2016 臺灣醫用迴旋加速器學會年會
調製法規協和暨品質輔導相關訓練第二次教育訓練暨討論會

鍺-68/鎵-68發生器
法規與輻防議題

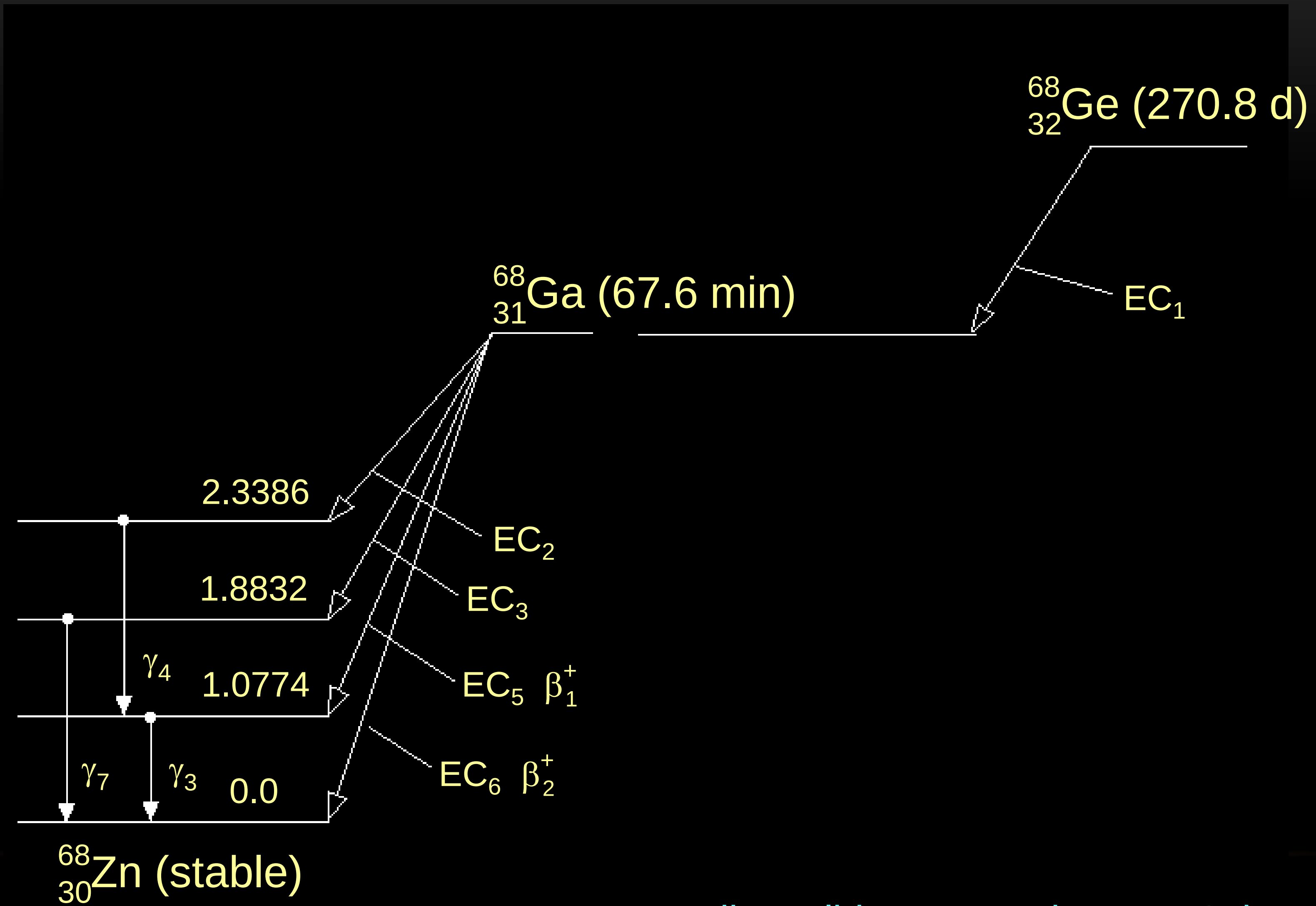
魏孝萍

臺灣醫用迴旋加速器學會

衛生福利部食品藥物管理署105年「斷層掃描用正子放射性同位素調製法規協和研究暨品質輔導相關訓練」計畫

What is a ^{68}Ge/ ^{68}Ga Generator?

Decay Schemes of ^{68}Ge-^{68}Ga

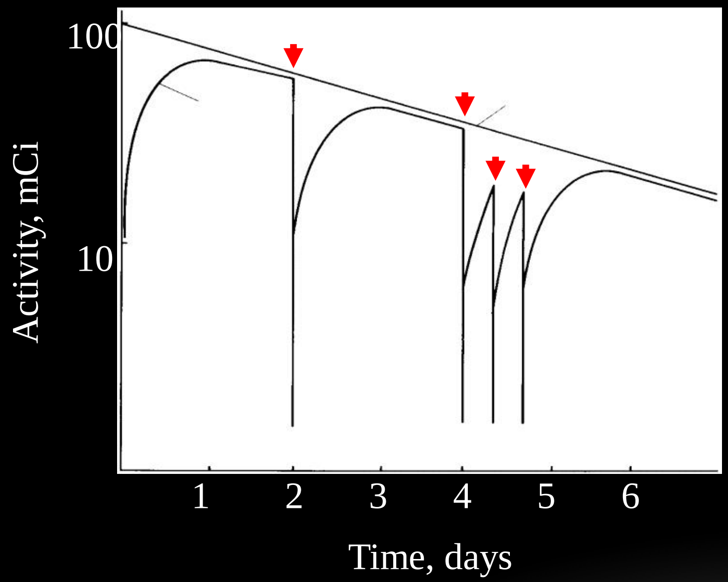


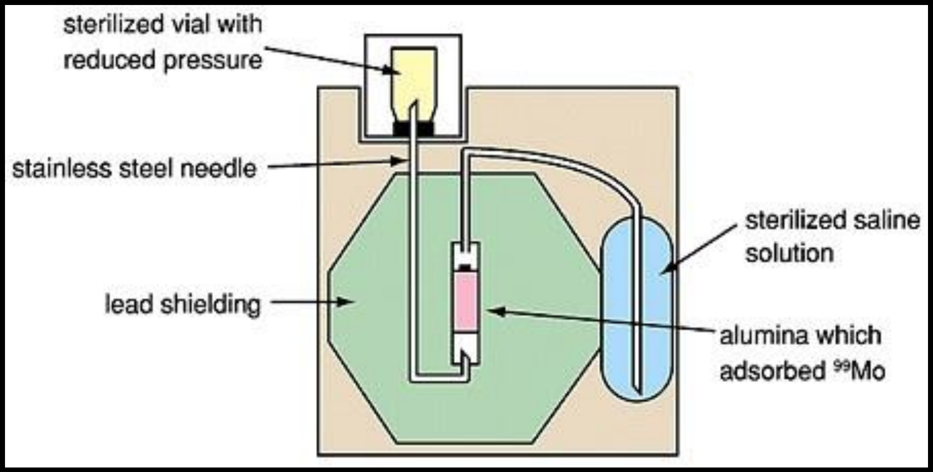
MIRD Radionuclide Data and Decay Scheme

^{68}Ge/ ^{68}Ga Generators

- Consists of a short glass column packed with a solid support.
- ^{68}Ge is absorbed onto the solid matrix.
- ^{68}Ge (parent) decays to ^{68}Ga (daughter), which further decays to ^{68}Zn (stable).
- The ^{68}Ga is washed off the column with an appropriate solution.
- Allow for simple and fast preparation of ^{68}Ga-radiopharmaceuticals for PET imaging.
- ^{68}Ga-labeled peptides have shown promise for imaging neuroendocrine tumors (NETs).

Concept like a ^{99}Mo-^{99m}Tc generator





Milestones of ^{68}Ge/ ^{68}Ga generator development

1950–1970	First $^{68}Ge/^{68}Ga$ generator Clinical applications: ^{68}Ga-EDTA; ^{68}Ga-citrate; ^{68}Ga-colloid
1970–1980	Further development of $^{68}Ge/^{68}Ga$ generator: $^{68}Ga(III)$
1990s	Commercial generator: $^{68}Ga(III)$
2000s	Clinical use with advent of SST ligands
2011	GMP generators
2014	Marketing authorization

Velikyan I, et al. *Molecules* 2015; 20: 12913-12943

Nuclear reactions to produce ^{68}Ge

Nuclear reactions	Target	Projectile MeV	Projectile µA	Yield µCi/µA· h
^{69}Ga (p,2n)	$^{nat.}Ga_4Ni$	19.5-0	2-3	9.2
^{69}Ga (p,2n)	$^{nat.}Ga_2O_3$	55-13	2	45
^{69}Ga (p,2n)	Ga	22	50	15
$^{nat.}Ge$ (p,xn)	Ge	64-28	1	48
^{69}Ga (d,3n)	Ga_2O_3	30	10	1.7
$^{nat.}Zn$ (α,xn)	Zn	40-20	0.5	1
^{66}Zn (α,2n)	Zn	40-20	0.5	1-2

Major parameters of a ^{68}Ge/ ^{68}Ga generator performance

- Chemical separation specificity
- Radiation resistance
- Chemical stability of column material
- Eluate sterility and apyrogenecity
- ^{68}Ge breakthrough
- Eluent type
- Elution profile

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Some commercial ^{68}Ge/ ^{68}Ga generators

	Eckert & Ziegler Cyclotron Co. Ltd.	Eckert & Ziegler IGG100 and IGG101 GMP; Pharm. Grade	I.D.B. Holland B.V.	Isotope Technologies Garching
		 		
Column matrix	TiO_2	TiO_2	SnO_2	SiO_2/organic
Eluent	0.1 M HCl	0.1 M HCl	0.6 M HCl	0.05 M HCl
^{68}Ge breakthrough	<0.005%	<0.001%	~0.001%	<0.005%
Eluate volume	5 mL	5 mL	6 mL	4 mL
Chemical impurity	Ga: <1 μg/mCl Ni < 1μg/mCl	Fe: <10 μg/GBq Zn: <10 μg/GBq	<10 ppm (Ga, Ge, Zn, Ti, Sn, Fe, Al, Cu)	Only Zn from decay
Weight	11.7 kg	10 kg 14 kg	26 kg	16 kg

- Most of the generators use acidic eluent since it provides cationic Ga(III) for the further direct chemistry.
- Inorganic column sorbents are used more widely as they are less sensitive to radiolysis.

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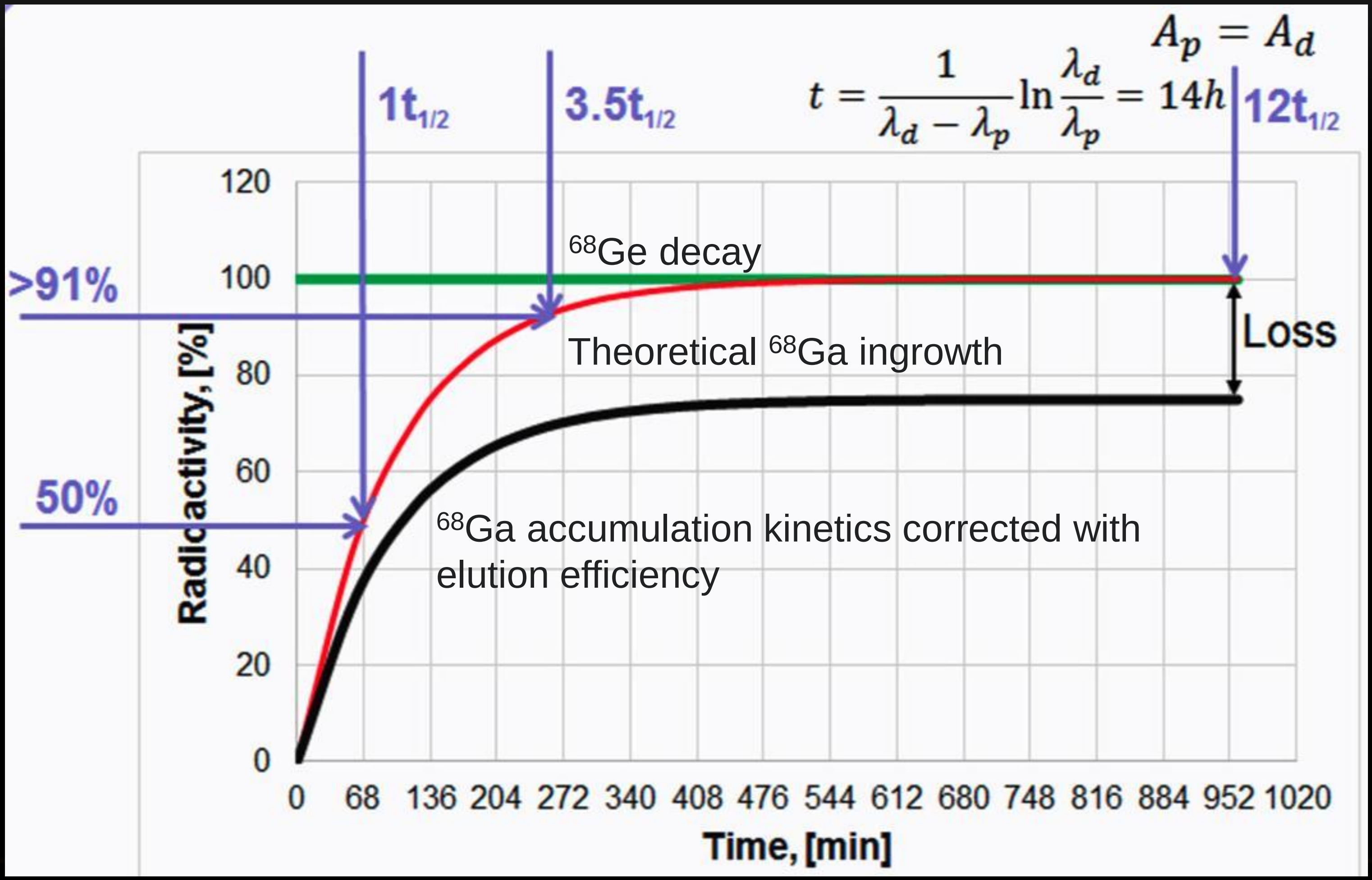
Problems associate with the use of a ^{68}Ge/ ^{68}Ga generator?

- Elution efficiency decreases with time.
- Stable ^{68}Zn (daughter of ^{68}Ga) interferes ^{68}Ga-labeling reactions.
- Acidity and other metallic impurities may not favor the ^{68}Ga-labeling reactions.

Secular equilibrium with ^{68}Ge decay and ^{68}Ga accumulation



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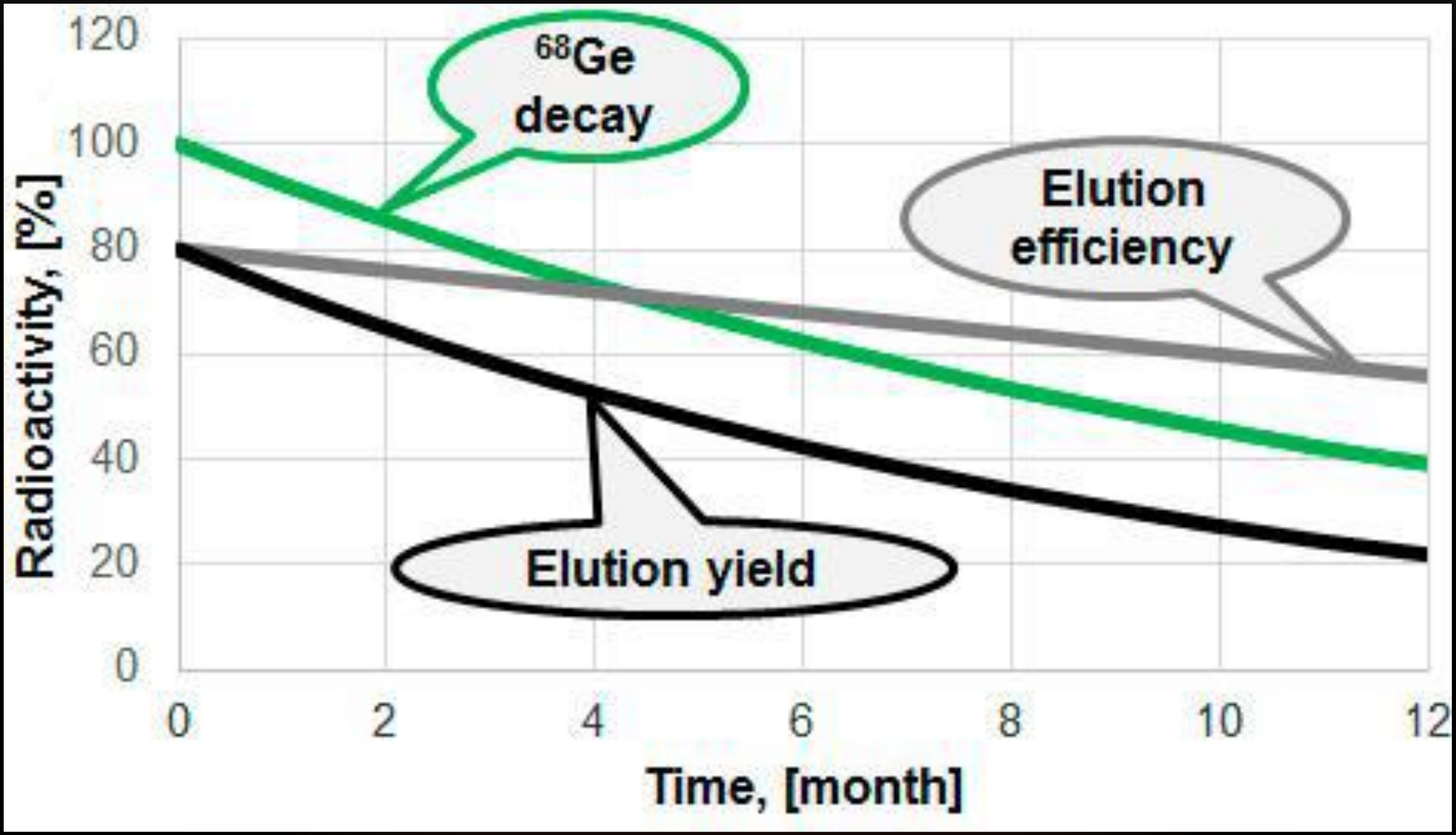
Hypothetical graphs showing ^{68}Ge decay, elution efficiency and non-decay corrected elution yield



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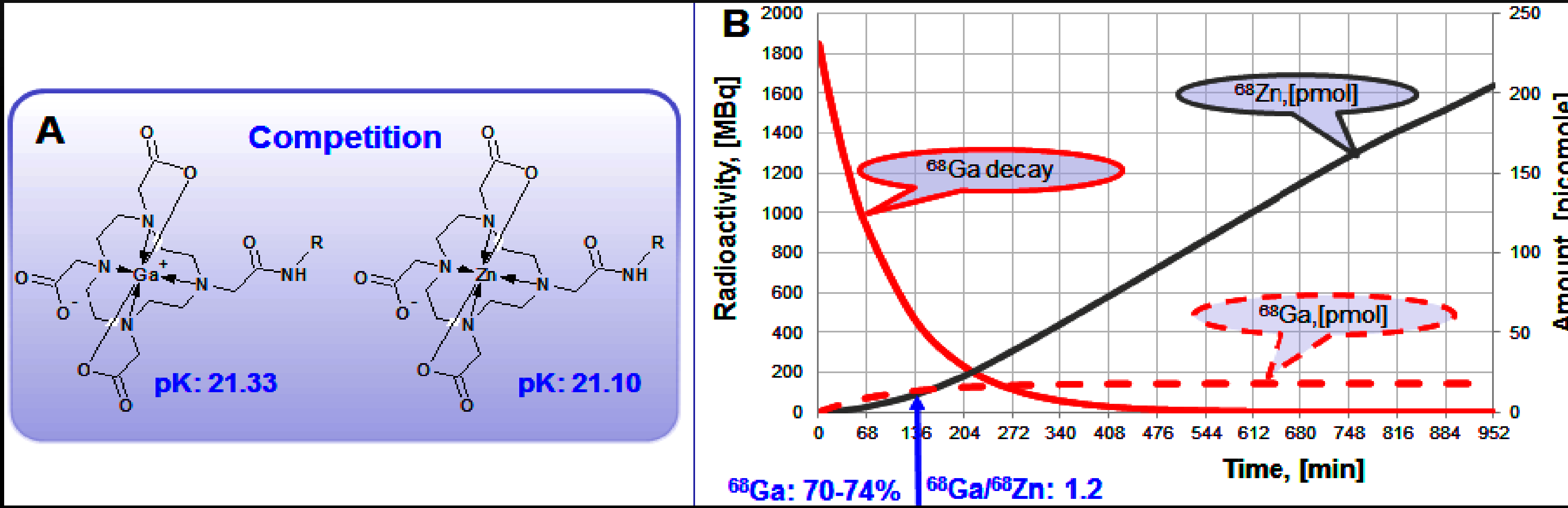
^{68}Zn interferes ^{68}Ga-labeling reaction



- Regular elution and elution prior to the synthesis.
- Purification of the eluate prior to the labeling synthesis.
- Enhanced amount of the ligand.
- Use of chelators with high selectivity for Ga(III).

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Post-processing of $^{68}Ge/^{68}Ga$ eluate

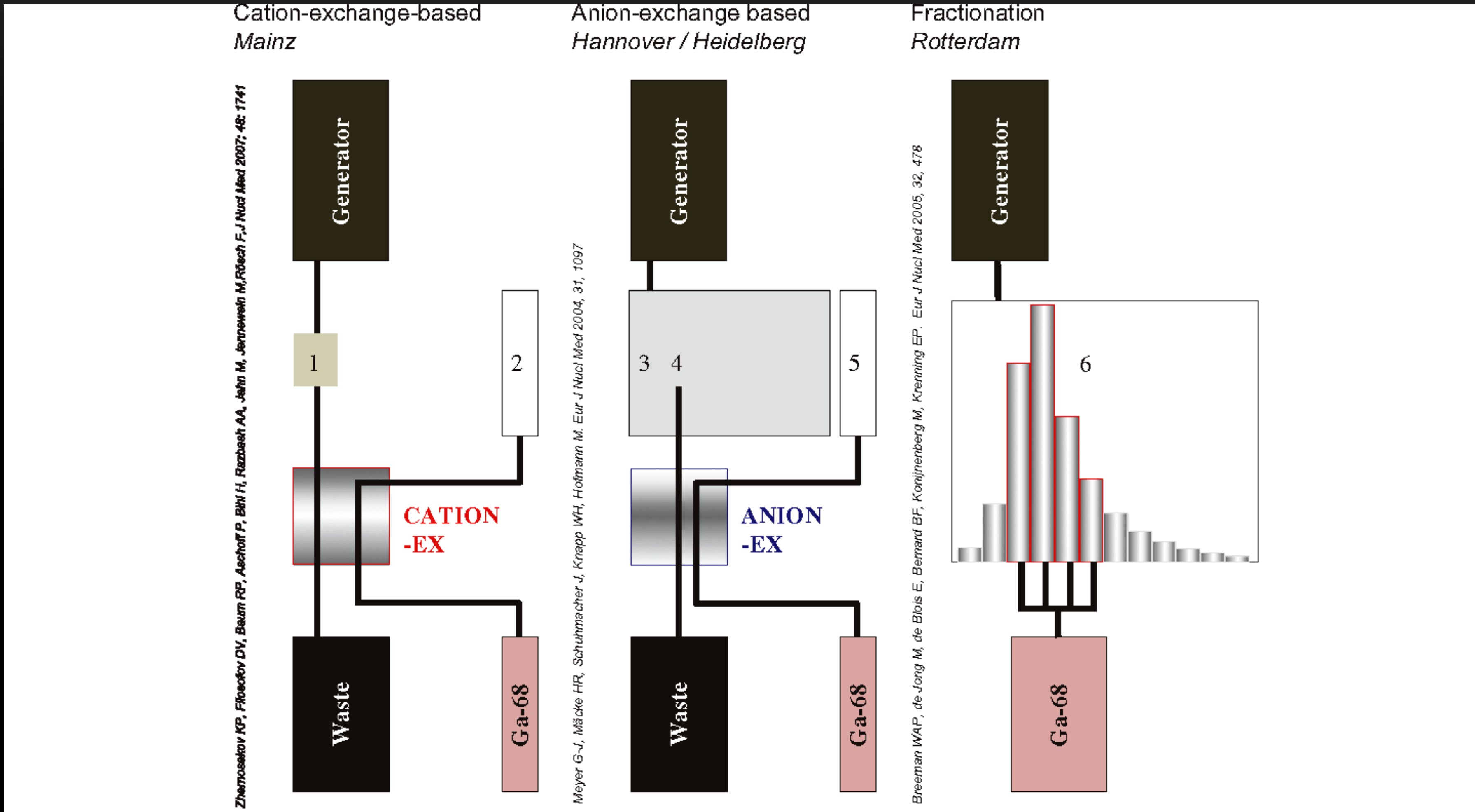


Fig. 8. Overview on post-processing technologies for commercial $^{68}Ge/^{68}Ga$ radionuclide generators. (1): Direct generator elution through cation-exchange cartridge, (2): desorption of purified ^{68}Ga using HCl/acetone or HCl/ethanol mixtures, (3): generator elution into HCl reservoir, (4): subsequently elution through anion-exchange cartridge, (5): desorption of purified ^{68}Ga using water, (6): identification of the eluate fraction representing at least 2/3 of the ^{68}Ga activity and use without further purification.

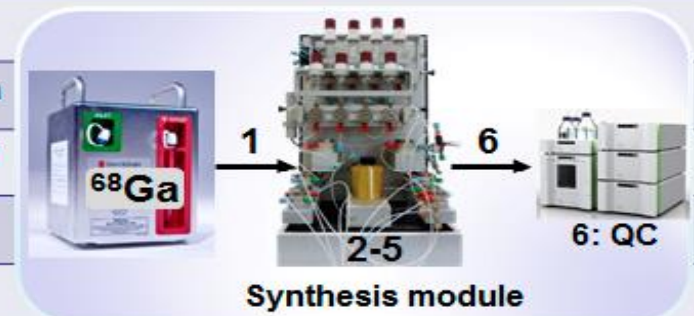
Rösch F, et al. *Appl Radiat Isotopes* 2013; 76: 24-30

Regulatory issues about ^{68}Ge/ ^{68}Ga generator and its application?

- 適用於調製作業要點嗎?
- 適用於一般醫院核醫科嗎?
- Should either a ^{68}Ge/ ^{68}Ga generator or its eluate need NDAs (查驗登記) approval?
- Can hospital radiopharmacists “compound” a ^{68}Ga radiotracer, as they do for ^{99m}Tc radiopharmaceuticals?

Preparation of ^{99m}Tc-RP vs. Manufacturing of ^{68}Ga-RP

Preparation (^{99m}Tc)	Manufacturing (^{68}Ga)
1. Generator elution into **product** vial with API	1. Generator elution into **reaction** vial
2. Labelling in the **product** vial	2. Labelling in the reaction vial
	3. **Purification** of the product
3. Formulation	4. Formulation
	5. **Sterile filtration**
	6. **Quality control**
	7. Dispensing
4. Release	8. Release



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Ge-68/Ga-68 Generators-FDA Perspective

John K. Amartey, MS, PhD
FDA/CDER/OPQ/ONDP

SNMMI Annual Meeting
June 6-10, 2015
Baltimore

Regulatory Pathway for Ge/Ga Generator

In contrast to the Mo-99/Tc-99m generator, the Ge/Ga generator has no current stand alone clinical indication, and therefore cannot be submitted as a NDA. A drug master file (DMF Type II) is currently the preferred pathway

(DMFs are not approved or disapproved by the FDA, rather they are reviewed for adequacy/acceptance in relation to a submitted application using the indicated generator)

Some Information needed in a Ge-68/Ga-68 Generator DMF

- Source of the Ge-68
- Target composition and irradiation parameters
- Production method (Cyclotron, etc.)
- Isolation/separation method for Ge-68
- Column and generator preparation
- Quality control (Ge-68 and Ga-68 eluate)

  -(21 CFR 314.420)-

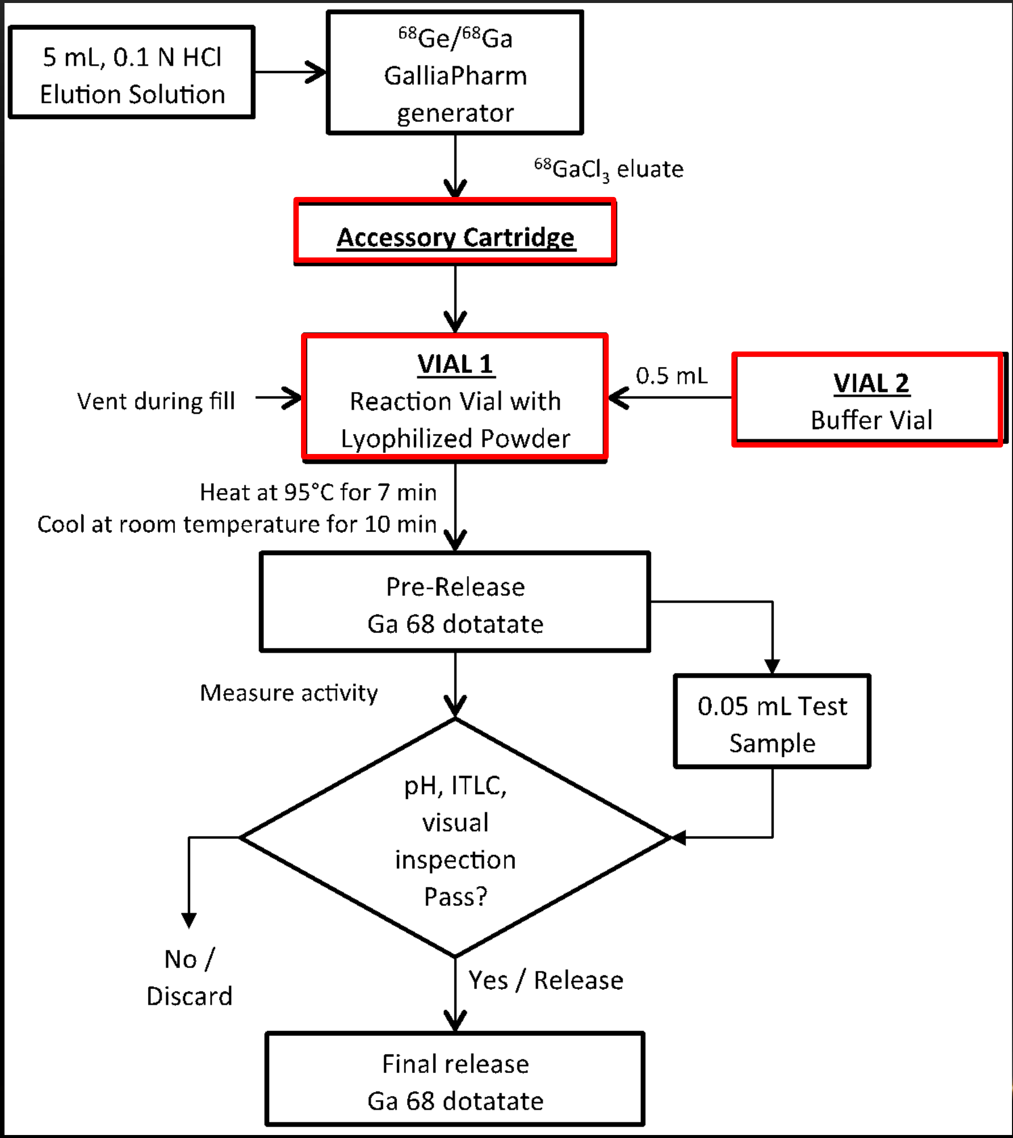
Ga-68-Radiopharmaceutical INDs

- Currently FDA is making Ga-68-radiopharmaceuticals available through IND studies.
- The quality of the Ga-68-radiopharmaceutical is assured by CMC review.

Ga-68-Radiopharmaceuticals: kit formulation

- The FDA encourages that the Ga-68-radiopharmaceutical and the kit formulation from which it is prepared should be submitted under a single NDA
- The kit should be compatible with one or more commercial generators.

Preparation of ^{68}Ga-DOTATATE from NETSPOT™ kit



- NETSPOT™ (Somakit-TATE) designated as an orphan drug by the EMA and the FDA.
- FDA approval 2016.
- Distributed by Advanced Accelerator Applications, US (AAA).

http://www.adacap.com/products/

Non-generator-based ^{68}Ga Production

Am J Nucl Med Mol Imaging 2014;4(4):303-310
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0000152

Original Article

Cyclotron production of ^{68}Ga via the ^{68}Zn(p,n)^{68}Ga reaction in aqueous solution

Mukesh K Pandey[1], John F Byrne[2], Huailei Jiang[1], Alan B Packard[3], Timothy R DeGrado[1]

[1]*Department of Radiology, Mayo Clinic, Rochester, MN 55905, USA;* [2]*Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA;* [3]*Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA*

Press release |

iba

IBA and ICNAS Announce Ga-68 production on Cyclone® 18 using IBA liquid target & Synthera®

IBA is proud to announce a patent application EP15170854 on a process for producing and purifying Ga-68 using a liquid target system on a medium energy cyclotron to obtain Ga-68 labelled radiopharmaceuticals for human use

Radiation protection about ^{68}Ge/ ^{68}Ga generator and its application

Ge-68

- Half-life: 271 days
- Decay type: EC
- Gamma & X-ray: 9.22 keV (13.1%), 9.25 keV (25.6%), 10.3 keV (5.46%)
- Hazard category:
  C-level (low hazard): ≤ 10 μCi
  B-level (moderate hazard): > 10 μCi to 1 mCi
  A-level (high hazard): > 1 mCi
- The exposure rate from 1 mCi (at equilibrium with daughter Ga-68) = 5375 mR/h @1 cm.
- A 10 mCi generator should be shielded with 1.5 cm of lead (minimum) to reduce the exposure to 5 mR/h @1 feet; 3 cm of lead will reduce the exposure to 0.5 mR/h @1 feet.
- ALI = 540 μCi

Radionuclide Safety Data Sheet, Stanford University

Ga-68

- Half-life: 68.3 days
- Decay type: β^+ [1.90 MeV (88%), 822 keV (1%)] + EC
- Gamma & X-ray: 511 keV (178%); 1077 keV (3%)
- Hazard category:

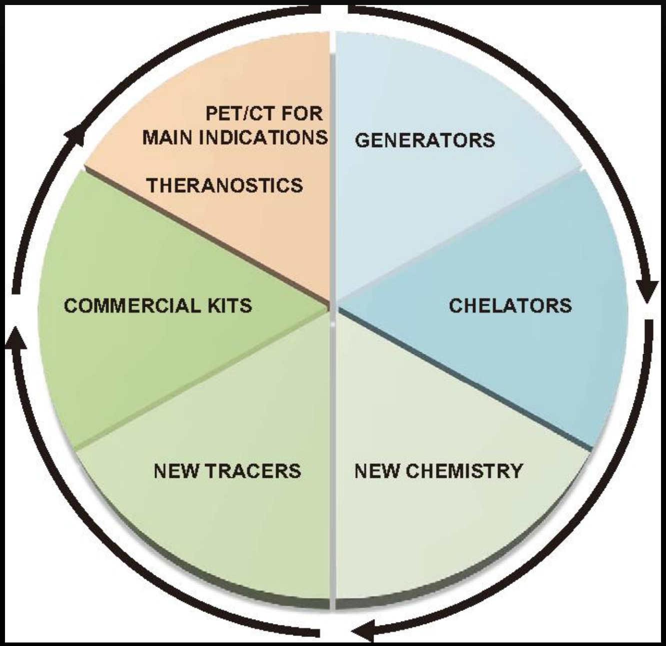
  C-level (low hazard): ≤ 1 mCi

  B-level (moderate hazard): > 1 mCi to 100 mCi

  A-level (high hazard): > 100 mCi
- The exposure rate from 1 mCi = 5375 mR/h @1 cm.
- A 10 mCi generator should be shielded with 1.5 cm of lead (minimum) to reduce the exposure to 5 mR/h @1 feet; 3 cm of lead will reduce the exposure to 0.5 mR/h @1 feet.
- ALI = 1.62 mCi

Prospects

- Technology advancement/ maturation
- Who prepares ^{68}Ga tracer?
- Cost down



Thank you for your attention