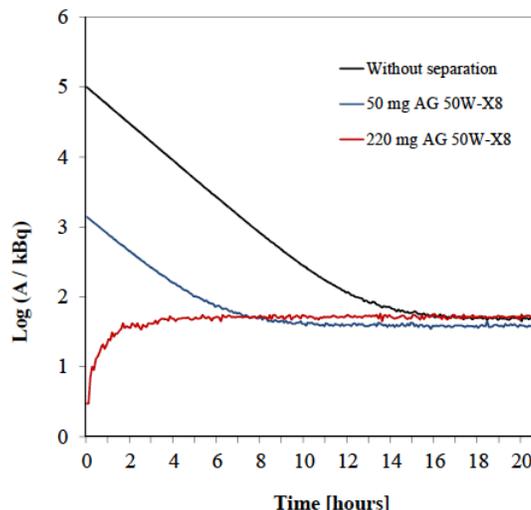
**iii) Post-processing towards labelling lipophilic compounds in non-aqueous systems for:** While almost all currently used  $^{68}\text{Ga}$  radiopharmaceuticals represent compounds and in particular labeling precursors, easily soluble in aqueous solutions, some promising  $^{68}\text{Ga}$  tracers, may be developed, requiring non-aqueous synthesis conditions [5]. The cation-exchange post-processing allows to transfer  $^{68}\text{Ga}$  conveniently into non-aqueous solvent systems and thus the labeling under anhydrous conditions. Again, the initial aqueous generator eluate is first transferred online onto a cation exchange resin. From this resin,  $^{68}\text{Ga}$  is eluted with different acetone-based, non-aqueous solvent systems [39] e.g. as a



**Fig. (8).** Elution profile of gallium-68 from the cation exchange resin using different acetone containing eluents. The CEX column was loaded with 150 μL of these eluents first and the resin bound <sup>68</sup>Ga was allowed to equilibrate with the eluent for 2 min [39].

[<sup>68</sup>Ga]Ga(acac)<sub>3</sub> complex when using 2% acetylacetonate in acetone. More than 95% of the generator-eluted <sup>68</sup>Ga was obtained from the cation exchange resin with 600 μL of a 98% acetone/2% acetylacetonate mixture, cf. Fig. (8). Water-insoluble macrocyclic polypyrrole derivatives have been chosen as model compounds for a proof-of-principle labeling of lipophilic compounds with <sup>68</sup>Ga. Labeling of two different porphyrin derivatives, *meso*-tetraphenyl-porphyrin (Tpp) and (3-(1-hydroxyheptyl)deuteroporphyrin)dimethyl-ester (HHD PD) was performed in chloroform in a focused microwave synthesis system in yields of up to 90% within 5 min using phenol as co-ligand. Total time of synthesis, consisting of generator elution, post-processing, labeling and purification, was 17 minutes for both compounds [40].

**iv) Instant quantification of generator <sup>68</sup>Ge breakthrough:** The potential of the cation exchange resin to almost quantitatively discriminate chemically between <sup>68</sup>Ga<sup>III</sup> and <sup>68</sup>Ga<sup>IV</sup> can be applied to analyze the breakthrough of a <sup>68</sup>Ge/<sup>68</sup>Ga generator. The concept lies in quantitatively separating <sup>68</sup>Ga on line from <sup>68</sup>Ge, which completely passes the cation exchange resin. If <sup>68</sup>Ga free, the (relative) count rate or (absolute) activity measured in that <sup>68</sup>Ge fraction will immediately begin to increase by ingrowth of <sup>68</sup>Ga from <sup>68</sup>Ge decay. This facilitates an instant measurement of <sup>68</sup>Ge breakthrough within about one hour post-elution already. For almost complete separation, the amount of the cation exchange AG 50W-X8 has to be increased compared to standard cleaning columns. Efficiencies of removing <sup>68</sup>Ga from <sup>68</sup>Ge breakthrough for



**Fig. (9).** Effects of Removing <sup>68</sup>Ga from <sup>68</sup>Ge Breakthrough for Selected Cation Exchange Resins. <sup>68</sup>Ga Activities Measured in kBq for initial, Non-processed <sup>68</sup>Ge/<sup>68</sup>Ga Radionuclide Generator Eluate (1) over time for <sup>68</sup>Ge Waste Solutions after Passing Through of 50 mg AG50 Wx8 (2) and 220 mg AG50 Wx8 (3), Respectively. Measurements of Absolute <sup>68</sup>Ga activity were Performed in a dose Calibrator every 5 Minutes (Automated Mode) for at least 20 hours [40].

selected cation exchange resins are illustrated in Fig. (9), comparing <sup>68</sup>Ga activities measured in kBq over time for initial, non-processed <sup>68</sup>Ge/<sup>68</sup>Ga radionuclide generator eluate (1) with measurements obtained after online “filtering” the <sup>68</sup>Ga [41]. <sup>68</sup>Ge and <sup>68</sup>Ga are separated quantitatively using 220 mg AG 50W-X8. <sup>68</sup>Ge can thus be directly quantified after the initial elution, just letting <sup>68</sup>Ga to grow for one (or ½) half-life of 67.7 minutes.

Table 4 summarizes the features of the post-processing via cation-exchangers.

**CONCLUSION**

Today, several <sup>68</sup>Ge/<sup>68</sup>Ga radionuclide generators are commercially available, either TiO<sub>2</sub>- or SnO<sub>2</sub>-based or using an organic resin. They are all eluted using hydrochloric acid (though of varying concentration) and thus provide cationic <sup>68</sup>Ga species ready for radiopharmaceutical syntheses. <sup>68</sup>Ga

**Table 4. Features of the Post-processing via Cation-exchangers**

	Feature	Benefit	Comment
Basic process	Fast and efficient for small volume mixtures of HCl / acetone or HCl / ethanol	Chemically and radiochemically pure <sup>68</sup> Ga with 97±2% referred to initial generator eluate within < 4 min	Instant removal of <sup>68</sup> Ge guarantees safety in terms of <sup>68</sup> Ga-preparations
Option 1	Simultaneous use of used and fresh <sup>68</sup> Ge/ <sup>68</sup> Ga generators	Extended shelf-life of generators	Cost-effective
Option 2	Combination with successive anion exchange processing	<sup>68</sup> Ga in acetone-free, pure aqueous solution of highest chemical purity	Ca. 80% referred to initial generator eluate <sup>68</sup> Ga activity
Option 3	Transfer of <sup>68</sup> Ga from aqueous to non-aqueous solvents	<sup>68</sup> Ga in pure non-aqueous solution via <sup>68</sup> Ga(acac) <sub>3</sub> synthon	At ca. 70% referred to initial generator eluate
Option 4	Instant analytics of <sup>68</sup> Ge breakthrough in initial generator eluate	Detection of ultra-low <sup>68</sup> Ge levels within an excess of <sup>68</sup> Ga activity within one hour post elution	Maybe required prior to the release of <sup>68</sup> Ga radiopharmaceutical preparations

eluate yields range from about 65 to 90% for fresh generators, with more or less pronounced decrease over time.  $^{68}\text{Ge}$  breakthrough is at levels of about 0.01% to 0.001%, with however increasing percentages over longer periods of generator usage.

$^{68}\text{Ga}$  radiopharmaceuticals are being synthesized routinely and safely applying post-processing technologies. In particular post-processing of  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generators using cation exchange resin provides chemically and radiochemically pure  $^{68}\text{Ga}$  with  $97\pm 2\%$  within 4 min, with  $^{68}\text{Ge}$  almost completely removed, and ready for subsequent labeling [31]. This simple, fast and efficient technology can be easily extended for new applications. Among those features, there are options to simultaneously use used and fresh  $^{68}\text{Ge}/^{68}\text{Ga}$  generators to obtain  $^{68}\text{Ga}$  free of any  $^{68}\text{Ge}$  breakthrough either in acetone-free, pure aqueous solution of highest chemical purity of ca. 80% (referred to initial generator eluate  $^{68}\text{Ga}$  activity) or in pure non-aqueous solution via  $^{68}\text{Ga}(\text{acac})_3$  as a synthon for syntheses in organic solvents with ca. 70% recovery. Moreover, by simple increase of the amount of the cation exchanger an elegant option towards instantaneous  $^{68}\text{Ge}$  analytics is provided.

In the future,  $^{68}\text{Ga}$  radiopharmaceuticals may be synthesized “on-resin” using eluents for the cleaning column containing the labeling precursor.

Currently, commercial  $^{68}\text{Ge}/^{68}\text{Ga}$  generator systems are distributed in part with post-processing technologies integrated within automated modules. In addition, these modules often also possess an option for subsequent  $^{68}\text{Ga}$ -radiopharmaceutical syntheses and product purification. To date, there is still a lack of clinically approved generators.

With a view to legal aspects generator improvements are still desirable. For example, sophisticated new materials acting as solid phases may not only achieve high  $^{68}\text{Ga}$  elution yields greater than 90% but also minimize  $^{68}\text{Ge}$  breakthrough levels down to  $10^{-4}\%$  levels. This in particular may result in constant elution characteristics over longer periods, thus extending the shelf-life of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators.

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## CONFLICT OF INTEREST

Declared none.

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