Gallium-68 –
a candidate for use in clinical routine

M. Harfensteller, R. Henkelmann, J. Moreno, O. Leib, T. August, O. Buck, T. Nikula

Isotope Technologies Garching

A. Türler, K. Zhernosekov

Uni Bern, Bern; Paul Scherrer Institut, Villigen

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Outline

1. ^{68}Ga and it‘s applications

2. The generator system and it‘s application

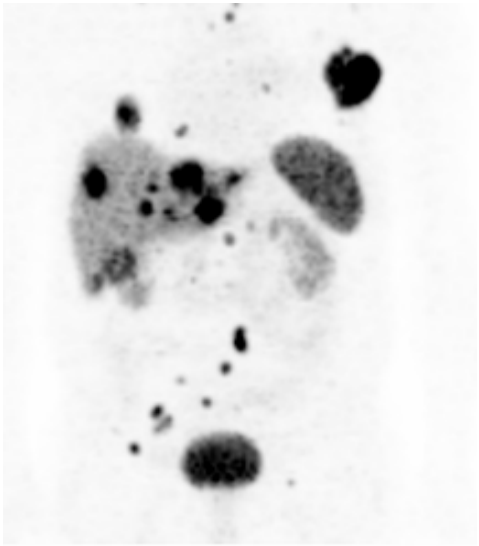
3. The way from a scientific proof-of-concept to a pharmaceutical product

^{68}Ga properties

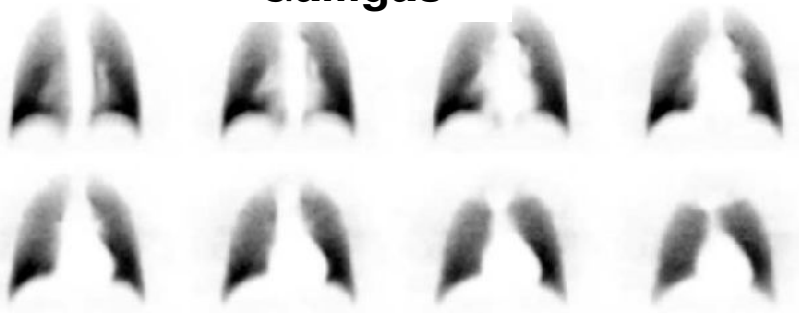
- **Physical properties**
  - **Halflife $T_{1/2}$ = 68 min**
  - **Positron branching 89% (PET nuclide)**
  - **Available via a ^{68}Ge/^{68}Ga generator**
  - **Mother ^{68}Ge cyclotron produced ($T_{1/2}$ = 271 d)**
- **Chemical properties of Ga**
  - **Trivalent metal**
  - **Chelation chemistry**
- **Applicability**
  - **Short half-life useful for molecules with fast biokinetics (Peptides, Ab-fragments, small complexes,…)**

Use of ^{68}Ga as PET nuclide

Somatostatin analogues

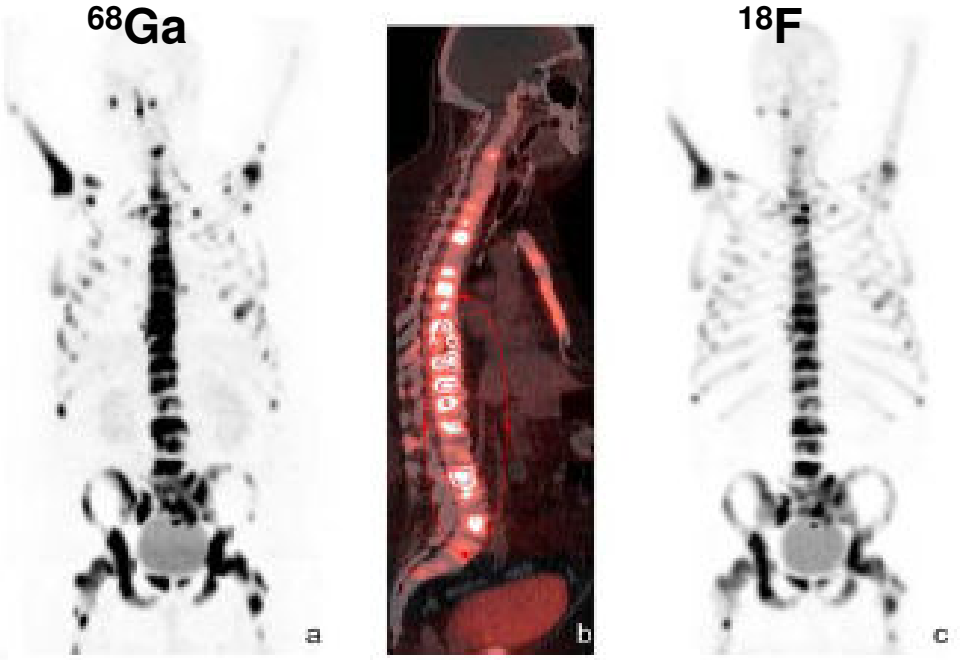


Galligas™



(Kotzerke et al.; Eur J Nucl Med Mol Imaging 2010)

Bisphosphonates (^{68}Ga compared to ^{18}F)



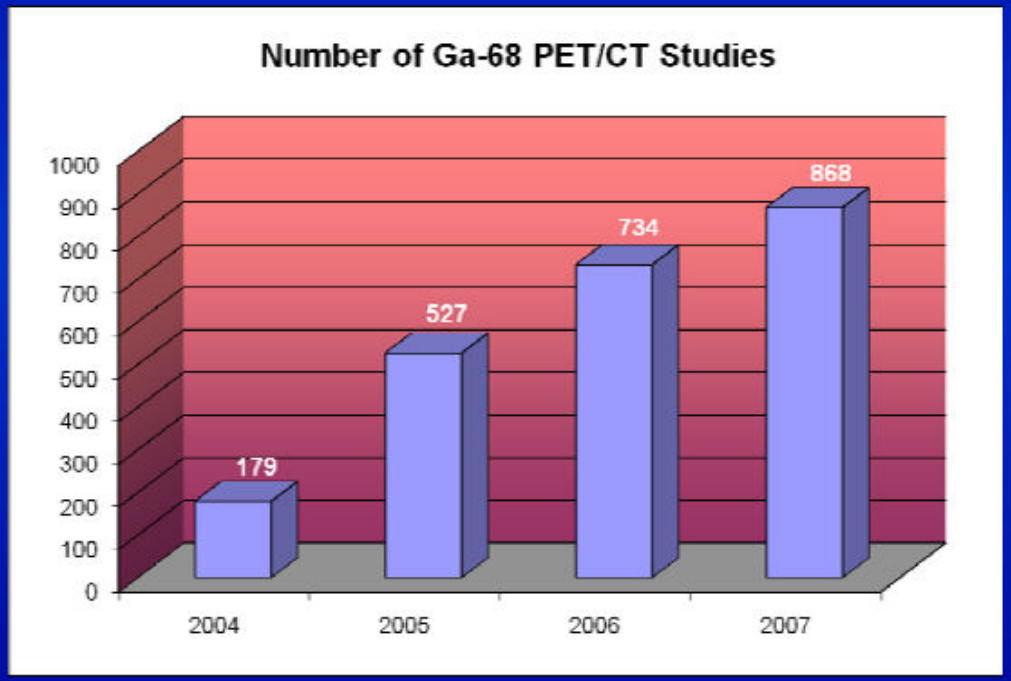
(Fellner et al.; Eur J Nucl Med Mol Imaging 2010)

Bombesin

Ga-microspheres

Use of ^{68}Ga as PET nuclide

Gallium-68 will become the Tc-99m for PET/CT!



Prediction by R.P. Baum (2004)

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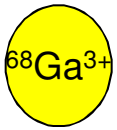
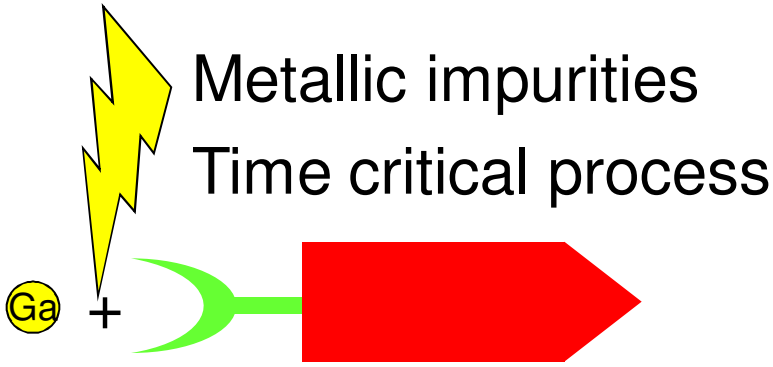
^{68}Ga application – Production of ^{68}Ga-DOTATOC

1. Production of **chelator** (DOTA) and **peptide** (TOC)

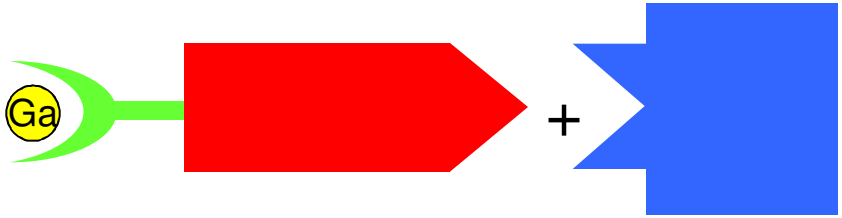
2. Elution of ^{68}Ga



3. Chelation reaction of ^{68}Ga with DOTATOC



4. Administration to the patient (receptor binding to **cell receptor**) and PET scan



^{68}Ga application

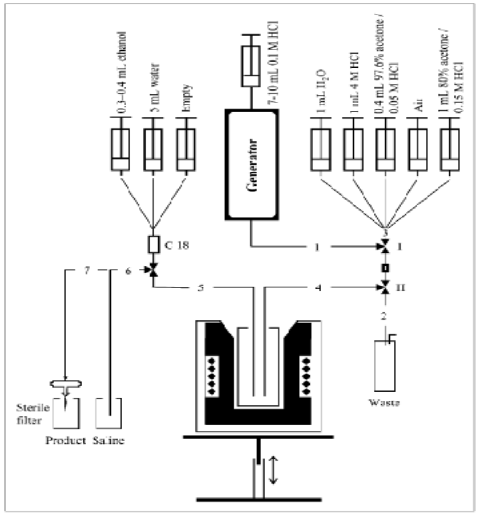
Generator elution

↓

Labelling of biomolecules

↓

Transfer in injectable form

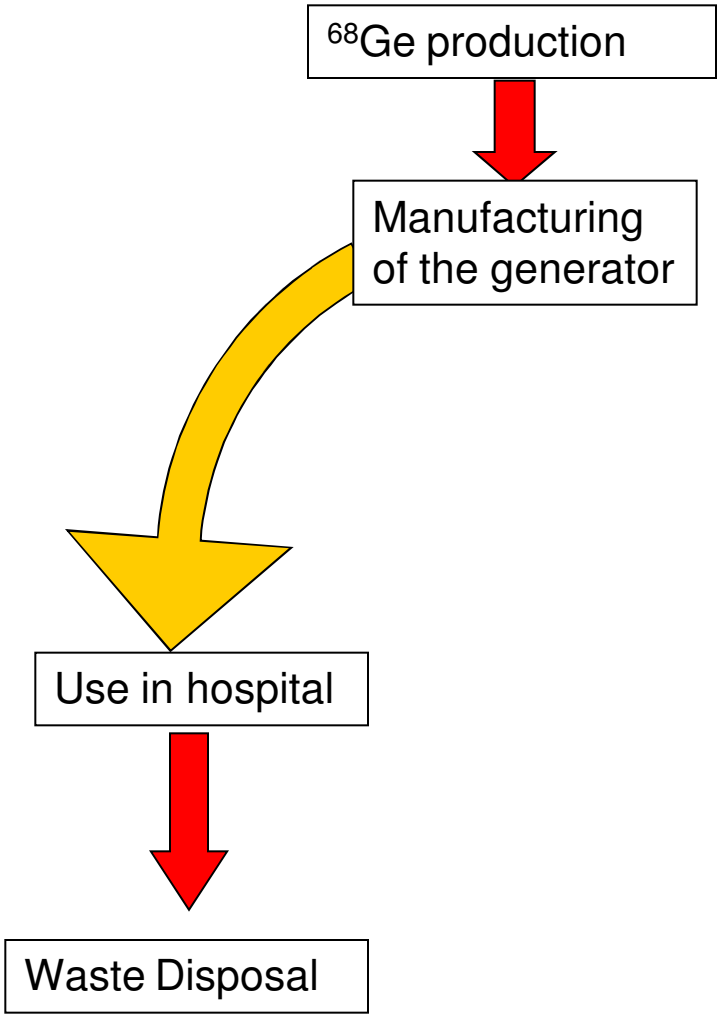


Zhernosekov et al. J Nucl Med 2007

- Decentralized distribution and compound manufacturing
- Automated elution and labelling systems in the hospitals
- 15-40 min synthesis time

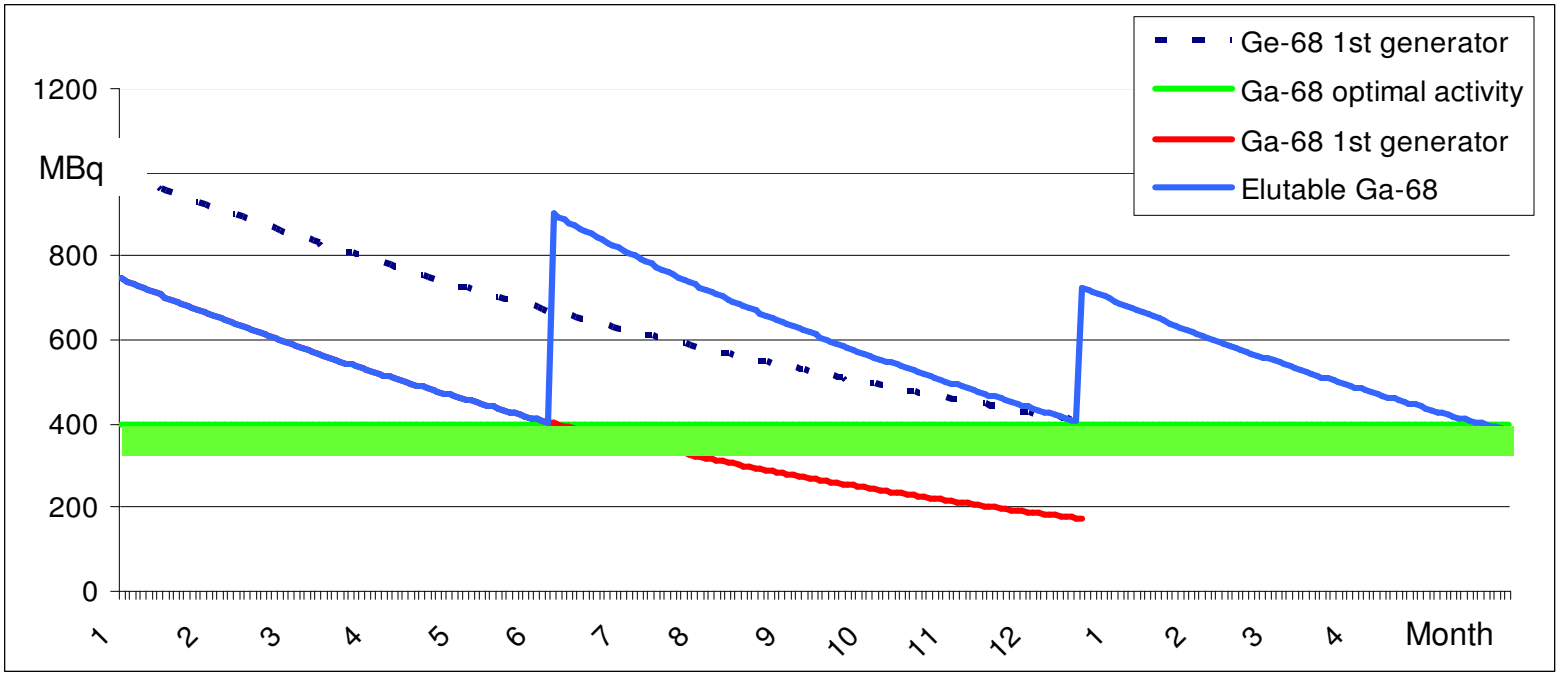
EZAG, Scintomics; Comecer

^{68}Ga generator cycle



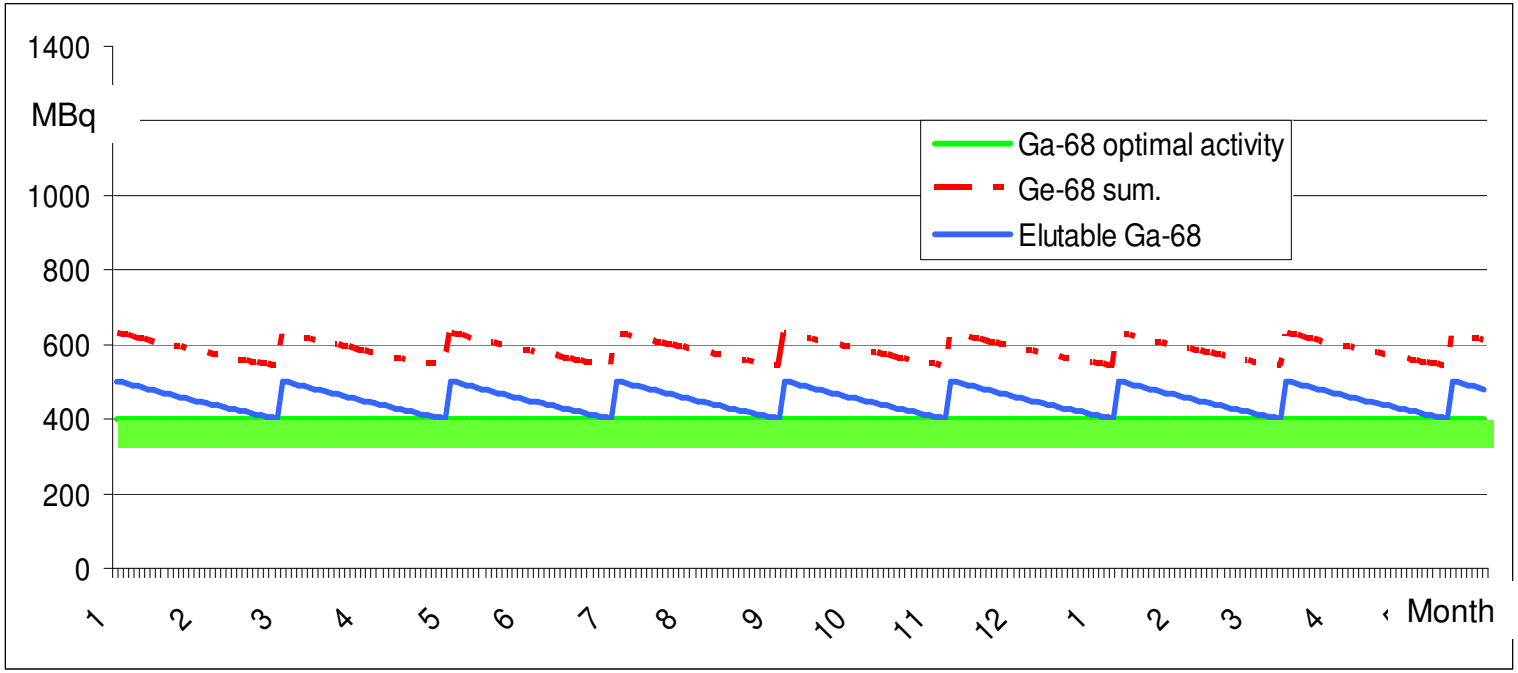
- Todays generators are not recycled and remain as long-lived waste in the hospitals (generating additional cost).
- Some hospitals couple generators to extend lifetime (not compliant to pharmaceutical requirements).
- Compared to Mo/Tc generators the shelf life of Ge/Ga generators is increased by at least one order of magnitude (3-10 months compared to 1-2 weeks). This increases the requirements of the generator performance.
- Poor logistics.

^{68}Ga generator logistics (nowadays)



- Generators have usually yield of up to 80% but drop to 50% over 1 $T_{1/2}$(Ge)
- Generators are coupled to extend shelf life („expert mode“)
- >50% of the ^{68}Ge activity is unused, in the beginning also of the ^{68}Ga (unnecessary dose for personnel)
- Today logistics is driven by economics not by pharmaceutical reasons!

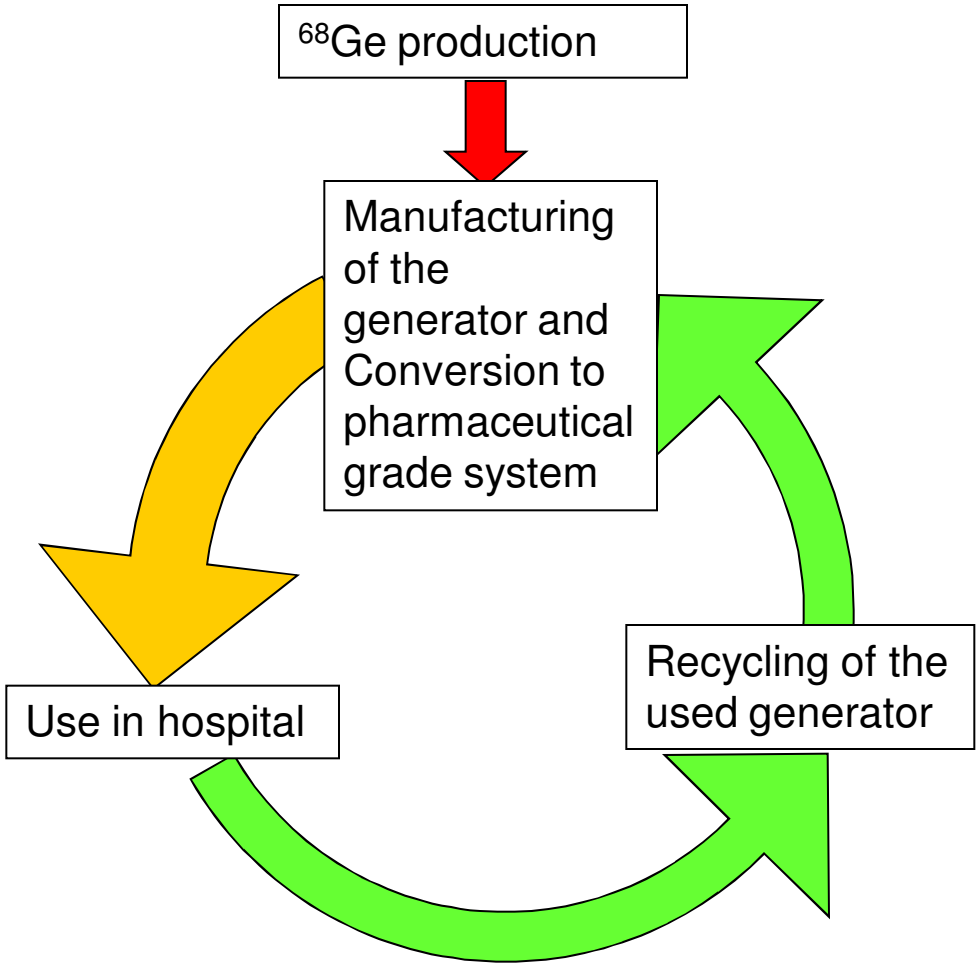
^{68}Ga generator logistics in a pharmaceutical environment



- Sterility and Endotoxin level
- Defined shelf-life depending on specifications
- Optimized activity for customer needs and radiation protection

→ **Shelf life of the generators will decrease for pharmaceutical demands**

^{68}Ga generator cycle



- Due to an expected shorter shelf-life the generators have to be recycled
- Customers want to have a guaranteed activity and quality

Overview of today's available generators

All generators on the market „not for human use“

	Cyclotron Co Ltd.	Eckert&Ziegler IPL	I.D.B. Holland B.V.	Isotope Technologies Garching
Origin	Russia	USA	South Africa	Germany
Resin	Titanium-dioxide	Titanium-dioxide	Tin-dioxide	Organic Material
Eluent	0,1M HCl	0,1M HCl	0,6M HCl	0,05M HCl
Elution Yield	60-75%	70-75%	80%	(>80%) *)
Breakthrough **)	<0,01%	<0,001% **)	<0,007%	(<0,001%)

*) Elution yield over lifetime

**) Breakthrough of ^{68}Ge in % of eluted ^{68}Ga at calibration

***) Breakthrough of ^{68}Ge in % of loaded ^{68}Ge on the column

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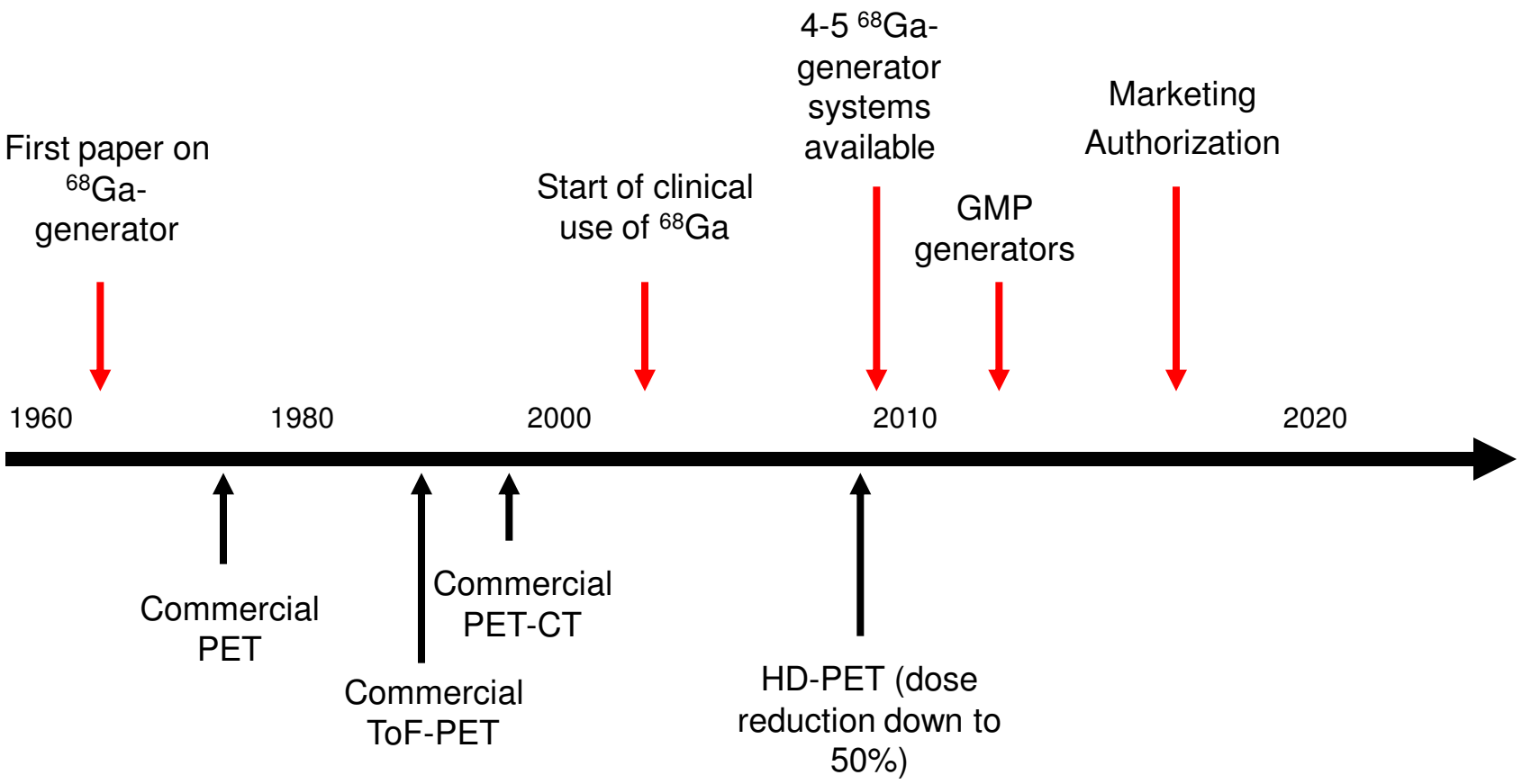
The way to a radiopharmaceutical product

Timeline



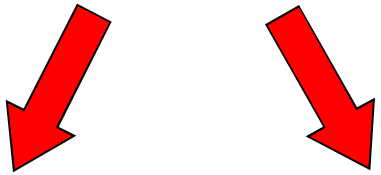
Research → **Industry**

The way to a radiopharmaceutical product

Principle

- Research on isotopes /isotope systems with potential in diagnostic use
- Development of the technical system (production, feasibility, logistics,…)
- Establishment of stable production and product parameters (breakthrough, yield,…)

Depending on application



Pharmaceutical Product

- Manufacturing Authorization
- Marketing Authorization

Medicinal Product

- CE certification

The way to a radiopharmaceutical product

GMP production = quality in production

- Qualification and validation of ALL product, production, production system and quality control related parameters
  - Definition of specifications
  - Radionuclidic purity
  - Chemical purity
  - Radiochemical purity
  - Biological properties (sterility, endotoxin load)
  - Excellence of production (production processes stable)
  - Quality control and release procedures
- Establishment of production environment according to pharmaceutical requirements
  - Production in clean room environments

→Manufacturing authorization

Timeline: 1-2 years depending on existing GMP facilities and processes

The way to a radiopharmaceutical product

Registration for a marketing authorization

- Decision to register pharmaceutical or API
  (active pharmaceutical ingredient; part of pharmaceutical == radioisotope)
- Decision on central or decentral application for the marketing authorization
  - Decentral (example: germany)
  - Application form consists of 5 modules thereof *one* includes the whole manufacturing description
  - Justification of specifications
  - Pharmacology (Toxicology,…)
  - Clinical trials (Dose, Indication,…)
  - Marketing authorization for the given country

→Marketing authorization for 1 country

Timeline:

Several years

Registration for a marketing authorization (cont.)

- Start of mutual recognition process (enlarge the marketing authorization to other countries)
  - Other authorities ask for changes in production → worst case: 10 changes in production methods for 10 countries

→Marketing authorization for other countries

Timeline:

Several years

Conclusion

- ✓ ^{68}Ga is a promising PET isotope
- ✓ Independant from cyclotron
- ✓ Generators are available
- ✓ Use is established in big PET centers

But:

- Not yet registered as radiopharmaceutical
- Logistics must be improved
- Waste problem must be solved


Thank You