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Gallium-68 Cyclotron Production

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GALLIUM-68 CYCLOTRON PRODUCTION

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 2019

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FOREWORD

Positron emission tomography imaging with ^{68}Ga-labelled tracers is increasingly being used for the detection of neuroendocrine and prostate cancers. Its use, however, is highly dependent on the availability of ^{68}Ge/^{68}Ga generators. Because of supply limitations and the high cost of these generators, there has been increasing interest in the production of ^{68}Ga using medical cyclotrons. To support Member States in this regard, the IAEA has prepared this publication to provide information on direct cyclotron production of ^{68}Ga. The publication is an outcome of the work of an international team of experts in the field carried out from 2016 to 2018.

The IAEA would like to thank all the experts involved for their many contributions. Special thanks are due to C. Hoehr (Canada) and J.S. Vera Araujo (Bolivarian Republic of Venezuela) for their valuable support. The IAEA officer responsible for this publication was A.R. Jalilian of the Division of Physical and Chemical Sciences.

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CONTENTS

1. INTRODUCTION

1.1.BACKGROUND

The growth of the imaging technique positron emission tomography (PET) has capitalized on the emergence of PET radionuclides beyond the classic light radionuclides of ^{11}C, ^{13}N, ^{15}O and ^{18}F. New positron-emitting radiometals with a wide variety of half-lives, coordination chemistry and imaging characteristics, have given the field of PET a powerful extended toolbox for the development of new radiopharmaceuticals. Particularly, ^{68}Ga based radiopharmaceuticals have attracted increasing interest in recent years due to its expanding clinical applications. This is fostered by the emerging interest in theragnostic applications in oncology where a diagnostic scan is made using a gallium-based molecule that is later labelled with a therapeutic radionuclide such as ^{90}Y or ^{177}Lu for treatment [1]. This development has been supported by the IAEA by several Coordinated Research Projects (CRPs), for example 'Development of Ga-68 based PET-Radiopharmaceuticals for Management of Cancer and other Chronic Diseases (F22050)', and publication initiatives, but the coverage is not yet complete. While currently ^{68}Ga is mainly coming from $^{68}Ge/^{68}Ga$ generators, supply challenges for ^{68}Ge remain. The aim of this publication is to summarize the alternative cyclotron-based production of ^{68}Ga.

1.2.OBJECTIVES

Due to the increasing number of ^{68}Ga radiopharmaceutical production and applications entering clinical trials worldwide, this publication includes recommendations and suggestions on targetry, irradiation, separation chemistry, quality control and quality assurance procedures for $^{68}GaCl_3$ using a medical cyclotron. This publication will open a new gateway for all Member States laboratories worldwide in charge of radiopharmaceutical production, for access to the important PET radioisotope: for the large scale production and application of ^{68}Ga radiopharmaceuticals.

1.3.SCOPE

This publication was designed to serve as a specific guide for production and quality control of metal radioisotope ^{68}Ga in chloride form for radiopharmaceutical production for all member states, with emphasis on the advances developed over the last few years. An overview of the target material choice and specifications, targetry methods possible to be used for production, irradiation factors, chemical purification from starting target material and other impurities as well as quality control processes, have been presented in a generic format with focus for final use in peptide radiopharmaceuticals production in-house. The recovery process for target material has been proposed. The publication also describes the legal matters related to the use of this method.

Annex I describes the general recommendations for production and application of metal radionuclides for radiopharmaceutical production, and Annex II describes practical experiences of some selected member states using this method.

The most important targetry approaches covered in this publication are liquid, fused and solid targets followed by generic chemical purification methods and quality control specifications.

1.4.STRUCTURE

This publication is provided to help cyclotron units for accessing knowledge to understand the background and standard operation procedures of in-target production of ^{68}Ga radioisotope appropriate for radiopharmaceutical production with respect to increasing worldwide need to this radioisotope.

2. ^{68}Ga PRODUCTION

2.1.IMPORTANCE OF ^{68}Ga

^{68}Ga has played a remarkable role in the worldwide growth of clinical research and routine clinical studies with PET over the last 20 years. Although ^{68}Ge/^{68}Ga generators were introduced over 50 years ago, the most important factors for the recent growth of ^{68}Ga radiopharmaceuticals were the progress in generator design. This newer generation of generators, rendering ^{68}Ga as [^{68}Ga]$GaCl_3$, has solved critical impurity problems and has allowed commercial availability of generators. The greater availability of commercial generators motivated increased efforts on ^{68}Ga radiopharmaceutical production. Furthermore, gallium chelation chemistry had matured from more of 30 years of research so that the design of ^{68}Ga radiopharmaceuticals, particularly peptide-based radiotracers became relatively straightforward for peptides with established high affinity/selectivity for their biological targets. Finally, in parallel to the advances in ^{68}Ga chemistry and radiopharmaceuticals, there has also been tremendous growth in recent years in the development of peptides and other molecules conjugated with radiotherapy isotopes such as ^{177}Lu for the treatment of various tumours. ^{68}Ga represents an ideal diagnostic isotope for pairing with radiometal therapy isotopes, particularly in the many examples of molecules that can utilize the same chelator for ^{68}Ga and the therapy isotope (e.g. ^{177}Lu, ^{225}Ac, etc.).

The small size and mobility of the ^{68}Ge/^{68}Ga generator has provided improved access of receptor-targeting PET radiopharmaceuticals at PET imaging centres. Also, the simple and robust chelation chemistry of ^{68}Ga allows the preparation of ^{68}Ga radiopharmaceuticals via relatively simple methods using commercially manufactured cold kits containing ligand-chelator conjugates. The use of cold kits is analogous to the commonly employed labelling of compounds with ^{99m}Tc for preparation of single photon imaging. Thus, many institutions are able to perform PET studies with ^{68}Ga due to the modest investment to purchase a generator.

^{68}Ga is most often used in PET radiopharmaceuticals in oncologic applications, however it has shown good potential for imaging of cardiovascular diseases, pulmonary perfusion and ventilation, inflammation, infection and cell trafficking [2].

2.2.WORKFLOW FOR PRODUCTION OF ^{68}Ga RADIOPHARMACEUTICALS

The most common method for obtaining ^{68}Ga is currently via a ^{68}Ge/^{68}Ga generator. Generators are convenient in a way that the long half-life of the parent nuclide ^{68}Ge (270.93 days) guarantees an ongoing supply of ^{68}Ga for a hospital or clinic for several months. The eluted ^{68}Ga is in the form of [^{68}Ga]$GaCl_3$ and can then be used as it is for labelling.

The usable ^{68}Ga activity from a generator is nevertheless limited by: the amount of activity loaded on the generator (typically up to 2.4 GBq nominal activity when new); the minimum interval between elutions (typically 3-4 hours); the maximum number of elutions (up to 450); the elution efficiency (~60-70%); and the possibility of the long-lived parent radionuclide (^{68}Ge) breaking through from the column. More importantly, the number of generators available today is presently unable to fulfil the current demand as is reflected by the long waiting time (i.e. 9-18 months) for a new generator as well as the ever-increasing price of generators. For a low number of ^{68}Ga doses needed per day, a generator provides good flexibility, but at the cost of a high price per dose.

As the number of doses per day increases, the utilization of the generator may improve and become more economical. However, an important limit is reached when the number of doses needed exceeds the generator capacity (both in activity eluted and number of elutions per day). Additionally, in certain countries and/or for certain products, regulations limit the user to one patient dose per elution. At some time point a new generator must be acquired and almost double the cost will have to be carried by a slight increase in the number of doses. If one-to-few patient doses are used per week, then the price per dose of the radionuclide will be very high. These constraints clearly illustrate that alternative production routes are necessary for better availability and increased use of ^{68}Ga radiopharmaceuticals.

^{68}Ga can be produced on a small to medium energy cyclotron via the ^{68}Zn(p,n)^{68}Ga reaction. The starting material can either be a solid target in the form of a target plate or foil, or a solution target (see FIG. 1). A solid target will always have a higher concentration of zinc than a liquid target, leading to significantly higher yields. The solid target needs to be transferred into the target holder on the cyclotron either manually or via an automated target transfer system. In contrast, the solution can be remotely loaded into the target holder similarly to an ^{18}F target system. After irradiation, the solid target must be removed either manually with the risk of high personnel exposure to the radioactive field of the target itself and activated parts of the cyclotron, or with an automated target transfer system. Again, for a liquid target, the target liquid is remotely pushed into a hot cell through capillary lines with over pressure of air or an inert gas. Once in the hot cell, the solid target must be dissolved. This step adds extra time for the post-process versus the liquid target process (fig. 1). The next step is the same for both solid and liquid target. Namely, the ^{68}Ga must be separated from the bulk parent ^{68}Zn isotope and purified to remove any unwanted metal contaminants. Recycling of the enriched ^{68}Zn starting material can be considered. The end product of the separation can be [^{68}Ga]$GaCl_3$, the same as the eluate from the generator. However, the concentration and pH may differ from one method to the other. At this point, labelling the desired radiopharmaceutical with ^{68}Ga is the same for all three production methods, generator, solid and liquid targets. Production of

^{68}Ga amounts exceeding the amount available from current generators is possible with both the solid and solution target system approaches [3–7].

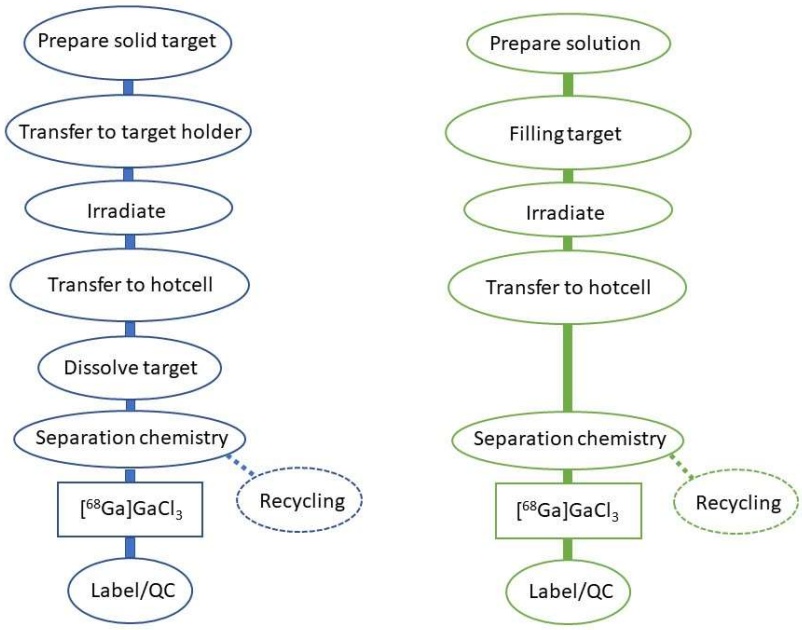


FIG. 1. Workflow of different cyclotron production methods.

2.3.PRODUCTION OF ^{68}Ga WITH SMALL TO MEDIUM CYCLOTRONS

The irradiation of ^{68}Zn by protons is the preferred among several possible nuclear reactions [8, 9] as it leads to a large production yield and uses protons, the simplest and most widely available of all cyclotron projectiles. It is generally necessary to bombard isotopically enriched ^{68}Zn since several radioisotopes of gallium with longer half-lives than ^{68}Ga are also co-produced when irradiating natural Zn. However, despite use of isotopically enriched ^{68}Zn, small amounts of ^{66}Ga and ^{67}Ga will occur as (i) it is not possible to acquire 100% pure ^{68}Zn, and (ii) even in the event of pure ^{68}Zn being available, the proton irradiation of ^{68}Zn leads to the production of ^{67}Ga radioisotopic impurity through the ^{68}Zn(p,2n)^{67}Ga reaction for proton energies larger than 12.2 MeV. Therefore, the composition of the isotopically enriched ^{68}Zn and the proton energy must be selected wisely to balance yield and achieve a purity suitable for human use [8, 9]. Examples of different enriched ^{68}Zn lots of isotopically enriched ^{68}Zn are shown in table 1. It is also important to assess other metal contamination in the ^{68}Zn starting material. Iron may be of concern as (if not purified) it may interfere with labelling of some precursors, for example those with a DOTA chelator.

TABLE 1. EXAMPLES OF DIFFERENT ENRICHED ^{68}Zn BATCHES

ZN LOT	DESCRIPTION	^{64}ZN [%]	^{66}ZN [%]	^{67}ZN [%]	^{68}ZN [%]	^{70}ZN [%]
A	Observed	0.76	0.61	0.27	98.33	0.03
B	Observed	0.03	0.16	0.62	99.16	0.03
C	Observed	0.46	0.43	0.29	98.8	0.02
D	Observed	0.01	0.10	0.61	99.26	0.02
E	Observed	0.58	0.32	0.26	98.82	0.02
F	Other lot [10]	0.66	0.57	0.30	98.46	<0.05
G	Other lot [11]	0.01	0.01	0.30	99.50	0.18
Nat	Natural zinc	49.17	27.73	4.04	18.45	0.61

Theoretical calculations were conducted to predict the production yields of the possible nuclear reactions resulting from the proton-irradiation of an example ^{68}Zn-based liquid target. An illustrative set of results, theoretical and experimental, is shown in table 2 for an example configuration of beam energy and isotopic composition of enriched ^{68}Zn. Experimental cross-sections from the EXFOR database [12] were used to fit the excitation function of interest and perform the calculations.

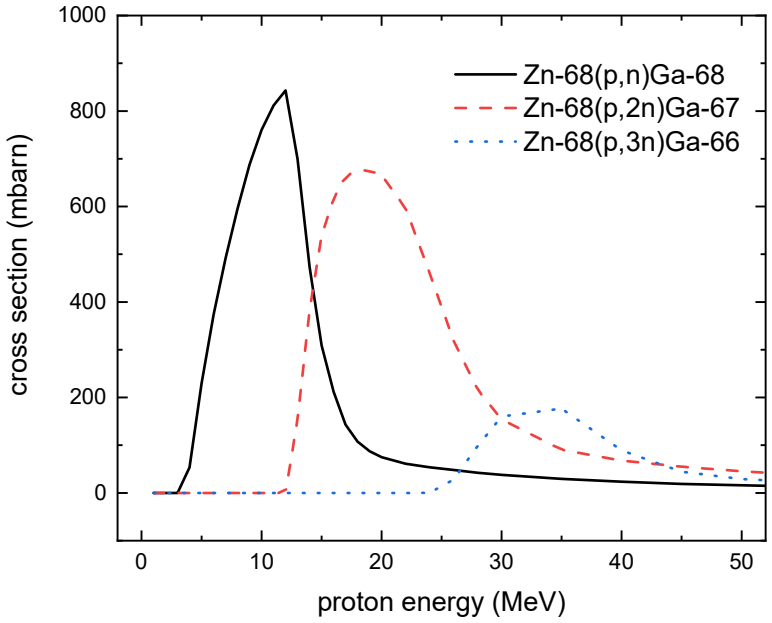


FIG. 2. Excitation function for the ^{68}Zn(p,n)^{68}Ga, ^{68}Zn(p,2n)^{67}Ga and ^{68}Zn(p,3n)^{66}Ga reactions. Data from [13].

TABLE 2. PROTON-INDUCED NUCLEAR REACTIONS OCCURING IN ^{68}Zn-ENRICHED ZINC AND THEORETICAL PRODUCTIONS YIELDS FOR A TYPICAL IRRADIATION: BOMBARDMENT OF A TARGET SOLUTION CONTAINING 200 mg OF ^{68}Zn (TOTAL VOLUME = 3 mL) WITH 14.2 MeV PROTONS.

ZINC NUCLIDE **(ABUNDANCE IN ^{NAT}ZN)**	ABUNDANCE **(%)**	NUCLEAR REACTION	DECAY					THEORETICAL YIELD **(MBQ/μA)**	ACTIVITY @ EOB **(MBQ) FOR 1 H, 50 μA**
			Half-life	β^- (MeV`)	β^+ (MeV`)	EC (%)	Main γ rays (keV)		
^{64}Zn 48.6%	0.01	^{64}Zn(p,α)^{61}Cu	3.33 h		1.215 (61.5%)	38.5	283 (12.0%) 511 (123%) 656 (10.4%)	$4.15 \cdot 10^{-3}$	0.039
		^{64}Zn(p,pn)^{63}Zn	32.4 s						
		^{64}Zn(p,γ)^{65}Ga	15.2 min					$4.44 \cdot 10^{-5}$	$2.08 \cdot 10^{-3}$
		^{64}Zn(p,n)^{64}Ga	2.63 min						
^{66}Zn **27.9%**	0.01	^{66}Zn(p,n)^{66}Ga	9.49 h		4.153 (56.0%)	44	511 (114%) 833 (5.9%)	0.037	0.130

						1039 (37%0 2190 (5.3%) 2751 (22.7%)		
		$^{66}Zn(p,2n)^{65}Ga$	15.2 min				0	0
		$^{66}Zn(p,pn)^{65}Zn$	244.0 d		0.33 (1.42%)	98.6	1115 (50.23%)	$3.95 \cdot 10^{-4}$	$2.34 \cdot 10^{-6}$
^{67}Zn 4.1%	0.3	$^{67}Zn(p,n)^{67}Ga$	3.26 d			100	93.3 (70.6%) 184.6 (21.3%) 300.2 (16.67%)	1.222	0.539
		$^{67}Zn(p,\alpha)^{64}Cu$	12.7 h	0.579 (38.5%)	0.653 (17.52%)	43.5	511 (35.04%) 1346 (0.475%)	$5.68 \cdot 10^{-2}$	0.151
		$^{67}Zn(p,2n)^{66}Ga$	9.49 h		4.153 (56%)	44	511 (114%) 833 (5.9%) 1039 (37%) 2190 (5.3%) 2751 (22.7%)	$9.31 \cdot 10^{-3}$	0.0328

^{68}Zn 18.8%	99.5	^{68}Zn(p,n)^{68}Ga	67.8 min		1.899 (88.9%)	11.1	511 (178%) 1077 (3.24%) 1883 (0.142%)	599.0	13732.9
		^{68}Zn(p,2n)^{67}Ga	3.26 d			100	93.3 (70.6%) 184.6 (21.3%) 300.2 (16.67%)	23.2	10.23
		^{68}Zn(p,nα)^{64}Cu	12.7 h	0.579 (38.5%)	0.653 (17.52%)	43.5	511 (35.04%) 1346 (0.475%)	2.31	6.12
^{70}Zn 0.6%	0.18	^{70}Zn(p,α)^{67}Cu	2.576 d					$9.39\cdot10^{-3}$	$5.24\cdot10^{-3}$
		^{70}Zn(p,n)^{70}Ga	21.14 min	1.656 (99.6%)		0.41	176 (0.29%) 1039 (0.65%)		
		^{70}Zn(p,pn)^{69}Zn	56.4 min	0.906 (100%)			319 (0.0012%)	$2.72\cdot10^{-3}$	0.071

Note that for references of cross sections see [3].

As shown and quantified for the irradiation example in table 2, proton-irradiation of the ^{68}Zn target solution leads to the production of other radio-isotopes of gallium. Special attention should be given to ^{66}Ga and ^{67}Ga, since these are the isotopic impurities that will be in the final purified solution of ^{68}Ga. While other production yields are greatly reduced by the use of highly enriched ^{68}Zn, significant production of ^{67}Ga may remain since it occurs on ^{68}Zn, through the competitive ^{68}Zn(p,2n)^{67}Ga reaction (see FIG. 2.)

Further, fig. 3 presents a theoretical prediction on the radioisotopic purity of ^{68}Ga taking ^{66}Ga and ^{67}Ga into account as a function of the incident beam energy and select example lots of ^{68}Zn as noted in table 1, with purity reported as a function of end of bombardment (EOB). As seen in FIG. 3, the selection of proton energy becomes even more important if a longer product-shelf life is desired.

The following study experimentally investigates the impact of proton energy on the radionuclidic purity of ^{68}Ga or rather, the co-production of ^{66}Ga and ^{67}Ga (no other non-Ga peaks were identified) for two commercially available batches of enriched ^{68}Zn (i.e. lots A and B of table 1). Impurities were assessed by gamma-ray spectroscopy measurement on an efficiency calibrated LaBr detector (samples were assayed for 1 hour life time, measured ~20-40 hr post EOB).

TABLE 3. NUMBER OF EXPERIMENTAL RADIONUCLIDIC PURITY MEASUREMENTS PERFORMED FOR THE LOTS OF ^{68}Zn FROM TABLE 1

ENERGY (MEV)	^{68}Zn LOT "A"	^{68}Zn LOT "B"	RELATIVE ^{68}Ga YIELD
13.1	3	3	100%
14.0	8	0	110%
14.3	0	16	112%
14.5	2	3	114%
15.2	4	4	118%

Irradiations were performed (see table 3) on a liquid ^{68}Zn target, and typically varied in length from 30 minutes to 2 hours. From the saturation yields of both ^{68}Ga and the impurities, we in turn derived impurity profiles assuming fixed irradiation times of 1.0 and 1.5 half-lives (i.e. 68 and 102-minute irradiations). Data is reported at the EOB, and decay corrected to 1, 3, 4, and 5 hours post EOB (table 4). It should be noted that slight differences may be expected for solid targets if not 'thick', and that data below is based on average of the noted number of samples and does not include error bars.

On reviewing table 4 and fig. 3, we observe a strong energy dependence on the formation of ^{67}Ga (i.e. attributed to the ^{68}Zn(p,2n)^{67}Ga reaction), whereas the production of ^{66}Ga is largely dependent on the batch of ^{68}Zn and the corresponding ^{66}Zn enrichment. We also note that depending on the anticipated 'shelf-life', e.g. 3 hours vs. 5 hours, this may play a role in energy selection – perhaps even more relevant if considering the much larger quantities of ^{68}Ga that can be produced with a solid target. –

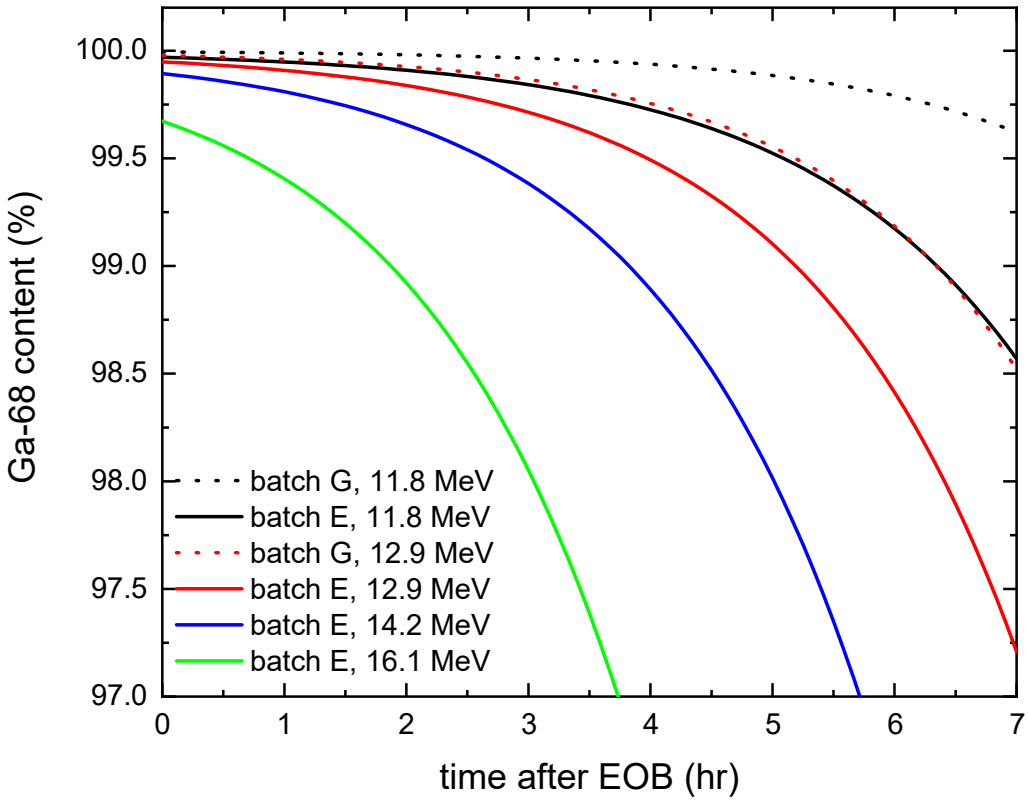


FIG. 3. Theoretical prediction of the purity of the produced ^{68}Ga as a function of time after EOB for different proton beam energies and two different batches of enriched ^{68}Zn, see table 1[1].

[1] This figure was partly made from data taken from F. Alves in [12].

TABLE 4. RADIONUCIDIC PURITY REPORTED AT DIFFERENT TIMES AFTER EOB AS DERIVED FROM SATURATION YIELDS [14]

ZN LOT	BEAM TIME	E	EOB			TIME POST EOB = 1 HOUR			TIME POST EOB = 3 HOUR			TIME POST EOB = 4 HOUR			TIME POST EOB = 5 HOUR		
		[MeV]	**^{66}Ga [%]**	**^{67}Ga [%]**	**^{68}Ga [%]**	**^{66}Ga [%]**	**^{67}Ga [%]**	**^{68}Ga [%]**	**^{66}Ga [%]**	**^{67}Ga [%]**	**^{68}Ga [%]**	**^{66}Ga [%]**	**^{67}Ga [%]**	**^{68}Ga [%]**	**^{66}Ga [%]**	**^{67}Ga [%]**	**^{68}Ga [%]**
A	1.0 t½	13.1	0.06	0.01	99.94	0.10	0.01	99.89	0.29	0.04	99.67	0.49	0.08	99.42	0.84	0.15	99.01
		14.0	0.06	0.08	99.86	0.11	0.14	99.75	0.31	0.48	99.20	0.53	0.88	98.58	0.91	1.59	97.50
		14.5	0.05	0.10	99.84	0.09	0.19	99.72	0.27	0.63	99.10	0.47	1.14	98.39	0.79	2.06	97.15
		15.2	0.07	0.21	99.72	0.12	0.38	99.50	0.36	1.25	98.38	0.61	2.27	97.12	1.03	4.06	94.91
	1.5 t½	13.1	0.06	0.01	99.93	0.11	0.02	99.87	0.33	0.05	99.62	0.56	0.09	99.35	0.96	0.17	98.87
		14.0	0.07	0.09	99.84	0.12	0.17	99.71	0.36	0.56	99.09	0.61	1.02	98.38	1.03	1.84	97.13
		14.5	0.06	0.12	99.82	0.11	0.22	99.68	0.31	0.72	98.97	0.53	1.31	98.16	0.90	2.37	96.73
		15.2	0.08	0.24	99.68	0.14	0.44	99.42	0.41	1.45	98.14	0.70	2.61	96.69	1.16	4.66	94.17
B	1.0 t½	13.1	0.01	0.01	99.98	0.02	0.02	99.96	0.05	0.08	99.87	0.08	0.15	99.77	0.14	0.27	99.59
		14.3	0.01	0.09	99.90	0.02	0.17	99.82	0.05	0.56	99.39	0.09	1.01	98.90	0.15	1.84	98.02
		14.5	0.01	0.10	99.89	0.01	0.19	99.80	0.04	0.63	99.32	0.07	1.15	98.77	0.12	2.09	97.79
		15.2	0.01	0.19	99.80	0.01	0.36	99.63	0.04	1.18	98.77	0.07	2.15	97.78	0.12	3.86	96.02
	1.5 t½	13.1	0.01	0.02	99.97	0.02	0.03	99.95	0.06	0.09	99.85	0.09	0.17	99.74	0.16	0.31	99.53
		14.3	0.01	0.11	99.88	0.02	0.19	99.79	0.06	0.64	99.30	0.10	1.17	98.73	0.17	2.12	97.71
		14.5	0.01	0.12	99.87	0.02	0.22	99.76	0.05	0.73	99.22	0.08	1.33	98.59	0.14	2.41	97.45
		15.2	0.01	0.22	99.77	0.02	0.41	99.57	0.05	1.37	98.58	0.08	2.47	97.44	0.14	4.44	95.42

3. SOLID TARGET PRODUCTION OF ^{68}Ga

3.1.ELECTROPLATED TARGETS

Electroplating can be used to deposit ^{68}Zn onto a solid support. In the electroplating process for ^{68}Zn, copper, silver, and platinum are reported as target supports (see table 5). Different plating methods are discussed in the following. Plating yields of around 90% can be achieved. Furthermore, the selection of the type of support could generate radionuclidic impurities and must be carefully evaluated. The properties of the target support should include high mechanical strength, high thermal conductivity during irradiation and chemically inertness for the respective dissolution and purification process. When choosing the target support material, radiation safety issues should also be considered in addition to chemistry constraints due to the activation of the target support material during the irradiation, which may yield high radiation doses during operation. The thickness of the zinc which has been deposited also plays a role on the level of support activation.

TABLE 5. POTENTIAL TARGET SUPPORT FOR ^{68}Ga PRODUCTION

TARGET SUPPORT	ADVANTAGES	DISADVANTAGES
Cu	✓ High thermal conductivity ✓ High melting point ✓ Inexpensive	✓ High activation
Ag	✓ High thermal conductivity ✓ High melting point ✓ Inexpensive	✓ High activation although lower than Cu
Pt	✓ High melting point	✓ Expensive ✓ Lower thermal conductivity than Cu and Ag

3.1.1. Copper backing

The optimized condition for electroplating ^{68}Zn on a copper support was reported previously [15] and was carried out in alkaline cyanide baths with a current density through platinum wire anode adjusted to 8.55mA/cm^2 for 3.5h. Copper has two properties that make it a good choice for cyclotron targetry: it is a metal with a high melting point (1084.6 °C), and it also has high thermal conductivity (401 $W \cdot m^{-1} \cdot K^{-1}$) for effective heat exchange during the irradiation [16, 17].

Natural copper contains 69.17% of ^{63}Cu and 30.83% of ^{65}Cu. Different Zn radioisotopes were reported during target irradiation with protons following these nuclear reactions: ^{65}Cu(p,n)^{65}Zn, ^{65}Cu(p,2n)^{64}Zn, ^{63}Cu(p,n)^{63}Zn, ^{63}Cu(p,2n)^{62}Zn. Between them, ^{65}Zn (half-life = 244 d) has the longest half-life and decays by electron capture to the 1115 keV excited state and by electron capture and β^+ emission to the ground state level of ^{65}Cu. The maximum cross-section for the reaction ^{65}Cu(p,n)^{65}Zn is around 11 MeV. Although significantly higher than the proton energy needed for the ^{68}Ga production, at 23.5 MeV (i.e. the proton energy used for the related ^{68}Zn(p,αn)^{64}Cu reaction), the cross-section of the ^{65}Cu(p,n)^{65}Zn reaction is high enough to produce ^{65}Zn. This radioisotope will produce high radiation doses for a long period; therefore, safety concerns might require a more careful design of target processing.

3.1.2. Silver backing

The electroplating on a silver backing has been reported with ^{nat}Zn (250-300 mg) in 0.05 N HCl (2.5 mL) with a 4 to 9 V current applied through a platinum wire anode (0.1mm diameter) for 20h [18]. Natural Ag is composed of the stable isotopes ^{107}Ag (51.83%) and ^{109}Ag (48.17%). During target irradiation with protons, different isotopes of cadmium (Cd) were produced via the following nuclear reactions: ^{107}Ag(p,n)^{107}Cd, ^{107}Ag(p,2n)^{106}Cd, ^{109}Ag(p,n)^{109}Cd, ^{109}Ag(p,2n)^{108}Cd. ^{106}Cd and ^{108}Cd are stable isotopes. At the energy range used to produce ^{68}Ga, the nuclear reactions on the Ag support will produce ^{107}Cd and ^{109}Cd. In addition, ^{107}Cd has a short half-life of 6.5 h, whereas ^{109}Cd has a long half-life of 453 d. This radioisotope has no gamma emission and decays by electron capture to the isomeric state (88 keV) of ^{109}Ag, which has an extremely short half-life of 39.6 s. Silver also has a higher thermal conductivity than Copper (429 $W \cdot m^{-1} \cdot K^{-1}$) and a high melting point of 961.8 °C, making Ag a suitable support.

3.1.3. Platinum backing

It is also possible to use platinum as support material for electrodeposition of zinc [6]. For electroplating, a solution of 25-30 mg/mL in 0.05N HCl at a current density of 25 mA/cm^2 was used. This material has the advantage to be resistant during the chemical operations for recovering ^{68}Ga and ^{68}Zn. But platinum is more expensive than copper or silver and has a much lower thermal conductivity (71.6 $W \cdot m^{-1} \cdot K^{-1}$).

3.2.PRESSED TARGETS

^{68}Ga can also be produced by cyclotron using ^{68}Zn pressed target mounted on aluminium target supports [19]. The target itself is a metallic disk with a central cavity in which the ^{68}Zn pressed pellet is positioned. The ^{68}Zn pellets of different diameter and thickness can be prepared by using a manual operated digital hydraulic press (Module number: 3912, Carver, Inc, Wabash, IN, US) as seen in table 6 below. The optimal pressed target thickness depends upon the irradiation angle of the beam and this value can be evaluated using SRIM software [20] for a proton energy range bellow 14 MeV. Once pressed, the pellets can be placed in the target holders and covered, if needed, with a degrader prior irradiation.

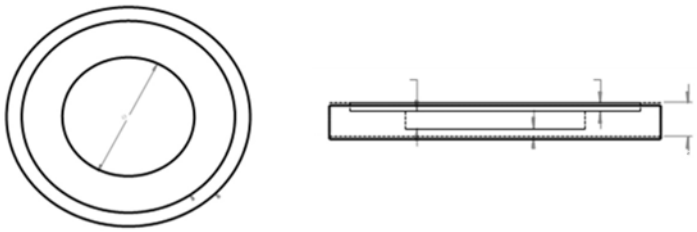


FIG. 4. Metallic target support for pressed target.

TABLE 6. COMPARISON OF SOLID TARGETS (EP – ELECTROPLATED)

PROCESS	TARGET PREPARATION TIME	STARTING MATERIAL AMOUNT/ THICKNESS/DIAMETER	DISSOLUTION TIME (MIN)	STARTING MATERIAL COMPOSITION	SOLID SUPPORT	PRESSURE [BAR]	REFERENCES
EP	N/A	60-120 mg	5	$[^{68}Zn]ZnCl_2$	Pt	N/A	[6]
EP	20 h	250-300 mg	N/A	$[^{66}Zn]ZnCl_2$ $[^{nat}Zn]ZnCl_2$	Au/Ag	N/A	[18]
EP	3.56 h	434 mg, 52 µm	N/A	$[^{nat}Zn]ZnO$	Cu	N/A	[15]
EP	6 h	N/A	25	$[^{68}Zn]ZnCl_2$	Pt	N/A	[21]
EP-Pressed	1 h	2000 mg	Not dissolved	$[^{68}Zn]ZnCl_2$	Ni	300	[22]
Pressed	10 min	96 mg / 500 µm /6mm 250 mg /500 µm /10mm	1	^{68}Zn	Al Al	241 1213	[19]
Pressed	-	300µm	Not dissolved	^{nat}Zn	-	5230	[23]
Foil	-	250-800 mg 50 -1000 µm	N/A	^{68}Zn		N/A	[24]
Foil	-	50-100-150 µm	1	^{nat}Zn	-	N/A	[25]
Foil	-	300 µm	Not dissolved	^{nat}Zn	-	N/A	[23]
Foil	-	10 µm	Not dissolved	^{nat}Zn	-	N/A	[26]
Foil	-	10-25 µm	Not dissolved	^{nat}Zn	-	N/A	[27]
Foil	-	N/A	Not dissolved	^{nat}Zn	-	N/A	[28]
Heat	-	254 µm	Not dissolved	$[^{68}Zn]ZnO$	Ta	N/A	[29]
Fused	2 min	150-200 mg / 0.2-0.3 mm / 10 mm	5	^{nat}Zn	Al	N/A	[30]

3.3.FOIL TARGETS

^{68}Zn foil targets can also be used to produce ^{68}Ga [24]. Although a foil target is easy to manipulate and has a better density than electroplated and pressed targets, commercial availability of ^{68}Zn foil is limited.

3.3.1. Thermal diffusion targets

The use of foils, pressed and plated zinc opens the possibility to apply thermal diffusion to extract gallium from the target without having to dissolve it [25, 31]. This is performed by heating the zinc and then by etching the zinc surface with a weak acid. Approximately 60-70% of the gallium activity can be isolated in the solution while the foil stays almost intact. The foil can be reused, but yield diminishes over time.

A) 

B) 

FIG. 5. A) Press with punch for pressing of zinc. B) Pellet of ^{68}Zn manufactured by the pressing method.

3.4.FUSED TARGETS

Due to the low melting point of zinc (420 °C), another technique to produce a solid target is to heat zinc (Zn) pellets [30]. To produce such a fused target, 0.17 g of natural abundant zinc pellets from Sigma-Aldrich were placed into a 0.3 mm recess in an aluminium disk. The disk was placed on a hotplate and heated up to 550 °C to melt the pellets. Nearly 100 % bulk density was achieved. The disk was then mounted in an in-house manufactured solid target holder at the cyclotron. The irradiation used a beam of 10 μA of 12.8 MeV protons on target for 15 minutes. For initial experiments, the target plate was left on the cyclotron overnight to reduce dose to the cyclotron staff and experimenter. After removal of the target plate, no visible effect due to the irradiation was observed. The ^{66}Ga activity was measured to be 400 MBq decay corrected to EOB. From this, it is estimated that about 3 GBq of ^{68}Ga

was produced at EOB. The target was dissolved in 6N HCl in about 5 minutes. Separation was performed with an efficiency of ~95% [18].

3.5.CONSIDERATION FOR TARGET HOLDERS

There is therefore a strong motivation for cyclotron-based methods for direct production of ^{68}Ga to be developed. These techniques have been known to the scientific community for many years and can generally be divided into two different alternatives: using the target metal in solid form (solid targets) or dissolved in a liquid (solution targets, section 4).

Several solid target holders are commercially available, and in select cases, users may design their own in-house systems given adequate expertise and in consideration with the potential target transfer system. The importance of a solid target system is both to ensure adequate coupling to a cooling system, and in many cases (particularly in the case of routine production), automation for handling of the target transfer.

Many small cyclotrons are capable of delivering beam intensities of more than 100 μA for energies about 10 to 20 MeV. This corresponds to beam powers of 1-2 kW (μA x MeV=W). Due to the low melting point of zinc, adequate target cooling is critical. For the case of ^{68}Zn irradiation, one might opt to limit beam currents to several tens of μA.

Factors which may be incorporated into a solid target holder to improve cooling might include angled beams to spread out the beam power (i.e. decrease beam power density), cooling flow rates and/or geometries may be adjusted, as well as the thermal conductivities of materials (e.g. target support) may be considered. Furthermore, depending on the type of cyclotron being used – the proton energy can be variable or fixed – it is common to use a thick foil in front of the target foil as an energy degrader. One must also consider degrader activation and the power deposition to the degrader to ensure sufficient cooling.

The produced ^{68}Ga can give a high dose burden if manual removal from target holder is required and therefore it is preferable to have a means for remote handling of the activated ^{68}Zn foil (or pressed pellets) if the target is going to be used for larger and/or routine productions. All parts and materials in contact with ^{68}Zn might introduce metal contaminants that will compete for ^{68}Ga chemistry despite seemingly low quantities. Therefore, it is necessary to pay careful attention to all metal contaminants stemming from cooling water, backing material, degrader, plating solutions, dissolution reagents, and other components since these will disturb subsequent chemistry and may decrease apparent specific activity.

3.6.SOLID TARGET TRANSFER SYSTEM

Various systems have been developed to transport irradiated solid targets from the target holder in the cyclotron vault to the processing hot cell within the radiochemistry laboratory. Loading of the target within the holder may be done in an automated fashion or manually for small production. The choice of the system depends on several factors, including the compatibility of the system with the target holder, the physical layout of the cyclotron facility, cost, and access restrictions to the cyclotron vault. A commonly employed approach for target transfer systems is the use of pneumatic tubes with carriers that shuttle the target from the cyclotron to the hot cell. The unsymmetrical aspect of the target support

itself is another consideration to ensure that the target is in proper orientation for irradiation. For those systems that employ automated target loading, the system must robustly place the target in correct orientation with regards to the beam path. An example of a pneumatic transport system has been described by Tomov *et al.* [32]. An alternative approach is to employ a carrier that is translocated by use of cables and motorized winches at each end of the path. Finally, several commercial transfer systems are also available, see for example in [6].

3.7.DISSOLUTION OF SOLID TARGETS

Hydrochloric and nitric acids are used for dissolution of ^{68}Zn. Extremely pure grades of acid with high grade specifications (trace metal basis) are highly recommended. Prices for these may be considerably higher than for low grade acids. Water should be metal free (Ex. Optima LC/MS Fisher.) The crude ^{68}Ga/^{68}Zn solution can be directly transferred onto the pre-activated resin column [6] or pH adjustment (pH 2-2.5) might be required prior ^{68}Ga/^{68}Zn separation on hydroxamate resin [19], see Section 7.

4. SOLUTION TARGET PRODUCTION OF ^{68}Ga

The irradiation of a ^{68}Zn solution in a liquid target, i.e. 'a solution target', provides a practical and inexpensive alternative to produce clinical quantities of ^{68}Ga in a short amount of time. A solution target system greatly expands the availability of ^{68}Ga, especially when demand is infrequent, and the purchase of a generator is not economical, or when the amount of ^{68}Ga needed exceeds the capacity of a generator. It must be noted that a solution target will have a smaller fraction of ^{68}Ga compared with a solid target.

Solution-target ^{68}Ga production can be performed by leveraging existing infrastructure and competencies of personnel already in place to produce other PET radionuclides, such as ^{18}F. Vogg *et al.* [33] demonstrated the concept of nitrate solution targets and proposed the applicability to the production of ^{68}Ga among other isotopes. In 2011, Jensen *et al.* [34] have initially demonstrated ~2 GBq ^{68}Ga production in a liquid target using an aqueous enriched [^{68}Zn]$ZnCl_2$ target. The first successful ^{68}Ga production in a liquid target using enriched ^{68}Zn nitrate in dilute nitric acid was reported by Pandey *et al.* [5] and was followed by other works [3, 7, 35]. By using solution targets, technical difficulties of solid target manufacturing and handling can also be avoided. While a separate target body should be used, the same, or similar, target body geometry as used for ^{18}F can be loaded and unloaded remotely via transfer lines. No special additional equipment is needed but care needs to be taken to avoid metal contamination in all aspects of the solution preparation and handling including control of the materials where the solution is exposed to in the load/transfer system and target. Corrosion of the target body and entrance foil must be avoided. Excess pressure rises in a closed solution target due to radiolysis must be minimized.

4.1.TARGET SOLUTION PREPARATION

Liquid targets employing both zinc chloride and zinc nitrate have been reported [5, 34, 35]. While zinc chloride has a higher solubility in aqueous solution, caution is required as the chloride salts produce extremely high target pressure during irradiation [36]. Also, the zinc chloride solution is highly

corrosive under irradiation conditions, especially in contact with metals containing iron [35]. Therefore, the current standard of practice is to use zinc nitrate solutions [5, 35, 36].

There are currently three known routes to obtain the target solution of [^{68}Zn] zinc nitrate in dilute nitric acid:

1. Vendor supplied solution;
2. In-house preparation of solid [^{68}Zn] zinc nitrate salt followed by dissolution in dilute nitric acid as needed; or
3. In-house prepared [^{68}Zn] zinc nitrate/ dilute nitric acid solution (without first preparing the ^{68}Zn nitrate salt).

4.1.1. Use of enriched ^{68}Zn compounds

It is important to note that when using enriched materials, enriched isotope suppliers tend to report the elemental mass, and not the mass of materials (e.g. 1.000 g elemental ^{68}Zn in the form of [^{68}Zn]ZnO would correspond to ~1.235 g on a balance). Therefore, it is advised to confirm if the mass indicated is 'elemental' or 'molecular'. For the following indications, the mass of materials that one would measure on a balance (i.e. not the elemental mass) is noted. An enriched isotope vendor should provide a certificate of analysis for the batch of material that includes ICP-MS data on isotopic and elemental impurities. One should be aware that the levels of isotopic and elemental impurities may differ significantly by batch and between the metal and oxide forms, which may, in some cases, impact radionuclidic purity and labelling as noted in Section 2.3.

4.1.2. Vendor supplied [^{68}Zn]zinc nitrate target solution

Solutions of [^{68}Zn]zinc nitrate in dilute nitric acid can be obtained from Fluidomica, Lda, Coimbra, Portugal [11]. Four concentrations of [^{68}Zn]zinc nitrate are available (0.5, 1.0, 1.5, and 2.0 M), all in 0.01 N HNO_3. These solutions have expiration dates of one year after date of manufacture. Fluidomica provides a certificate of analysis with their products that includes information on isotopic enrichment and levels of impurities.

4.1.3. Preparation of [^{68}Zn]zinc nitrate salt followed by dissolution in dilute nitric acid

To prepare a 1M, ^{68}Zn-nitrate in 0.8 M HNO_3 nitric acid, weigh out approximately 1.0 g [^{68}Zn]Zn metal powder (MW=68) and add slowly 5-7 mL 70% trace metal grade nitric acid, while keep the flask at 0 ^{o}C with constant stirring. [^{68}Zn]Zn metal powder typically dissolves within 2 h. After complete dissolution of metal powder, nitric acid is removed under vacuum initially at 40 ^{o}C and latter at 110 ^{o}C overall within 2 h. The trace quantity of acid is removed by freeze-drying the ^{68}Zn-nitrate salt overnight. After completion of freeze drying, amount of ^{68}Zn-nitrate salt is weighed as anhydrous ^{68}Zn-nitrate (MW = 192 g/mol) and dissolved in appropriate quantity of 0.8 M HNO_3 nitric acid to make 1M solution. For precaution, obtained solution should pass through a 0.22 μm filter and can be stored at room temperature. ^{68}Zn concentration should be confirmed by use of ICP-MS or MP-AES.

Recipe to prepare 10 mL of a 1M [^{68}Zn]zinc nitrate target solution in 0.8 M HNO_3:

- In a 10 mL volumetric flask, add 1.92 g [^{68}Zn]$Zn(NO_3)_2$ followed by slow addition of 6 mL 0.8

M HNO_3 trace metals basis) with constant swirl.
- After the salt is dissolved, take up the solution to 10 mL using required 0.8 M HNO_3.
- Finally, pass the solution through a 0.22 μm millex GV filter. Store at room temperature.

This method can also be used for the preparation of higher molarity (>1M) [^{68}Zn]zinc nitrate target solution in different normality of nitric acid as needed.

4.1.4. Preparation of target solution of [^{68}Zn]zinc nitrate in diluted nitric acid

To prepare a ^{68}Zn solution, one may start directly from the [^{68}Zn]ZnO.

Recipe to prepare 10 mL of a 1M [^{68}Zn]zinc nitrate target solution in 0.2 M HNO_3:

a) Weigh out approximately 840 mg [^{68}Zn]ZnO;
b) Add 5-6 mL high purity water;
c) Drop-wise add a total of 1.4 mL 70% high purity (e.g. trace metal grade) nitric acid, mixing periodically (e.g. agitate or vortex);
d) Top up the solution to a total volume of 10 mL with high purity water;
e) Wait several hours until clear; and
f) Pass the solution through a 0.22 μm filter. Store at room temperature.

The recipe may be adjusted for desired HNO_3 concentration; however, one must account for the fact that two moles of nitric acid are consumed for each mole of zinc. For example, an excess of 0.3 M HNO_3 would require addition of ~1.5 mL HNO_3 and not 2.1 mL.

4.1.5. Specific [^{68}Zn]zinc nitrate shelf-life

When preparing the [^{68}Zn]zinc nitrate target solutions in-house, it is important to establish a shelf-life [3, 11].

4.2.TARGETRY AND SUPPORTING HARDWARE

4.2.1. Target body

Many designs for solution targets exist, some design considerations are noted in table 7. The specific choice of target may depend on local expertise/existing target/cyclotron setups, availability of cooling, etc. However, many of the targets reported in this publication are commercially available and can be explored as desired.

With regards to contact materials with the solution, success with both niobium and tantalum target bodies have been reported. The use of aluminium has been tested but is not recommended due to the highly corrosive environment during irradiation, which led to pitting of the target walls and loss of the ^{68}Ga activity in the target. With regards to the foil in contact with the solution, success has been noted with both niobium and havar foils, however, depending on the chemical purification method used, the direct use of havar may pose challenges due to the presence of iron. Any O-rings or gaskets used to separate the target liquid from the cyclotron should similarly be selected to not introduce competing metals.

The need for a degrader will depend on the extraction energy of the proton beam and potential co-production of ^{67}Ga as described in Section 2.3. Depending on the target design, the degrader, and/or other foil(s) may be physically separated or directly adjacent to one another.

TABLE 7. EXAMPLE TARGET DESIGN FEATURES

TARGET DESIGN FEATURE	SELECT EXAMPLES
Shape	Cylindrical, conical
Angle of incidence	90°, slanted
Type of target	Completely filled, Headspace, Reflux
Target body material	Niobium, tantalum
Cooling mechanisms	Water only, water and helium
Foil in contact with ^{68}Zn solution	Niobium, HAVAR
Target isolation	Valves closed, pre-pressurized, continued overpressure
Degrader	Built in, upstream of target, not required

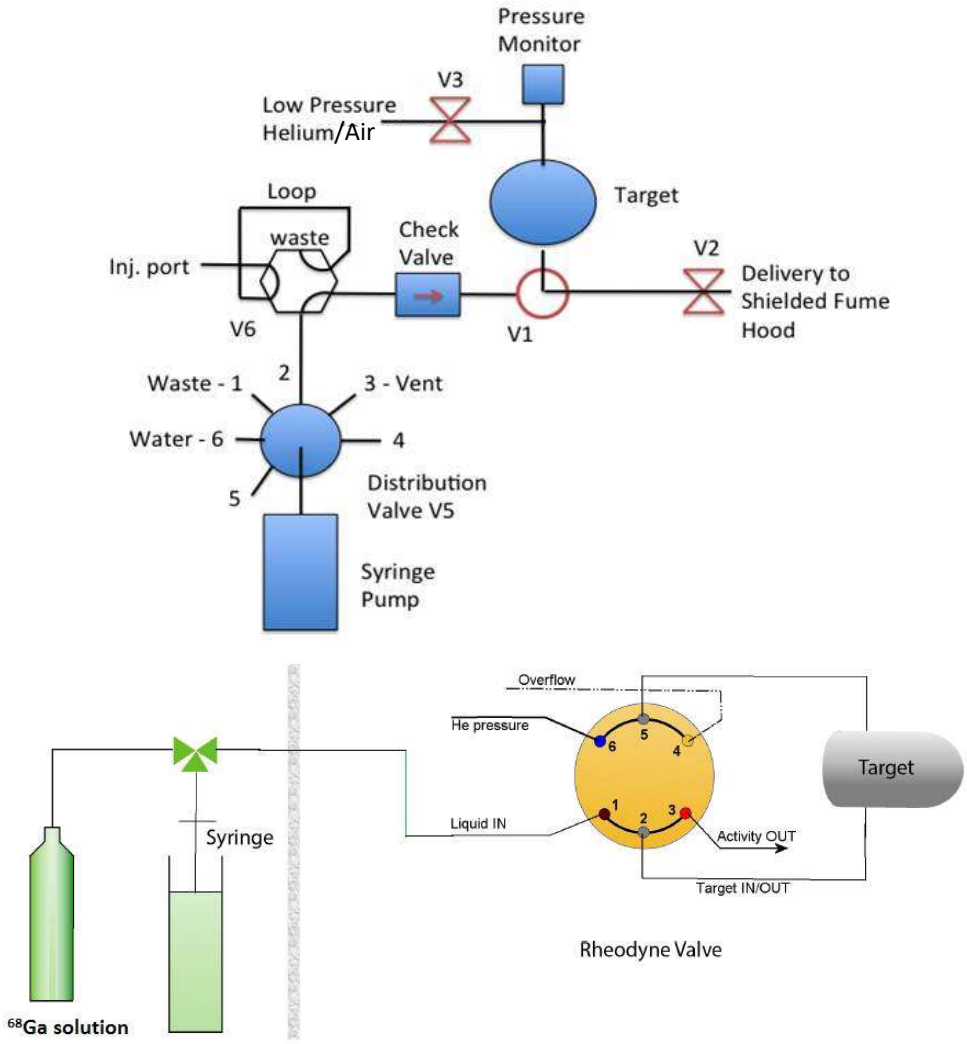
4.2.2. Loading/unloading system

A mechanism for loading and unloading of the ^{68}Zn solution as described in Section 2.3 is required. It is recommended that such a system is automated, both for consistency of loading, and for radiation safety. Such loading systems are common for other liquid targets (e.g. ^{18}F, ^{13}N, etc), and often consist of one (or more) syringe pump, a set of valves, vials with solutions (e.g. ^{68}Zn, rinse solution, etc.), lines (e.g. to connect to valves, connection to the target, connection to the hot cell, etc.) and may also encompass the pressure transducer for the target. Selected examples are noted in fig. 6.

It is important that the loading/unloading system is kept separate from the ^{18}F loading system to prevent chemical cross contamination. One unique consideration to the loading/emptying of ^{68}Zn vs. traditional liquid targets is that one must not use metal (in particular stainless steel) components in contact with the ^{68}Zn solution (e.g. valves, syringes, lines, connectors, etc). PEEK connectors are commonly employed. A pressure sensor may be metallic, but only if kept far from the liquid, [5] reports that the pressure transducer does affect the chemical purity of the target solution. Non-metallic pressure transducer options are also available.

Common line materials may include PTFE, Tefzel, PEEK, etc., however, depending on the transfer distance to the hot cell, and the molarity of the ^{68}Zn, which in turn affects the viscosity, line materials and diameters, may play a role in the ease of transfer.

When loading the solution, depending on the target setup, the target may be loaded at atmosphere, or in some cases may be pre-pressurized (e.g. 5 bar) with helium. As the solution contains significantly more target ^{16}O nuclides than ^{68}Zn, the main product during liquid target production of ^{68}Ga is ^{13}N. Co-production of small amounts of ^{11}C or ^{18}F are also noted. The co-production of these nuclides must be considered in the context of radiation shielding of transfer lines, and the need for appropriately ventilated hot cells.



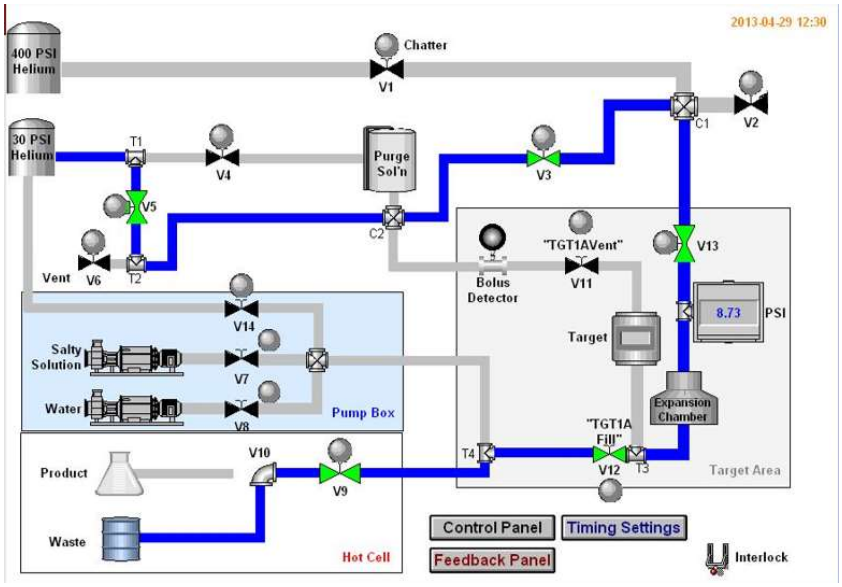


FIG. 6. Example of target loading/unloading systems (courtesy of T. DeGrado and M. Pandey [top], IBA [middle] and C. Hoehr [bottom]).

4.2.3. Irradiation

Several approaches to the irradiation of ^{68}Zn targets have been used as described below:

Approach #1 (beam only): In this strategy, one fills the target, irradiates, and then empties the target liquid to the hot cell/chemistry unit. There is no rinsing that takes place before or after the next irradiation.

Approach #2 (beam + rinse): In this strategy, one fills the target, irradiates, and then empties the target liquid to the hot cell/chemistry unit. In addition, there is a rinse step which takes place following irradiation. Such a rinse may be water or dilute nitric acid. Such a rinse may be discarded to waste, or, might be combined with the downloaded ^{68}Ga target activity. However, if adding to the ^{68}Ga target activity with the intent of increasing the yield, any gain must outweigh the loss due to ^{68}Ga decay during the time it takes to rinse.

Approach #3 (beam + irradiation rinse): In this strategy, one fills the target, irradiates, and then empties the target liquid to the hot cell/chemistry unit and the isotope separation process is commenced. At some time later, there is an irradiation rinse step which takes place, namely – a short (e.g. 10 min) irradiation on dilute nitric acid which is then discarded to waste.

The main intent of the rinse is to remove residual ^{68}Zn, and to reduce the potential for Zn precipitation, whereas the main intent of the irradiation rinse is to mitigate the decline in ^{68}Ga yield and to reduce the frequency of target maintenance. The optimal approach for a site may, however, depends on line lengths/material, frequency of target use, and concentration of both the [^{68}Zn]zinc nitrate and nitric acid.

4.2.4. Maintenance/cleaning

The need for target maintenance/rebuilding may be evidenced by a drop of ^{68}Ga yield, and/or may form part of a site's routine preventative maintenance program. Such target maintenance may include replacement of the O-rings/seals and foils. Use of grease on target window O-rings is cautioned.

Additional cleaning of a niobium target body has also been reported which has included first several soakings of the Nb insert in an alkaline solution, rinsing with ultra-pure water, repeated soaking in 35% nitric acid, and rinsed with water prior to rebuilding and testing the target.

Following any target maintenance, it is recommended to perform a short irradiation with dilute nitric acid to clean the production lines and ensure the system is well sealed. If yields are not resolved following target maintenance, a site may also consider replacement of the transfer lines (e.g. PTFE, Tefzel, polyproylene, PEEK) between target and hot cell.

Most of the liquid targets that were tested in the different experiments with ^{68}Ga production relied on modified ^{18}F targets. All experiments are reporting the use of niobium or tantalum target bodies. Some substantial differences can be noticed regarding the use of foils: Al, Nb, HAVAR. The thickness of the degrader foil is defined by the desire to degrade the proton energy delivered by the cyclotron to ≤~14MeV or below. Several main factors to compare when assessing different methods are the

achieved beam current on the target, acid concentration, the zinc nitrate concentration as well as the target volume. A comparison of liquid targets is seen in table 8.

TABLE 8. COMPARISON OF LIQUID TARGETS

Incoming energy [MeV]	16.4	18	13	13.8	16.4
Effective energy [MeV]	14	14	12		14
Degrader	0.2mm Al	Al	none	none	0.2mm Al
Target foil	25µm HAVAR	35µm HAVAR + 125 Nb	38 µm HAVAR	38 µm HAVAR	Nb+HAVAR 25µm each
Target body	Ta, conical shape	Nb	Nb	Nb	Nb
Target volume	1.6 ml	3.2 ml	0.9 ml	6.6 ml	1.8 ml
Loaded volume	1.8 ml	3 ml	6 ml	6.5 ml	2.2 ml
Nitric acid concentration	0.2 to 1.5M HNO3		1 M	0.5 M	0.2 M
^{68}Zn concentration	1 to 1.7 M	0.5 M	3.9 to 4.7 M	1.3 M	1 M
^{68}Zn required per batch	122 mg @ 1M	100 mg @ 0.5 M		0.5 mg per load	150 mg @ 1M
Cooling	Helium between foils and water at the back	Helium between foils	Helium between foils and water at the back	Helium between foils and water at the back	Water only
Beam current	20-50 µA	45 µA	7 µA	20 µA	30 µA
Saturation yield [GBq/µA]	0.43 @ 1.7M 0.35 @ 1M	0.19 @ 0.5M	0.14	0.22	0.32 @1M
Activity ^{68}Ga EOB [GBq]	4.8 for 1 hour and 30 µA @ 1M	3.7 for 1 hour	0.5 for 1 hour	1.8 for 1 hour	4.4 for 1 hr and 30 µA @ 1M
Brand	In-house design	IBA ^{68}Ga liquid target	In-house design	ACSI	GE ^{68}Ga liquid target
Pre-loading pressure	3 bar	0	0	0	5 bar
Typical max pressure	6 bar	35 bar	31 bar	9 bar	10 bar
References	[5]	[3]	[35]*	[7]	[4]

**Natural abundant zinc was used.*

5. PURIFICATION OF CYCLOTRON PRODUCED ^{68}Ga

As discussed, the direct cyclotron production of ^{68}Ga is based on the proton irradiation of enriched ^{68}Zn target material. The quantity of zinc used in cyclotron targets will vary based on the target design but will be on the order of tens to hundreds of milligrams, and therefore, one must chemically process the irradiated ^{68}Ga/^{68}Zn target to remove the bulk zinc prior to radiolabelling. Furthermore, as ^{68}Ga radiolabelling uses chelation-based chemistry, when addressing ^{68}Ga/Zn separation, it is not only

important to consider separation of the bulk zinc, but also the removal (and/or avoiding introduction) of other metals which may compete with the ^{68}Ga labelling chemistry.

There are many publications that address the wet separation of Ga and Zn from a solution target or dissolved solid target, typically ending with [^{68}Ga]$GaCl_3$ as the product – see table 9 and references within.– Such approaches include solid phase extraction, solvent extraction, and precipitation. In addition, thermal diffusion of ^{68}Ga from foils [25], followed by a final wet chemistry purification [37] has also been reported. While many examples in the literature have been applied to only a solid or liquid target, it is anticipated that many of the separation chemistries described below could be adapted for either solid or liquid targets.

Solid-phase separation is often preferred as it is amenable to radiochemistry automation. Separation of different metals is best achieved using either cation exchange resin or hydroxamate resin [5, 38]. To further reduce the quantity of metallic contaminants, an additional purification step can be performed. The resins widely used are either anion-exchange AG-1X8, TK200 (Trioctylphosphine oxide), UTEVA® (diamyl, amylphosphonate), DGA (tetra-n-octyldiglycolamide) or CUBCX (benzenesulfonic acid + C8). The use of a secondary resin also allows for reduction of the HCl concentration which may be more in line with [^{68}Ga]$GaCl_3$ obtained from generators. However, if, for example, eluting with water, one must consider that the solution will still be acidic (and in some cases, may contain >0.1M HCl) depending on the residual HCl present following loading of the second column. A summary of recent literature using solid phase separation techniques is provided below in TABLE 9.

Other separation methods of Ga from Zn targets using solvent extraction [39, 40] and precipitation techniques [41] have also been reported.

For sites looking to implement cyclotron-based ^{68}Ga production, the choice of chemical separation strategy to implement will depend on local expertise and equipment, however, several factors should be considered, including:

- **Separation time:** With the short half-life of ^{68}Ga, not all published literature methods for Ga/Zn separation (e.g. ^{67}Ga production) will be appropriate due to lengthy processing times;
- **Concentration and volume of acids:** Minimizing concentration and/or volume of acids may ease handling and reduce corrosive environments in the hot-cell, towards equipment, and other surfaces;
- **Use of organic solvents (e.g. acetone, methanol):** Quality control testing of residual solvents must be considered;
- **Commercial availability of reagents:** If the process requires any high quality (e.g. trace metal grade) reagents, these reagents should be readily available. Cost of such reagents should also be considered if the process requires large quantities. Complexity of preparing any non-commercial resins should also be considered;
- **Hot cell compatibility:** A protective layer may be advised in the hot cell compartment where post-processing will take place;
- **Robustness of chemistry:** Chemical separation should be robust in design (e.g. avoid sensitive/manual steps) to ensure a reliable supply of ^{68}Ga; and
- **Ease of automation:** The ability to automate (or semi-automate) the chemistry should be considered, not only for reducing intra- and inter-operator variability, but also to minimize

potential radiation dose to operators. Several commercial units are available for cyclotron-based ^{68}Ga processing.

In addition to the above, ^{68}Ga has one further consideration - the chemical similarity (concentration and pH) of cyclotron-based ^{68}Ga and the [^{68}Ga]$GaCl_3$ that comes from today's generators. Having [^{68}Ga]$GaCl_3$ with a similar quality and formulation is an important step to facilitate a direct replacement/exchange/use of either source as an input to radiolabelling. The final solution ready for labelling should be in low volumes (< 5 mL) for more effective ^{68}Ga-peptide labelling.

TABLE 9. COMPARISON OF DIFFERENT METHODS FOR ^{68}Ga PURIFICATION

(L)liquid target, (S)solid target

APPLIED TO	FIRST RESIN	[ELUENT]	SECOND RESIN	[ELUENT]	SEPARATION TIME	DECAY-CORRECTED YIELD (%)	REFERENCES
L	1.3g AG-50W-X8	7 mL 3 M HCl	Not used			92-96	[5]
L	AG 50 WX8 resin column (7 g)	20 mL 4M HCl	DGA resin (50 mg)	1 mL water	> 1h	92 ± 8	[35]
L	Hydroxamate (in-house) (100mg)	2 mL 2M HCl	Not used			92-96	[42]
L	Hydroxamate (in-house) (100mg)	7 mL 5.5 M HCl	AG-1 X8 anion exchange resin	2 mL water	20-25 min	> 85	[43]
L	Hydroxamate (commercial) (700 mg)	5 mL 1.4M HCL	TK200 (700 mg)	3 mL water	24 min	77 ± 2	[4]
L	SCX (DOWEX 50W-X8, 200-400 mesh),	6 mL 3M HCl	SAX anion exchange resin (BIORAD 1x8, 100 mesh, Ø: 1 cm; h: 2 cm,),	0.1M HCl	30 min	82.7±5.3	[3]
S	AG50W-X4, 100–200 mesh (7g)	5-10 mL 4M HCl	Not used				[18]
S	AG50W-X8 (90 mg)	2 ml 5M HCl	UTEVA® resin (15 mg)	0.1M HCl	45 min	-	[37]
S	5g AG® 50W-X4 cation resin	12 mL 4M HCl	UTEVA® resin (100 mg)	2 mL 0.05 M HCl	10 min	75	[6]
S	Hydroxamate (in-house) (200mg)	2 mL 0.75M HCl	CUBCX strong cation exchange resin (200mg)	NaCl 5 M (500 µL) /HCl 5.5M (12.5 µL)	10 min	88.7 ± 1.4	[19]

5.1.TARGET SOLUTION TRANSFER

In the transfer of liquid target solutions, it is necessary to use transfer lines between the cyclotron and hot cells, for practical and radioprotection reasons. These transfer lines usually consist of Teflon or, preferably, Tefzel, a polymer used in a variety of applications due to its excellent physicochemical properties, such as high resistance to corrosion and a low coefficient of friction.

6. RECYCLING OF ^{68}Zn

Although not a common practice due to the currently affordable prices of commercially available ^{68}Zn or ^{68}Zn zinc nitrate ready to use solutions, should the economics change, ^{68}Zn can be readily recovered from the irradiated solution. Recycling of [^{68}Zn]zinc-nitrate depends on the method of purification used to process ^{68}Ga. Provided no impurities (e.g. iron) were present, then a straight forward multiple dry down with nitric acid can be performed as described below.

The procedure consists of:

1) Evaporation to dryness;
2) Dilution in concentrated nitric acid (> 10 m);
3) Repeat evaporation;
4) Dilution in 10 mm nitric acid; and
5) Evaporation to dryness or preparation of a ready-to-use solution.

Recovery of >90% of the ^{68}Zn is expected. All reagents used should be trace metals grade.

Analysis of the recovered [^{68}Zn]zinc nitrate by ICP-MS or MP-AES is strongly recommended for quality control of eventual metal impurities. As above, [^{68}Zn]zinc-nitrate salt is assumed to be in the form of [^{68}Zn]$Zn(NO_3)_2 \cdot (H_2O)_6$, however, different hydration states are possible, and should be considered.

7. QUALITY CONTROL OF [^{68}Ga]$GaCl_3$

While specific requirements may differ between regulatory jurisdictions or applications, considerations related to [^{68}Ga]$GaCl_3$ quality, and possible test methods, are noted below.

— pH may, for example, be assessed by using pH test strips or a pH meter;
— Chemical purity, including for example, testing for impurities of iron, zinc, and other metals. Example test methods may include atomic absorption, ICP-AES, ICP-MS or colorimetric test strips. Caution should be exercised regarding interpretation of ICP-MS results when assessing components that are not of natural isotopic abundance. Elemental-based techniques might therefore be preferred for quantification of zinc. Furthermore, if the purification process employs organic solvents, testing of such impurities must be considered;
— While assessment of individual metals may be informative, the usefulness of the [^{68}Ga]$GaCl_3$ preparation for labelling may also be assessed by means of titration against an appropriate

chelator;

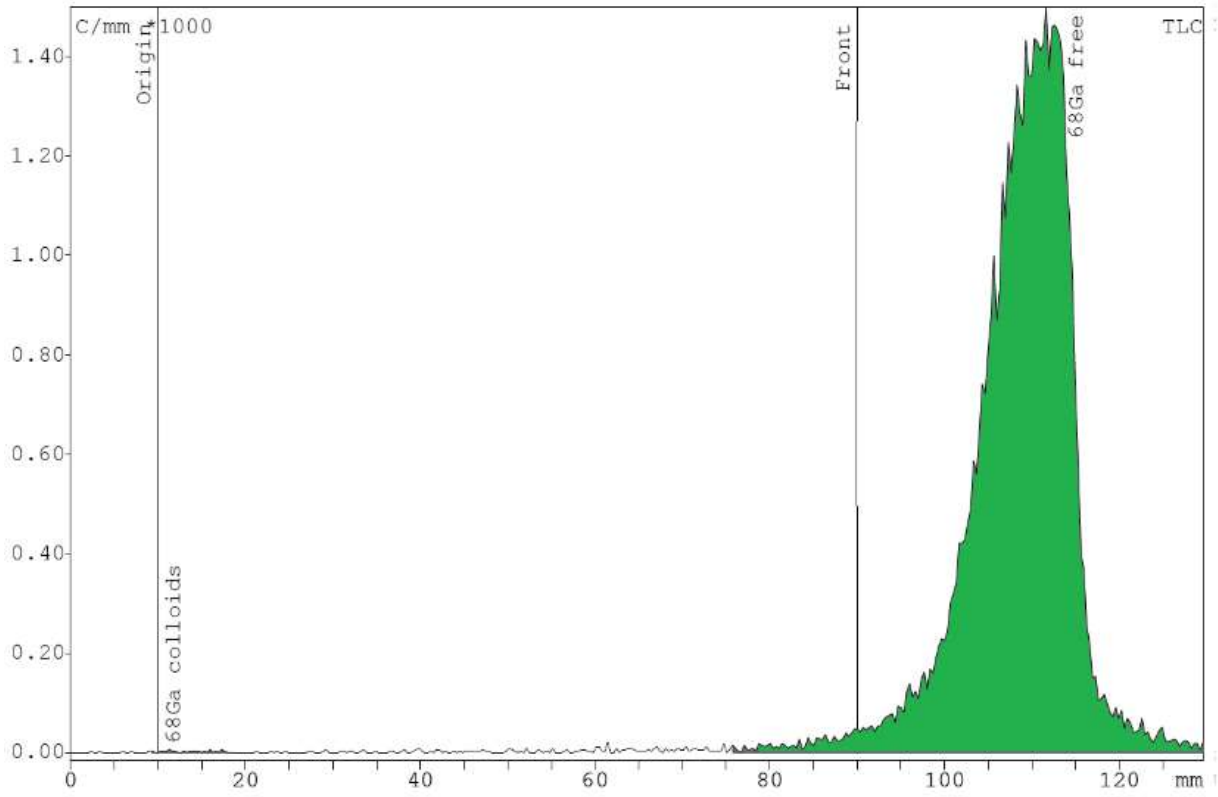
- Radiochemical purity. This may, for example, be assessed via instant thin layer chromatography or high-performance liquid chromatography;
- Radionuclidic purity: Contaminants such as ^{66}Ga or ^{67}Ga, may be assessed via γ ray spectroscopy (e.g. HPGe, LaBr, NaI(Tl), etc). This may be of particular importance if there is a risk in variation in target material enrichment and/or from the selected proton energy due to overlap with the (p,2n) excitation function, as described above. Testing for ^{68}Ge is not necessary for the cyclotron-based route. However, the highest possible radionuclidic purity should be targeted. A new monograph of the European pharmacopoeia (3109) is in preparation for accelerator-produced ^{68}Ga solution. The draft version available from Pharmeuropa (http://pharmeuropa.edqm.eu/) requires 98% radionuclidic purity of [^{68}Ga]$GaCl_3$ produced from a cyclotron, considering the unavoidable co-production of small amount of ^{67}Ga during cyclotron irradiation; and
- Other tests such as identity, appearance, half-life, sterility, bacterial endotoxin, etc. may be necessary for the labelled drug.

The extent or selection of which tests and test methods noted above may also depend on whether one is using the tests for development, periodic testing or routine production purposes. Tests should be adjusted, as appropriate, in the context of the ^{68}Ga-labelled products. As stated above, a new monograph of the Eur. Pharm. (3109) is in preparation for accelerator-produced ^{68}Ga solution and a draft version is available from Pharmeuropa[2].

7.1.RADIOCHEMICAL PURITY

The radiochemical purity (RCP) of purified [^{68}Ga]$GaCl_3$ solution can be assessed using thin layer chromatography (TLC) [44]. TLC can be performed using glass-microfiber silica gel strips (iTLC-SG) and a mobile phase of 0.1 M sodium citrate solution (pH adjusted to 4-4.5). The RCP is determined as the area of the peak with an Rf of free ^{68}Ga divided by the area of all peaks (Rf of colloidal ^{68}Ga should be 0.1-0.2). Plates can be analyzed using a radio TLC chromatograph (e.g. miniGita star, Raytest) (as seen in fig. 7 or by cutting and counting the strip using a dose calibrator. The draft monograph of Eur. Ph. for accelerator-based [^{68}Ga]$GaCl_3$ describes an iTLC-SG based measurement, with an ammonium acetate/methanol based mobile phase, and additional reactivity of the [^{68}Ga]$GaCl_3$ with pentetic acid/ diethylenetriaminepentaacetic acid (DTPA).

[2] Pharmaeuropa can be found at http://pharmeuropa.edqm.eu/



Substance	R/F	%Total %	Type	Area Counts	%Area %
68Ga colloids	0.017	0.11	DD	20.00	0.11
68Ga free	1.278	98.90	DD	17504.00	99.89
-	-	-	-	-	-
Sum in ROI	-	-	-	17524.00	100.00
Total area	-	-	-	17699.00	-
Area (total) RF	-	-	-	452.00	-
-	-	-	-	-	-

FIG. 7. iTLC analysis using a Raytest miniGita detector. Stationary phase: iTLC-SG strips; mobile phase: 0.1 M sodium citrate (pH adjusted to 4-4.5). Rf=0.1-0.2 for colloidal form and Rf=1.0 for free radioisotope.

7.2.RADIONUCLIDIC PURITY

Radionuclidic purity may be assessed using gamma-ray spectroscopy (e.g. HPGe, LaBr, NaI(Tl), etc) specially to assess the presence of radioisotopic contaminants such as ^{66}Ga or ^{67}Ga. This may be of importance if there is a risk in variation in target material enrichment and/or possibly variation in the proton energy due to the competing (p,2n) excitation function, as described in section 2.3. Such ^{6x}Ga impurities cannot be chemically separated, and the labelled compounds will have the same biodistribution and kinetics as ^{68}Ga. Measurements of ^{67}Ga and ^{66}Ga, should be made after a minimum 12 hours decay of ^{68}Ga, and possibly >24 h for lower resolution detectors such as LaBr or NaI(Tl). The impact on the grow of the impurities as a function of time can be seen in section 2.3.

7.3.CHEMICAL ANALYSIS OF [^{68}Ga]$GaCl_3$

As defined in the draft of the new monograph of the European Pharmacopeia for accelerator-produced ^{68}Ga solution the content of Zn and Fe should be below 10µg/GBq. The presence of these impurities will depend on numerous factors including the Zn chemical purity, contact materials, purification methods, solid vs. liquid target, etc. Although these factors will vary based on production methods, Fe and Zn content over the duration of the product shelf-life is noted (fig. 8 and fig. 9) for an example cyclotron-based [^{68}Ga]$GaCl_3$. In this example, for the Zn content, the shelf-life of 5h EOP could be easily achieved whereas for Fe, the limit was too restrictive. If the shelf-life is established at 4h EOP, which is quite reasonable for ^{68}Ga, the specification of 10 µg/GBq can be easily achieved for both Zn and Fe over the entire shelf-life (fig. 8 and fig. 9). An ICP-MS is a highly sensitive technique to determine the iron and zinc content of the final purified solution, however, elemental-based techniques might be preferred for quantification of elemental zinc due to the non-natural abundance which complicates analysis. Semi-quantitative colorimetric test strips (sensitive to the few to tens of µg/mL of iron and zinc) are also available and may be particularly useful for immediate in-house measurement.

If the product to be tested is not [^{68}Ga]$GaCl_3$, but a Ga labelled radiopharmaceutical, quality control should instead be carried out for the respective pharmaceutical. For [^{68}Ga] Edotreotide injection, an European Pharmacopeia monograph (2482) is available, although the specifications are still based on generator-produced ^{68}Ga. This monograph, in conjunction with the draft monograph for accelerator-produced ^{68}Ga solution (found in EP monograph 3109), may serve as useful references.

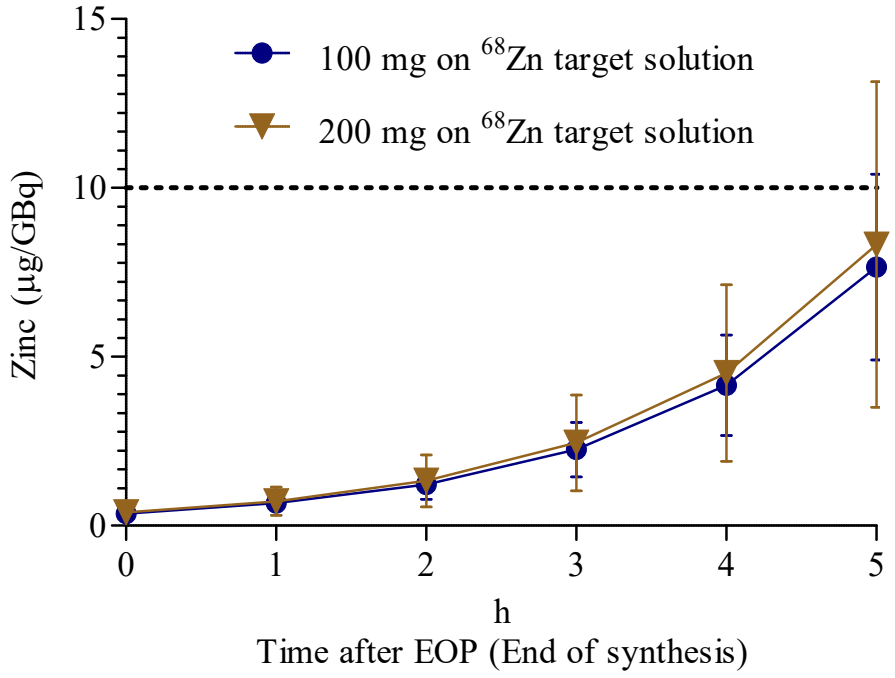


FIG. 8. Average of elemental zinc present in purified [^{68}Ga]$GaCl_3$ post-processed solution until 5h after EOP. Two different starting amounts of ^{68}Zn were loaded and analysed. Limit is 10µg per GBq of ^{68}Ga at end of shelf-life.

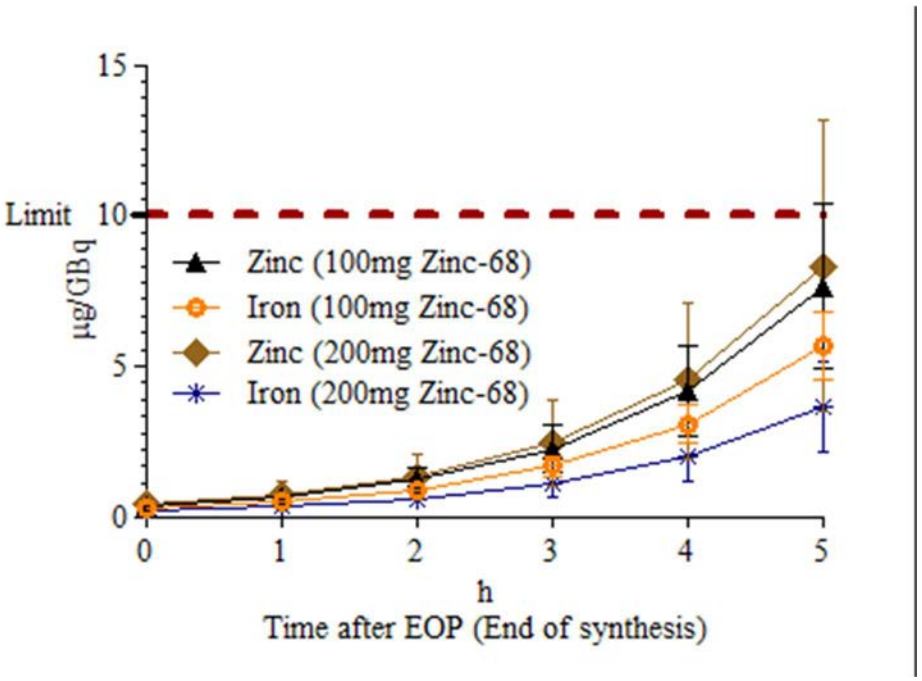


FIG. 9. Average of iron present in purified [^{68}Ga]$GaCl_3$ post-processed solution until 5h after end of purification. Two different starting amounts of ^{68}Zn were loaded and analysed. Limit is 10µg per GBq of ^{68}Ga at end of shelf-life.

8. PRACTICAL CONSIDERATIONS OF WORKING WITH RADIOMETALS

Working with radiometals poses unique work practices that sites which currently produce only ^{18}F may not be familiar with. Extra care and diligence are required to minimize introduction of unwanted metal ions. Iron, copper, and others may compete with gallium when it comes to labelling. While some metals may be removed during the gallium chloride purification steps, the use of disposable plastic contact materials (e.g. spatulas, vials, pipettes, etc.) is recommended at all stages of chemical preparation.

When preparing reagents, avoid placing pipettes, spatulas, vials, etc. onto any metal surfaces. Use of protective surface (e.g. paper towel, bench coat, Bytac®, etc) are recommended.

Some additional tips/suggestions:

1) Store supplies in a dedicated, clean cupboard within bags and/or plastic containers;
2) Work on a clean dedicated tray, and/or ensure a barrier (e.g. small cut-out of fresh bench coat, paper towel, etc.) is put down to protect supplies from the counter top;
3) Do not use standard laboratory glassware (e.g. beakers, graduated cylinders, etc.);
4) Use only 18 MΩ-cm water, ultrapure water, or equivalent. If using a shared laboratory squirt bottle for water, ensure it has only been used with high purity water, and empty/refill the bottle prior to use; and
5) Consider application of Bytac FEP adhesive coating if working in older (e.g. rusty) fume hoods and/or wanting to protect existing hoods.

9. REGULATORY ASPECTS FOR [^{68}Ga]GaCl$_3$

The cyclotron-based production of ^{68}Ga can be easily integrated into routine production at a typical PET production facility (see fig. 1), with such adoption can be further simplified based on the commercially available systems. Nevertheless, for the process to be GMP-compliant, some regulatory aspects must be addressed.

The existing [^{68}Ga]GaCl$_3$ European Pharmacopeia monograph is based on the commercially available ^{68}Ge/^{68}Ga generators (Eur. Ph. 2464). A new monograph (3109) is in preparation for accelerator-produced ^{68}Ga solution[3]. Most of the specifications are similar except for the radionuclidic purity. In the new monograph, a limit of <2% for radionuclidic impurities is proposed for cyclotron produced ^{68}Ga solution. This is meant to account for impurities that arise from the cyclotron process mostly ^{67}Ga and ^{66}Ga mainly because of isotopic impurities in the target and the competing (p,2n) reaction on ^{68}Zn (see section 2.3). This is considered very reasonable as ^{67}Ga citrate has been approved as a human drug many years ago and its Pharm. Eur. monograph (01/2008 0555) specifies a limit of 0.2% for ^{66}Ga. Additionally, both ^{67}Ga and ^{66}Ga are isotopic impurities, therefore share the same biodistribution of ^{68}Ga and the specification can be met over the proposed shelf-life of the product (see section 2.3). The impact of such impurities on radiation dosimetry was recently presented by Graves *et al.* [14].

As an example to test the quality of the labelled pharmaceutical, [3] cyclotron-based [^{68}Ga] DOTA-NOC was obtained with 66.64 ± 7.58 % DC yield in a 20 minute process time, with high radiochemical purity as shown by HPLC (fig. 10). As there is no explicit Eur. Ph. monograph for [^{68}Ga] DOTA-NOC, quality data was compared with relevant specifications of [^{68}Ga] DOTA-TOC (i.e. Edotreotide). The final product was found to meet the relevant specifications of the European Pharmacopeia [^{68}Ga]Ga Edotreotide Injection [Eur. Ph. monograph 01/2013 2482)] with RNP as specified on the draft monograph for cyclotron produced ^{68}Ga (3109), as shown on table 10. The final pH of the product is approximately 5. The product was sterile (as assessed by an independent laboratory) and apyrogenicity (gel-clot) was < 175 UI/V (where V=max volume is meant to be used for the preparation of a single patient dose).

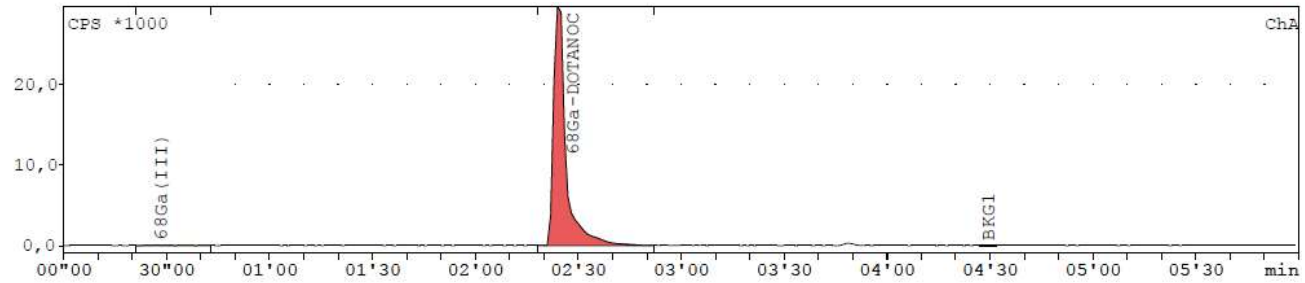


FIG. 10. Analytical HPLC of a final solution of [^{68}Ga]DOTA-NOC (Rt: 2.5 min).

[3] A draft version is available from Pharmeuropa (http://pharmeuropa.edqm.eu/).

TABLE 10. QUALITY CONTROL OF ^{68}Ga-DOTA-NOC

SPECIFICATION	METHOD	ACCEPTANCE CRITERIA	RESULT
pH	Potentiometric	4.0 to 8.0	4.80 ± 0.08
Radionuclidic purity	Half-life determination	62 to 74 min	68.20 ± 0.28
Radiochemical purity	HPLC & TLC	≥ 91%	98.77 ± 1.41 %
Residual HEPES	TLC	≤ 0.2 mg/10ml	< 0.2 mg/10ml
Zinc	AAS	≤ 10 µg/GBq at end of shelf-life	7.99 ± 0,47
Iron	AAS	≤ 10 µg/GBq at end of shelf-life	4.67 ± 1.44
Residual acetone	GC-FID	≤ 50 mg/10ml	0.77 ± 0.56 mg/10ml

In summary, irradiation of ^{68}Zn targets on a cyclotron can readily produce a ^{68}Ga-solution which can be validated as a GMP process. Pharmacopoeia monographs, both for [^{68}Ga]$GaCl_3$ and ^{68}Ga-labelled products are being adapted to include the specifics of the cyclotron process specially in relation with the radionuclidic purity criterion.

10. RADIOLABELLING WITH [^{68}Ga]$GaCl_3$

At present, the majority of ^{68}Ga-labelled compounds used in molecular imaging are somatostatin (SST) analogues. SST receptors are known to be overexpressed in neuroendocrine tumours (NETs) and provide important targets for imaging as well as therapy. SST analogues can be labelled with ^{68}Ga via a bifunctional chelators such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) or 1,4,7-triazacyclononane-N,N',N″-triacetic acid (NOTA), and have demonstrated high ‘in vitro’ and ‘in vivo’ stability, suitable bio distribution, and high receptor affinity [45]. Additionally, DOTA and NOTA conjugates can also be labelled with β^- emitters, such as ^{177}Lu or ^{90}Y, for peptide receptor radionuclide therapy (PRRT) of receptor-positive tumours [46]. The most clinically relevant ^{68}Ga SST analogues used for PET are DOTA-NOC, DOTA-TOC and DOTA-TATE.

The past few years have shown a growing interest in development of tracers targeting the prostate-specific membrane antigen (PSMA). Of those, [^{68}Ga]HBED-CC (PSMA-11, Glu-urea-Lys(Ahx)) being the most studied in the clinical setting [47]. The overexpression of PSMA in the majority of primary and metastatic prostate cancers and a positive correlation of PSMA with traditionally adverse prognostic factors further potentiate PSMA as a promising target for imaging and therapy.

The quantitative incorporation of clinical dose quantities of ^{68}Ga into a small amount of a DOTA- or HBED-CC- based bioconjugate (typically up to 30-50 µg), is strongly pH dependent and is also critically affected by the level of competing metal contaminants [35]. To this end, ^{68}Ga (cyclotron or generator-based) must be adequately free of zinc, iron and other competing metal impurities prior to labelling of bioconjugates. Furthermore, if considering the ability to use either cyclotron or generator-based ^{68}Ga sources as inputs to radiolabelling, it is imperative to have a similar formulation (i.e. acid concentration and solution volume) for the generator eluted and cyclotron-processed [^{68}Ga]$GaCl_3$. It is also critical that all chemicals and solvents are trace-metal grade.

^{68}Ga either from the purification of a cyclotron-irradiated ^{68}Zn target or from a ^{68}Ge/^{68}Ga generator elution can be used directly or preconcentrated in an exchange resin. The obtained ^{68}Ga solution is used to label peptides by chelator-mediation (table 11).

The [^{68}Ga]$GaCl_3$ is mixed with chelator-peptide complex diluted in a suitable buffer at desired pH into a reaction vessel. The reaction solution is heated and allowed to react in accordance with the radiolabelling kinetics of different chelators.

After the reaction, the reaction mixture is transferred to a pre-conditioned C18 reversed phase extraction (SPE) cartridge for purification from unreacted ^{68}Ga species (table 12).

TABLE 11. DIFFERENT CHELATORS FOR $^{68}Ga^{3+}$ RADIOMETAL ION, RADIOLABELLING CONDITIONS AND THERMODYNAMIC STABILITY CONSTANTS (log KML)

CHELATOR	RADIOMETAL ION	RADIOLABELLING CONDITIONS	LOG K_{ML}	REFERENCE
DOTA	$^{68}Ga^{3}$	37-90ºC, 10-30 min, pH 4.0-5.5	21.3 (pM 15.2, 18.5)	[47, 48]
HBED	$^{68}Ga^{3+}$	25ºC, 10-20 min, pH 4-4.5	38.5 (pM 28.6)	[49]
NOTA	$^{68}Ga^{3+}$	25ºC, 30-60 min, pH 4-4.5	31.0 (pM 26.4, 27.9)	[47, 48]
DTPA	$^{68}Ga^{3+}$	25 ºC, 30 min, pH 3.5	24.3, 25.5 (pM 20.2)	[47]

After loading the SPE cartridge and washing with water, the ^{68}Ga-peptide can be eluted with a mixture of ethanol (min 50%) and saline, or phosphate-buffered saline (PBS), followed by saline (or PBS) dilution through a sterile filter into a final sterile vial.

TABLE 12. EXAMPLE OF DIFFERENT REVERSED PHASE CARTRIDGES USED TO PURIFY ^{68}Ga-PEPTIDES FROM UNREACTED ^{68}Ga SPECIES

PEPTIDE	REVERSED PHASE CARTRIDGE	^{68}GA-PEPTIDE TRAPPED ON CARTRIDGE YIELD %	^{68}GA-PEPTIDE ELUTED FROM CARTRIDGE YIELD %	REFERENCES
DOTANOC	Oasis HLB light	94.5	87.3	[50]
DOTANOC	Sep-pak C18 light	91.1	80.2	[50]
PSMA-11	Sep-pak C18 light	95.2-99.2	85.0-98.6	[51]

Optimized methods for radiolabelling peptides with ^{68}Ga for clinical use should provide a radiopharmaceutical within a short period of time with high yield, high specific activity, and suitable radiopharmaceutical quality. Therefore, a simple and reproducible process for labelling peptides with ^{68}Ga independent of the source (i.e. generator or cyclotron) is of importance. Currently, the advantages of using automated synthesis modules coupled with disposable cassettes (and possibly kits) are preferable to facilitate GMP compliance. The choice may depend on patient volume and regulatory jurisdiction.

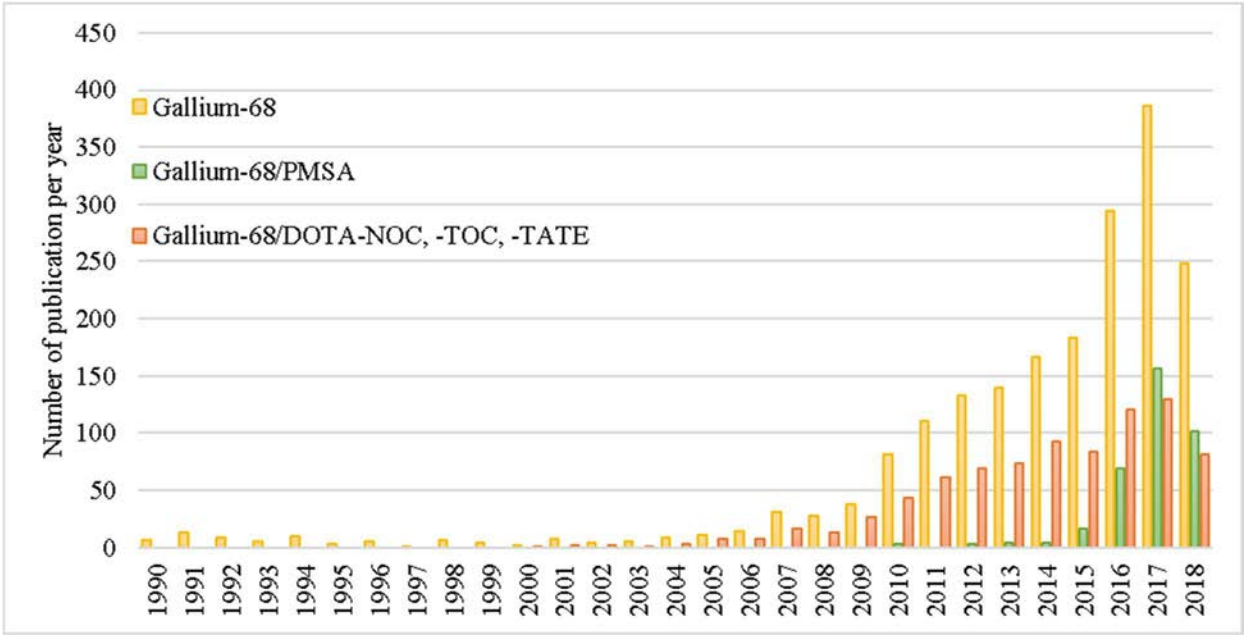


FIG. 11. Publications in PubMed in the past 30 years.

Note that values in Fig.11 are of 2018 and comprised half the year. Search terms: ^{68}Ga, Ga68, Ga-68, Gallium-68 and PSMA, PSMA-11 or DOTA, DOTANOC, DOTATOC, DOTATATE.

In all cases, the final product should fulfil the specifications of the relevant regulatory requirements and may include pH, radionuclidic, radiochemical, and chemical purity as appropriate. Additional validation/testing may be required as radioactivity levels are scaled (e.g. due to potential radiolysis, etc.).

11. AUTOMATION OF THE [^{68}Ga] PEPTIDE LABELLING PROCEDURE

Automation of the synthesis of ^{68}Ga-based peptides improves the robustness of production, reduces the radiation exposure of the operator, and importantly provides traceable documentation of the manufacturing process for GMP compliance. A wide range of semi- or fully-automated modules are available on the market making use of disposable cassettes and dedicated consumables [50, 52, 53]. These consumables offer the possibility of different synthesis routes: pre-concentration of ^{68}Ga on cation or anion exchange resins and direct addition of [^{68}Ga]$GaCl_3$ to a buffer solution.

For the cyclotron-based approach, methods to consider include:

1) Preparation of both [^{68}Ga]$GaCl_3$ and labelling of product on the same automated synthesis unit (i.e. single cassette);
2) Preparation of [^{68}Ga]$GaCl_3$ on one automated synthesis unit, and labelling on another; and
3) Preparation of [^{68}Ga]$GaCl_3$ on one automated synthesis unit, followed by cold kit labelling

Examples of each of the above in the context of cyclotron-based ^{68}Ga are given below.

11.1. PREPARATION OF BOTH [^{68}GA]GACL$_3$ AND PRODUCT ON THE SAME AUTOMATED SYNTHESIS UNIT – EXAMPLE, PSMA–

The following describes the preparation of [^{68}Ga] HBED-CC (i.e. PSMA-11) on a commercial platform, though applicability to other in-house/commercial automated systems may be considered. Namely, a single cassette was prepared to allow for both [^{68}Ga]GaCl$_3$ purification as per [4] followed by subsequent [^{68}Ga] HBED-CC labelling including C18 Sep-Pak purification.

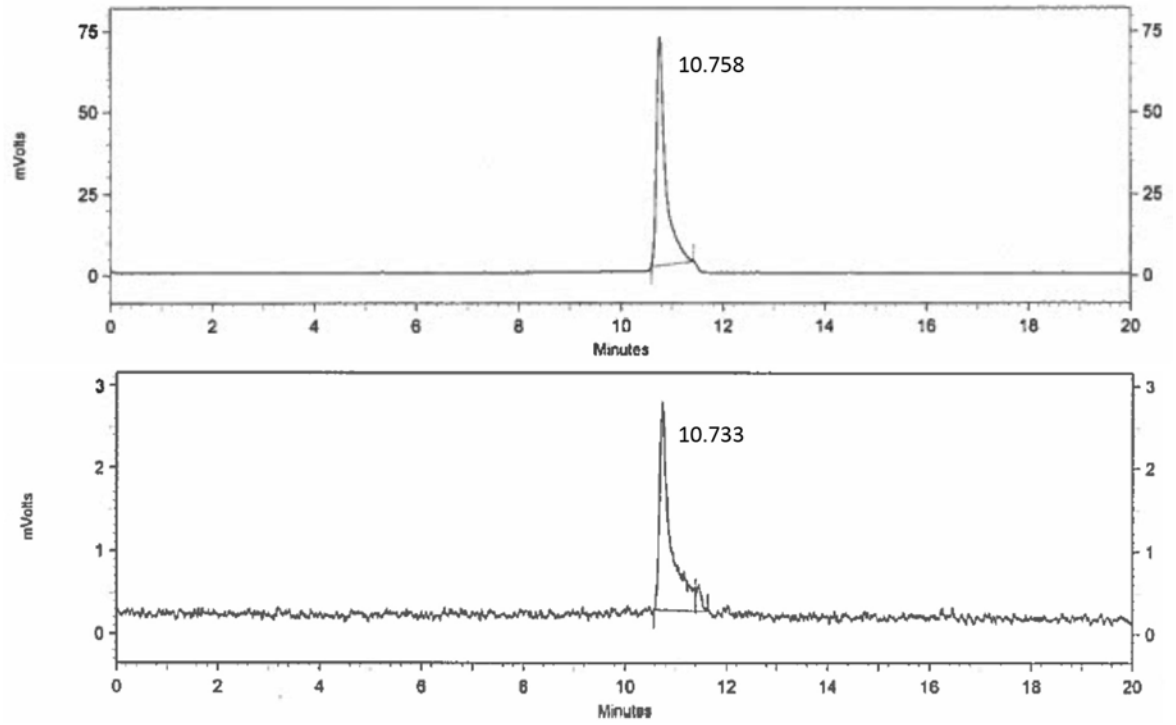


FIG. 12. HPLC radiotracer for both cyclotron- (top) and generator- (bottom) based [^{68}Ga] HBED-CC. (Image courtesy of P.J.H. Scott and M. Rodnick, Dept. of Radiology, University of Michigan)

In short, on a single cassette, the [^{68}Ga]GaCl$_3$ is purified and concentrated, whereby the [^{68}Ga]GaCl$_3$ is then eluted to the reactor which is preloaded with the buffered PSMA-11 precursor. Following the reaction, the labelled product is then purified with a C18 Sep-Pak, rinsed, and finally eluted to a product vial (pre-loaded with the desired volume of PBS).

In-hand [^{68}Ga]Ga-HBED-CC (i.e. PSMA-11) yields of up to 1.85 GBq (50 mCi as per original author) have been reported with a liquid target [50]. An example of a HPLC radiotracer is shown in

FIG. 12, with comparison to a generator-based [^{68}Ga] HBED-CC. Both traces note identical retention times and similarly show no radioactive by-products.

11.2. PREPARATION OF [^{68}GA]GACL$_3$ ON ONE AUTOMATED SYNTHESIS UNIT, AND LABELLING ON ANOTHER –EXAMPLE OF DOTA-NOC–

The following describes labelling of DOTA-NOC. This example uses a particular commercial system, though applicability to other in-house and commercial systems may be considered. In this example, the radiolabelling of [^{68}Ga] DOTA-NOC is performed at the module using the pre-concentration method

following standard procedures as described in the literature [50, 54], whereby process steps can be monitored and controlled with the supplied software, according to the diagram indicated in fig. 13

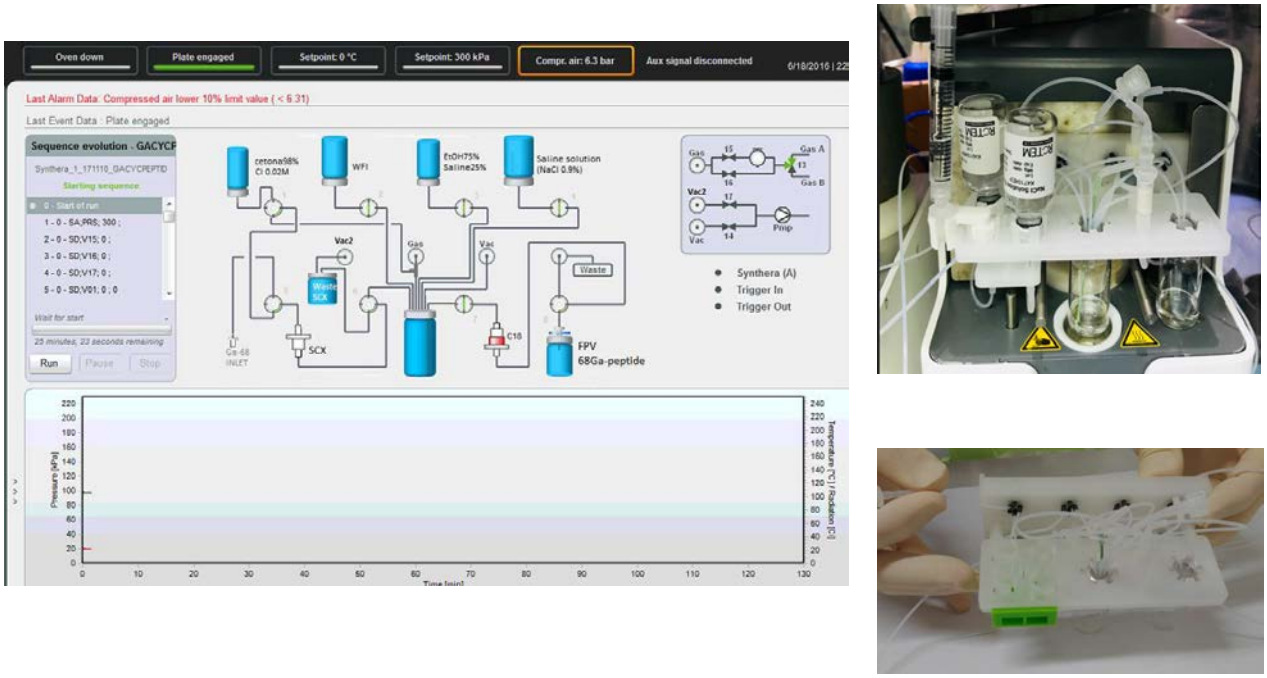


FIG. 13. Module used for the automated synthesis of [^{68}Ga]DOTA-NOC with ^{68}Ga obtained from the purification of an irradiated liquid target. Software view with disposable cassette diagram and automated sequence (left), disposable cassette – IFP (bottom right) and mounted in a synthesis module (top right).

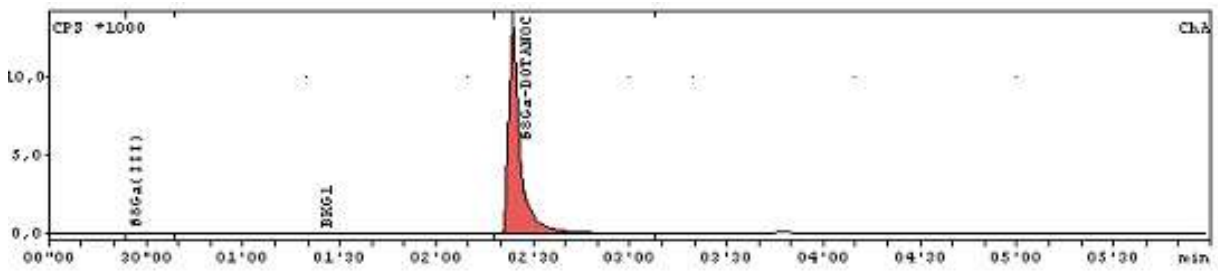


FIG. 14. Radio-HPLC chromatogram of an injection on HPLC of radiolabelled [^{68}Ga] DOTA-NOC synthesized on automated module with disposable single-use commercial available kits and using [^{68}Ga] GaCl3 produced on liquid target. Note: The [^{68}Ga] DOTA-NOC retention time is 2.4 minutes.

In short, the ^{68}Ga eluate obtained from purification of an irradiated solution can be concentrated on a cation exchange SCX cartridge. The cartridge is dried with inert gas to remove traces of HCl and eluted with a mixture of acetone (98%)/HCl 0.02 M directly into the reaction vial pre-loaded with the required amount of DOTA-NOC peptide dissolved in 1 mL of 0.5 M HEPES buffer (pH=3.9). The reaction mixture is then heated at 105°C for 10 minutes. After the reaction, the mixture is cooled by dilution with 5 mL of sterile water and with a steam of compressed air external to the reactor, before being loaded onto the C18 SPE cartridge where a quantitative adsorption of the peptide on the cartridge is obtained. After washing with 5 mL of sterile water, ^{68}Ga-DOTANOC is eluted from the cartridge with

a mixture of ethanol:saline (75:25), followed by dilution with saline solution to obtain pure [^{68}Ga]DOTA-NOC filtered through a 0.22 μm filter to a final sterile vial.

Decay-corrected radiochemical yields of 86.0±5.5% (n=10) are reported considering a 20 minutes labelling step. Example HPLC and TLC traces are given in fig. 14 and fig. 15, respectively.

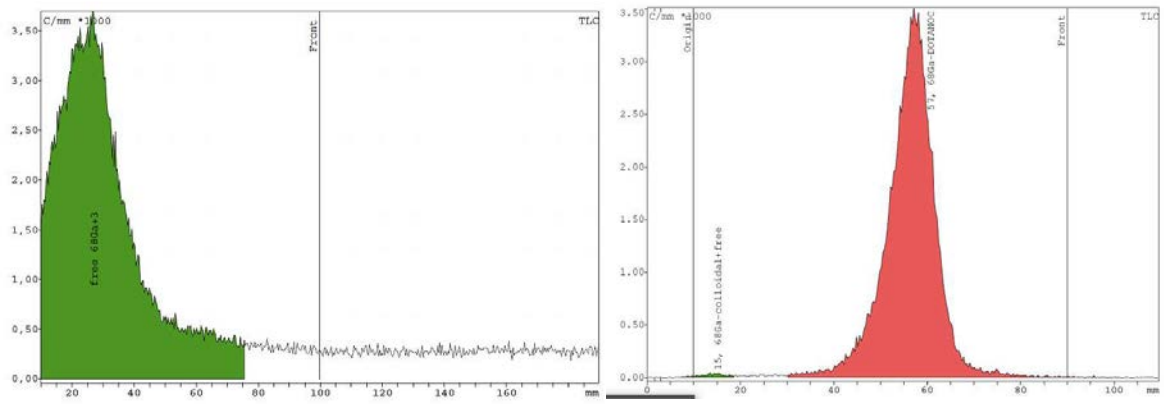


FIG. 15. Radio-TLC chromatogram of cyclotron-based and purified [^{68}Ga]$GaCl_3$ [left] and subsequent automated radiolabelling of [^{68}Ga] DOTA-NOC [right].

11.3. PREPARATION OF [^{68}GA]$GACL_3$ ON ONE AUTOMATED SYNTHESIS UNIT, FOLLOWED BY COLD-KIT LABELLING –EXAMPLE, PSMA–

The following describes labelling of [^{68}Ga] HBED-CC (i.e. PSMA-11). This example is noted again for a commercial platform, though applicability to other in-house and commercial systems may be considered.

In this example, the cassette is prepared to allow for [^{68}Ga]$GaCl_3$ purification with a nominal formulation of 5.0 mL of 0.1 M HCl. The [^{68}Ga]$GaCl_3$ 'product' line is directly connected to the cold-kit activity vial, upon which the combined buffer/PSMA precursor solution is subsequently added. [^{68}Ga] HBED-CC yields in excess of 1.85 GBq (50 mCi as per original author) have been reported for a ^{68}Ga liquid target. A sample of radio-TLC trace measured 4 hours post-labelling (ITLC-SG/1:1 MeOH:1M NH_4OH) is given in FIG. 16, whereby a RCP of 99.4% at 4 hours post-labelling is noted.

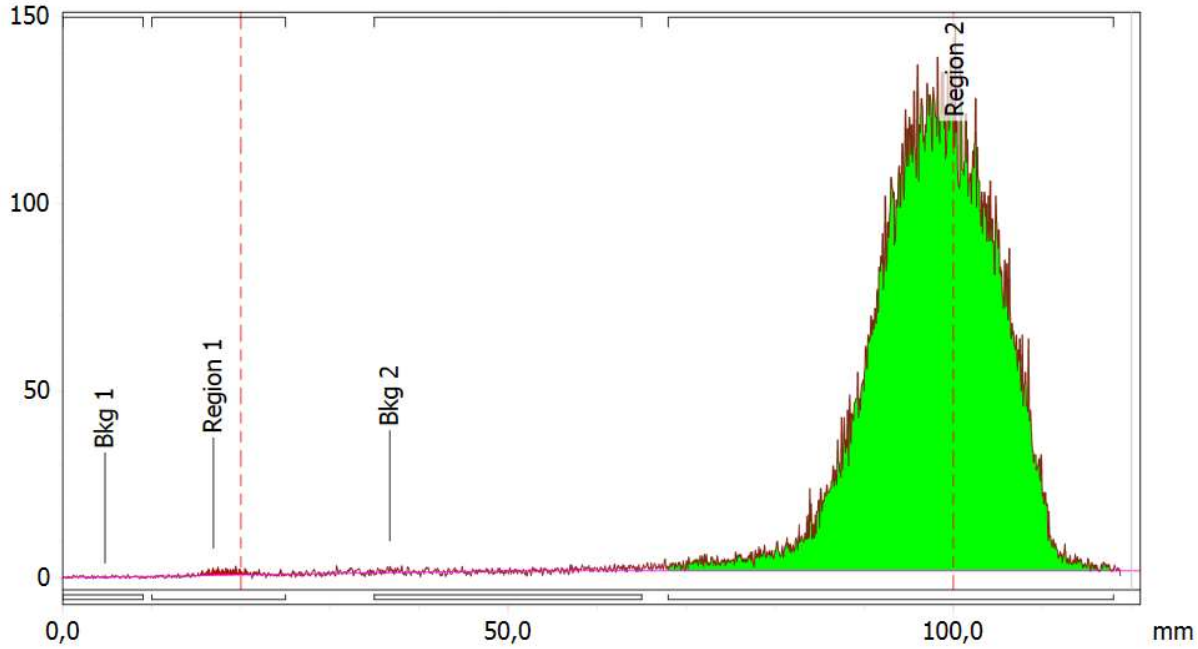


FIG. 16: Radiochemical purity exceeding 99% demonstrated out to 4 hours post-labelling with cyclotron-based cold-kit preparation of [^{68}Ga] PSMA-11 (ANMI kit; figure courtesy of GE/Telix Pharmaceuticals).

Automated synthesis modules based on sterile and single use disposable cassettes and reagents are the most preferred configuration in a clinical routine environment despite their higher cost as they reduce the risk of cross contamination, reduce the radiation exposure to the operator and improve reproducibility. It should also be noted that, where relevant, both hardware and software should be in compliance with good manufacturing procedures (GMP) and good automated manufacturing practice 5 (GAMP5).

11.4. LABELLING OF LYOPHILIZED COLD-KITS WITH [^{68}Ga]$GaCl_3$

As an alternative to the previously described labelling methods (i.e. whereby labelling occurs on a synthesis module), the obtained [^{68}Ga]$GaCl_3$, either from the purification of a cyclotron-irradiated ^{68}Zn target or from a ^{68}Ge/^{68}Ga generator elution can be used directly to manufacturer the ^{68}Ga labelled peptide by using a cold-kit vial, analogous to procedures widely used for ^{99m}Tc radiopharmaceuticals production, e.g. [55]. Namely, the purified [^{68}Ga]$GaCl_3$ is transferred directly to the vial containing the lyophilized precursor pre-diluted with buffer, or vice versa (i.e. diluted precursor/buffer solution may be added to the activity).

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ANNEX I: CONSIDERATIONS OF MEASURING APPARENT MOLAR ACTIVITY

Apparent molar activity (AMA) is a test to assess the impact of competing metals on ^{68}Ga labelling for a given chelator. One reason to perform this test might be to determine the minimum quantity of precursor (e.g. peptide) that is required. Alternatively, if poor labelling yields are noted, one may want to perform such a test to assess, for example, the impact of changing a grade of chemical, contact materials, etc. to one's process.

In short, this test is performed by measuring the radiochemical yield (via TLC) in the presence of different concentrations of a chelator. A test of AMA is specific to a chelator and labelling conditions; thus, this test should be repeated if a different chelator is used. Furthermore, as this test is a gauge of competing metals, it is critical that high purity (i.e. for trace metal analysis) reagents (e.g. water, buffer, acid, etc) are used. If glassware is used for preparing reagents, it is also important that appropriate cleaning procedures are followed (e.g. washing with sulfochromic acid followed by high purity water). Refer to section 8 for further details and considerations on working with radiometals.

The following describes an example measurement of AMA; however, one should adapt the procedure below based on the chelator (e.g. DOTA, NOTA, HBED, etc), buffer (NH_4OAc, NaOAc, etc), optimal pH for the chelator/buffer, etc.

Example AMA measurement via titration with DOTA using NH_4OAc buffer as adapted from [I–1].

Solution preparation/in advance of receipt of activity:

1) Prepare a series of DOTA stock solutions from 10 nM to 10 mM in water. All solutions are mixed before dilution. It may be advantageous to prepare on a log scale (e.g. 10 nM, 30 nM, 100 nM, etc.). Include preparation of a blank "0 nM" vial. (Note: mw = 404.42 (anhydrous basis)); and
2) Prepare 1M NH_4OAc and adjust pH of the solution to 4.5 with acetic acid.

Testing AMA of [^{68}Ga]$GaCl_3$ with DOTA:

1) Adjust the [^{68}Ga]$GaCl_3$ solution with NH_4OAc buffer (1M pH = 4.5) to a final pH of 3.0-3.2;
2) Start with 0 nM, add 150 µL of each of the above DOTA stock solutions to 1 mL microcentrifuge tubes;
3) Next, and once again start with 0 nM, add 10-20 µL of pH-adjusted [^{68}Ga]$GaCl_3$ to each tube to give a total volume of 160-170 µL, the pH should always be 3-3.2;
4) It is anticipated that the activity of each vial will be ~5-10 MBq, however, this will depend on the setup in question. Record the activity and corresponding measurement time for all vials (or a subset of the vials if pipetted radioactivity is consistent);
5) Mix (e.g. vortex) and heat at 80ºC for 30 min (or 100ºC for 12 min);
6) Run a TLC of each sample by spotting either (depending on site availability):
   a. ITLC-SG, and developing using 1/1 MeOH/10% NH_4OAc, or
   b. C18, and developing using 0.1M Sodium citrate, pH 5.5

Analysis of AMA

For the samples above, the percentage of complexation is determined by TLC. When using ITLC-SG, [^{68}Ga]$GaCl_3$ remains at the origin, and complexed [^{68}Ga]Ga-DOTA migrates with the solvent front. If using a C18 solid phase, the reverse is true.

It is important to note that two methods for calculating AMA are reported in the literature. As values may vary between the two methods, it is critical to state which analysis method is used. The two methods are described as follows:

(1) Method 1: Determining AMA based on complexation beyond a given percentage (e.g. >90%, >95%, etc.).

If we take for example the curve below, and note the quantity of chelator (i.e. DOTA) where >90% complexation is realized (i.e. 1E-6 mmol, or 1 nmol), and if we assume the activity of the sample was 5 MBq measured at 2 hours post-EOB, then the AMA for DOTA would be calculated at: 5 MBq/nmol (or 5 GBq/µmol) at 2 hours post-EOB.

It is important to state the reference time for which the data is recorded. For example, if decay correcting to EOB, for the case of ^{68}Ga, this would then translate to an AMA for DOTA of 17 MBq/nmol (or 17 GBq/µmol) at EOB. It is also important to state the threshold (e.g. >90%, >95%, etc) and labelling conditions (e.g. pH) that were used (Figure I–1).

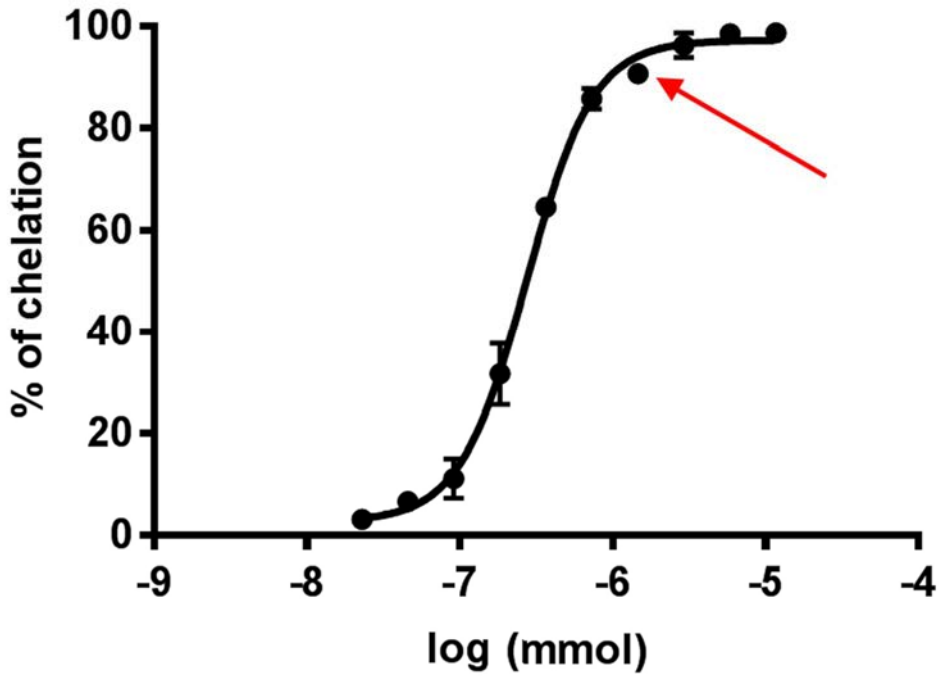

FIG. I–1. Example AMA curve noting first data-point for which DOTA complexation is greater than a noted threshold (e.g. >90%). Figure courtesy of B. Guérin.

(2) Method 2: Determining AMA based on complexation at 50%, then dividing by 2.

Given that the method above is sensitive to the threshold selected, it may be preferred to identify the quantity of chelator where 50% complexation is noted.

If we take for example the curve below, and note the quantity of chelator (i.e. DOTA) where 50% complexation is realized (i.e. 2.7E-7 mmol, or 0.27 nmol), and if we assume the activity of the sample was 5 MBq measured at 2 hrs post-EOB, then the 50% complexation would be calculated to be 5 MBq/0.27 nmol = 18 MBq/nmol at 2 hours post EOB.

However, since this is only at 50%, and since the quantity of chelator is on the denominator, the AMA for DOTA is then calculated as 9.2 MBq/nmol at 2 hrs post EOB (i.e. 5 MBq/0.27nmoL x 50%) (Figure I–2.).

As above, it is important to state the reference time for which the data is recorded. For example, if decay correcting to EOB, for the case of ^{68}Ga, this would then translate to an AMA for DOTA of 31 MBq/nmol (or 31 GBq/μmol) at EOB.

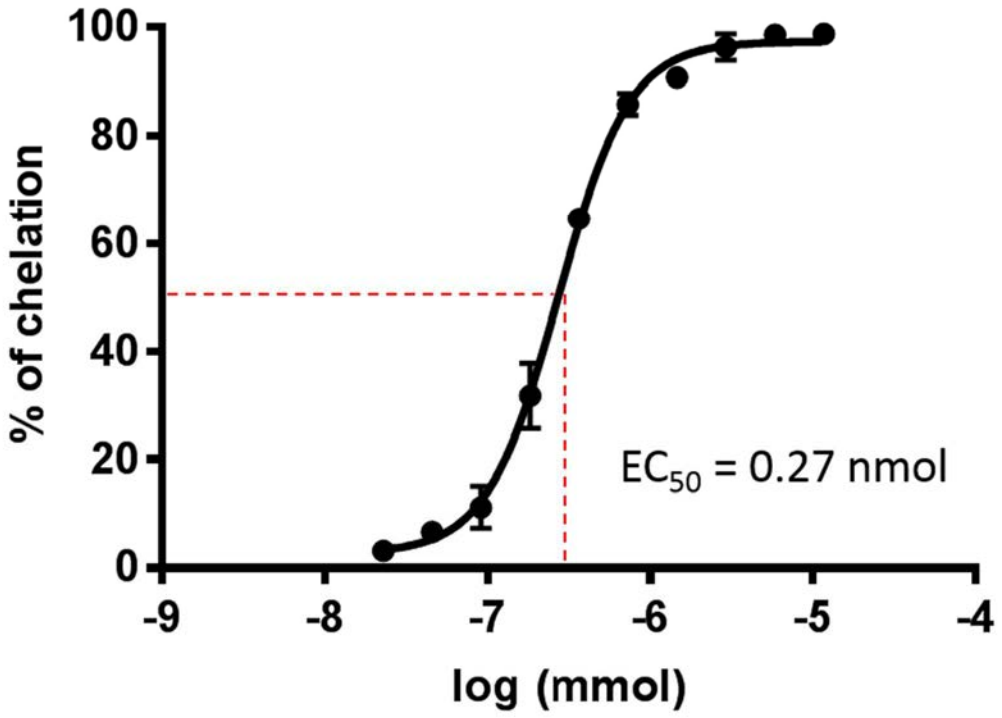

FIG. I–2. Example AMA curve noting complexation at 50%. Figure courtesy of B. Guérin.

REFERENCE TO ANNEX I

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ANNEX II: SUMMARY OF COUNTRIES' PRESENTATIONS

II.1 CYCLOTRON PRODUCTION OF ^{68}Ga via ^{68}Zn(p,n)^{68}Ga REACTION USING PRESSED TARGET: EXPERIENCE AT THE SHERBROOKE MOLECULAR IMAGING CENTER (CIMS) (B. Guérin, Canada)

II.1.1. Introduction

^{68}Ga (^{68}Ga, $T_{1/2}$ = 68 min) gives rise to several applications in nuclear medicine [II–1]. A Phase-II, prospective, open label, was initiated in June 2016 at the Sherbrooke Molecular Imaging Centre (CIMS, Sherbrooke, Qc, Canada) to assess the safety of ^{68}Ga-DOTA-TATE injection in patients with suspected or diagnosed with tumours expressing somatostatin receptors. Since, more than 600 patients were imaged at the CIMS with ^{68}Ga-DOTA-TATE. Currently, ^{68}Ga is produced via ^{68}Ge/^{68}Ga generator with limited lifetime restricting the number of patient per production. With the growing demand of over 300 patients in the last 7 months, the need to increase our ^{68}Ga production capacity is highly required. An alternative method to increase amount of ^{68}Ga is by cyclotron using high enriched ^{68}Zn with liquid [II–2, II–3] and solid [II–4] targets via the ^{68}Zn(p,n)^{68}Ga reaction. According to cross section data, high production yield of ^{68}Ga can be achieved using incident proton energy between 4.5-14 MeV [II–5]. The aims of this study were (i) to improve production yield of ^{68}Ga using pressed targets and (ii) the purification of ^{68}Ga by using an automated cassette-based purification process in order to obtain $^{68}GaCl_3$ with high effective specific activity (ESA) for labelling of DOTA-TATE and other radiopharmaceuticals.

II.1.2. Material and methods

^{68}Ga was produced by cyclotron using ^{68}Zn pressed target mounted on custom-made target supports. The optimal pressed target thickness was calculated for a proton energy range of 4.5-14 MeV using SRIM software [II-6]. Using a manual operated digital hydraulic press (Module number: 3912, Carver, Inc, Wabash, IN, US), different targets were then prepared using 95, 164 and 250 mg of enriched ^{68}Zn powder (99.26%, ISOFLEX, USA) to prepare pellets of 6, 8 and 10 mm diameters, respectively. Irradiations were performed using TR19 and TR24 variable energy cyclotrons (ACSI, Richmond, BC, CA) using a straight 90° target station (ACSI) with a beam diameter of ~10 mm. After irradiation pressed target was dissolved in 7M nitric acid. After pH adjustment of the irradiating solution (pH 2-2.5) with a base (NH_4OH or NH_4HCO_2), the purification process was performed using a Mini AIO Trasis module. The crude ^{68}Ga solution was loaded on hydroxamate resin (200 mg) that was washed with 0.01N HCl to remove parent isotope Zn. ^{68}Ga was eluted from the hydroxamate resin with 0.75N HCl solution. After dilution with 0.01N HCl to 0.2N, the resulting ^{68}Ga solution was loaded on a cation exchange CUBCX resin [II-7] to removed residual metal impurities. $^{68}GaCl_3$ was then eluted using NaCl 5 M (500 µL)/HCl 5.5N (12.5 µL) solution. After purification, the ESA was calculated via titration with DOTA. $^{68}GaCl_3$ (0.5 mL) was directly used for DOTA and DOTA-TATE radiolabelling.

II.1.3. Results

The optimal pressed target thickness was estimated at 0.5 mm for a proton energy range of 4.5-14 MeV. Preparation of pressed target is fast taking place in 10 min. The production yield results for 6, 8 and 10 mm pressed target were 2.7 ± 0.2, 4.2 ± 0.3 and 4.9 ± 0.4 GBq/µA·h, respectively. Up to 68 GBq of ^{68}Ga was prepared using home-made aluminium coin shape target support. The total purification time

was 11 min including the dissolution of pressed target. The overall recovery yield of $^{68}GaCl_3$ was 88.7 ± 1.6% in a total volume of 0.5 mL of saline/HCl solution. The ESA was 43.3 ± 0.8 GBq/μmol (134 ± 8.6 GBq/μmol at EOB). The radiolabelling yields of DOTA and DOTA-TATE peptide were 96.3 ± 1.3% and 93.2 ± 1.7%, respectively.

In conclusion, these results show that irradiation of ^{68}Ga pressed target is an effective process. The cassette-based purification process developed is rapid, simple, efficient and lead to high radiochemical yield and ESA of $^{68}GaCl_3$.

II.2 CYCLOTRON PRODUCTION OF ^{68}Ga VIA $^{68}Zn(p,n)^{68}Ga$ REACTION USIG SOLID AND LIQUID TARGETS: EXPERIENCE AT TRIUMF AND BCCA (C. Hoehr, Canada)

II.2.1. Fused target (TRIUMF)

To produce the fused target, 0.17 g of natural abundant Zn pellets from Sigma-Aldrich were placed into a 0.3 mm recess in an aluminium disk. The disk was placed on a hotplate and heated up to 550°C to melt the pellets. About 100 % bulk density was achieved.

The disk was then mounted in an in-house manufactured solid target holder at the TR13 cyclotron. The irradiation used a beam of 10 μA of 112.8 Me protons for 15 minutes. The target plate was left on the cyclotron overnight to reduce dose exposure to the cyclotron staff and experimenter.

After removal of the target plate, no visible effect due to the irradiation was observed. The ^{66}Ga activity was measured to be 400 MBq decay corrected. We estimate that about 3 GBq of ^{68}Ga was produced.

The target was dissolved in 6N HCl in about 5 minutes. Separation was performed according to [II-8] with an efficiency of~95%.

II.2.2. Liquid target (TRIUMF and BCCA)

^{68}Ga was produced at TRIUMF in a standard liquid target. This target geometry is routinely used to produce ^{18}F at the TR13 cyclotron. 75 grams of natural abundant Zn(NO3)2 x 6H2O was dissolved in 22.7 ml H2O and 2.3 ml conc. HNO3 at 40°C and stirred for several hours. The solution was then transferred into the target body via our in-house manufactured loading system. Irradiation took place with a proton beam of 12 MeV energy and a beam current of 7 μA. The solution was then transferred into a vial in an adjacent hot cell. The yield for a one-hour irradiation was 445 MBq decay corrected. Separation was performed with a AG 50W-X8 column as well as a DGA resin column. The efficiency was 92 %. Test labelling was carried out with [^{68}Ga] DOTA-NHS-Ester with an efficiency of over 85%.

At the Vancouver BCCA, 2.5 grams of enriched ^{68}ZnO (98% enriched) was dissolved in 130 ml of 0.5M HNO3, evaporated, and then added to 25 ml of 0.5 M HNO3. The target solution was transferred via an in-house designed loading system into a slanted target by ACS (Richmond, BC). The target was irradiated with 18 μA of 13.8 MeV protons for 108 minutes. The yield of ^{68}Ga was measured to be 133 GBq decay corrected. The produced ^{68}Ga was used to label Ga-DOTA-TOC. Generator-produced was used to label as well and PET images as well as biodistribution was carried out to compare the two different ^{68}Ga sources. No difference was found.

II.3 LIQUID TARGETS CYCLOTRON PRODUCTION OF RADIOMETALS: COIMBRA EXPERIENCE (F. Alves, Portugal)

The experience at ICNAS (Institute for Nuclear Sciences Applied to Health, University of Coimbra) in the cyclotron production of radiometals using liquid targets was presented, mainly for the production of ^{68}Ga, but also for the production of ^{64}Cu (reporting the production of clinical GMP compliant doses of labelled ATSM) and of the also ^{61}Cu (whose physical properties – half-life and positron energy – may potentiate its use in the forthcoming years).

About ^{68}Ga production from liquid targets, a project developed together with IBA, were details of target irradiation total yields were presented. A fully automated purification of the cyclotron outcoming solution, based in Synthera Extension commercial modules was disclosed, as well as labelling strategies that lead to clinical GMP compliant doses of [^{68}Ga] DOTA-NOC and [^{68}Ga] PSMA-11. Practical aspects of the complete process were discussed, mainly regarding metal contamination. Quality control results were presented, and regulatory aspects were addressed.

II.4 EXPERIENCE OF LIQUID TARGET AT THE MAYO CLINIC (T. DeGrado, M. Pandey, USA)

Dr. DeGrado presented the work of his laboratory in collaboration with Dr. Mukesh K. Pandey on the development of a liquid target for production of radiometals including ^{68}Ga. The historical development of the targetry was reviewed, starting with initial productions of ^{89}Zr from the inexpensive ^{89}Y [II-9]. Early work employed a commercial ^{18}F-fluoride production target (Bruce Technologies TS-1650). The initial runs identified two major problems for irradiation of yttrium salts in the target: excessive pressure rise and formation of precipitate within the target. Radiolytic decomposition of water in the solution was determined as the primary driver of the pressure rise in the target. The precipitate was identified as yttrium hydroxide by IR analysis. The identified problems were mitigated by employing nitrate salts of the metal ions within the target solution and inclusion of dilute nitric acid to keep the yttrium nitrate salt in solution [II-10]. To further mitigate the pressure rise, heat transfer characteristics were improved target volume by use of a small target volume (1.6 mL) and conical target geometry. Thus, a new target was developed, BMLT-2, that made use of these findings and employed a 0.2 mm Al degrader foil and a 25 mM HAVAR target window foil. The foils were separated by a helium cooling section and the back of the target was cooled by water.

The lessons learned from ^{89}Zr productions were then applied to ^{68}Ga production in the liquid target. Enriched ^{68}Zn nitrate salts with dilute nitric acid were employed as the target solutions. ^{68}Ga production yield and purity data were presented using the BMLT-2 liquid target [II-10]. The ongoing work on optimization for production yield was emphasized, although current yield of 4.8±0.7 Gbq (129±19 mCi as per original author) for 60 min irradiation at 30 μA (decay corrected to EOB) is sufficient to proceed for use in clinical trials with PSMA, DOTATATE and other important ^{68}Ga radiopharmaceuticals. The initial isotope purification methodology employed separation of ^{68}Ga from ^{68}Zn using AG-50W-X8 cation exchange resin. This method was successful but the use of organic solvents and HBr needed for this method was undesirable. Therefore, a novel method for isotope separation was developed employing in-house developed hydroxamate resin. The target dump was neutralized to a pH range 5.7-6.1 before trapping on the hydroxamate resin [II-11, II-12].

The ^{68}Zn was eluted from the hydroxamate resin using dilute nitric acid, then the ^{68}Ga was eluted in HCl (as $^{68}GaCl_4^-$ ion) and concentrated on a AG 1X8 anion exchange resin, then eluted from the AG

cartridge in 2 mL of water. Labelling steps proceeded after neutralization of this solution with sodium acetate. Overall efficiencies of isotope separation were in the 80% range. Automation of the isotope separation was developed on both FASTlab and Trasis radiochemistry modules. Our multi-isotope target filling system was described which is able to load target solutions from the radiochemistry lab through long delivery lines into the cyclotron vault. Within the vault there is a valve box and pressure transducer. The pressure transducer employs a tantalum isolator foil for separation of the pressure transducer from corrosive acid of the target. The pre-amplifier of the pressure transducer is located outside the neutron field of the cyclotron to avoid degradation. A third-generation liquid target was developed in collaboration with GE Healthcare that eliminated the helium cooling section of the target and employed a HAVAR/Nb sandwich foil for the target window.

II.5 ^{68}Ga PRODUCTION, IBA (S. Bertrand, Belgium)

IBA presented its solutions for the cyclotron production of ^{68}Ga. The collaboration with the university of Coimbra leaded to the industrialization of the patented process for producing and purifying ^{68}Ga using a liquid target on small medical cyclotron. This process allows to recover $GaCl_3$ with high levels of purity, and can then be used for labelling (PSMA, DOTATATE, DOTANOC) with Synthera® module, cold kits or other synthesizers. IBA and the University of Coimbra are actively providing data to the European Pharmacopeia for the establishment of the cyclotron-produced Ga68 monograph.

The different consumables, such as target material, reagents and cassettes are today commercially available at different suppliers. The SOPs, users guide, and technical datasheet have been created in order to facilitate the technology transfer for IBA customers. IBA solutions for ^{68}Ga solid target production were also introduced, using existing IBA compact or high power solid target station, an electroplating system for the target manufacturing, and the dissolution/purification modules commercially available.

II.6 CYCLOTRON-BASED ^{68}Ga PRODUCTION, GE (K. Gagnon, Sweden)

This presentation included both the solid and liquid target-based production of ^{68}Ga, with a focus on liquid targets on the PET-trace cyclotron. High level details on the target (e.g. materials, degrader/energy, cooling, etc.) were provided. A comparison of several liquid-target ^{68}Ga based separation chemistries, as reported in the recent literature was provided, i.e. [II-2, II-11, II-13, II-14]. These methods were compared with regards to quantity of HCl, use of organic solvents, the availability of commercial resins, and whether the [^{68}Ga]$GaCl_3$ was formulated with an HCl concentration comparable to that of today's ^{68}Ge/^{68}Ga generators. A two-column purification [II-15] was then described, and implementation on the FASTlab chemistry platform noted. With GE's involvement in contributing data to the European Pharmacopoeia, there has been a strong focus on the quality of the produced [^{68}Ga]$GaCl_3$. QC data was provided, and included half-life, pH, iron/zinc, radiochemical purity, radionuclidic purity, etc [II-15]. In addition, two detailed experimental tables were provided that reported on:

a. Radionuclidic purity as a function of energy. This was assessed for 4 energies (13-15 MeV) with two commercially available lots of ^{68}Zn; and
b. Metal analysis by IPC-MS screening both pre and post purification for 11 elements of known contact materials/potential concern related to the ^{68}Ga chemistry.

The presentation concluded with posing questions related to the importance of the regulatory framework on how the cyclotron-based ^{68}Ga can be best introduced given the existing use of ^{68}Ge/^{68}Ga generators.

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ABBREVIATIONS

AMA	Apparent Molar Activity
CRP	Coordinated Research Project
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
EOB	End of Bombardment
EOP	End of Purification
EP	Electro Plated
GAMP5	Good Automated Manufacturing Practice 5
GMP	Good Manufacturing Practice
PSMA-11	HBED-CC-PSMA: 3S,7S)-22-(3-(((2-((5-(2-Carboxyethyl)-2-hydroxybenzyl)(carboxymethyl)amino)ethyl)(carboxymethyl)amino)methyl)-4-hydroxyphenyl)-5,13,20-trioxo-4,6,12,19-tetraazadocosane-1,3,7-tricarboxylic acid
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HPGe	Higher Purity Germanium
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectroscopy
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
i-TLC	Instant- Thin Layer Chromatography
MP-AES	Microwave Plasma Atomic Emission Spectroscopy
NET	Neuroendocrine Tumour
NOTA	1,4,7-triazacyclononane-1,4,7-triacetic acid
PBS	Phosphate-buffered saline
PEEK	PolyEther Ether Ketone
PET	Positron Emission Tomography
PRRT	Peptide Receptor Radionuclide Therapy
PSMA	Prostate-Specific Membrane Antigen
PTFE	PolyTetraFluoroEthylene
RCP	Radio Chemical Purity
SRIM	Stopping and Ranges of Ions in Matter
SST	Somatostatin
TLC	Thin Layer Chromatography
Zn	Zinc
[^{68Ga}] DOTANOC	Ga-68-Nal3-octreotide
[^{68Ga}] DOTATATE	Ga-68-Tyr3-octreotate
[^{68Ga}] DOTATOC	Ga-68-Tyr3-octreotide

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