



SOCIETY OF
NUCLEAR MEDICINE
AND MOLECULAR IMAGING

Disclosure

- **Advanced Accelerator Applications**

Objectives

- After completion of this session, the participant will know the following about Kit for preparation of gallium Ga 68 dotatate
 - Regulatory, pre-clinical, clinical and CMC history on Ga 68 dotatate kit
 - Material and method for the reconstitution and radiolabeling of Ga 68 dotatate kit with source of Ga 68 chloride
 - Material and method for performing Quality Control of final product Ga 68 dotatate solution for injection

Diagnosis of NET with somatostatin analogs

- Ga 68 dotatate PET compared to existing radiopharmaceuticals and scintigraphy
 - Higher Sensitivity: Improved Lesion Detection¹
 - Rapid Image Acquisition / Higher Patient Throughput²
 - Increase Imaging Quality PET vs SPECT³
 - Improved binding affinity⁴
 - Decreased Radiation Dose⁵
 - Limited Availability (research, some clinical via Cost Recovery)
- Unmet need:
 - Ga 68 compounds availability commercially
 - Availability via radiopharmacy networks
 - Availability for in-house institutional compounding
 - Reimbursed

1. Deppen SA, et al. *J Nucl Med*. 2016 May;57(5):708-14., 2. Velikyan I. *Theranostics*. 2014; 4(1):47-80., 3. Buchmann I, et al. *Eur J Nucl Med Mol Imaging*. 2007; 34:1617–1626., 4. Reubi JC. *Virchows Arch*. 2007 Aug;451 Suppl 1:S47-50., 5. Walker RC, et al. *J Nucl Med*. 2013 Jun;54(6):855-60. 4

Significant contributors to project on clinical research support and collaboration

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Kit for preparation of gallium Ga 68 Dotatate

- First registered lyophilized kit for the preparation of Ga 68 injectable solution
- Regulatory History:
 - ✓ December 31, 2013 – AAA receives Orphan Drug Designation
 - ✓ July 1, 2014 - Pre-IND meeting with FDA
 - ✓ FDA Endorsed and agreed in 2014
 - GMP “Kit” → Less Manipulation
 - Kit = Lyophilized peptide drug precursor + buffer + cartridge
 - Components meet pre-defined specifications
 - A standardized reconstitution protocol / No purification steps
 - DMF required from Ge68/Ga68 generators manufacturers
 - Final product meets pre-defined specifications
- ✓ June 2016 – FDA approval

Kit for preparation of Ga 68 dotatate - Preclinical

- A complete preclinical package of toxicology, safety pharmacology and metabolism studies on the dotatate peptide was submitted for registration. The preclinical studies showed that the peptide has a benign toxicology/safety pharmacology profile, with a large safety margin.
- The ^{68}Ga -DOTATATE kit formulation (including all excipients at the final pH of 3.5 ± 0.3) was tested in single dose toxicity and local tolerability studies in rats and proved to be safe and well tolerated at doses approximately 450 times the maximum expected dose in human
- Biodistribution studies in sstr_2 -positive tumor-bearing rodent models showed that ^{68}Ga -DOTATATE has favorable pharmacokinetic properties for diagnostic imaging: high tumor uptake, fast blood clearance, relatively low kidney retention

Kit for the preparation of Ga 68 dotatate - Clinical

The high efficacy of Ga68 Dotatate was evaluated in three studies:

- Open label, single center
- Suspected of NETs
- Clinical reads are compared to:
 - CT and/or MR images,
 - Indium In 111 pentetreotide Images,
 - Histopathology
 - Clinical Presentations
- Readers
 - Independent readers blinded to clinical information
 - Consensus read between two on-site readers not blinded to clinical information
 - Central readers blinded to clinical information

Kit for the preparation of Ga 68 dotatate - CMC

The Drug Product is a sterile 2-vial kit which consists of:

- Vial 1 - containing the lyophilized active substance (40µg of dotatate, 5 mcg 1,10 phenanthroline, 6 mcg gentisic acid, 20 mg mannitol): to be reconstituted with Ga 68
- Vial 2 - containing the reaction buffer (60 mg formic acid; 56.5 mg sodium hydroxide and water for injection): to be added to the reconstituted Vial 1
- One Accessory Cartridge (660 mg porous silica): reduce potential Ge 68 release
- A full GMP development of the kit has been undertaken and all the components are currently prepared in an industrial GMP manufacturing facility
- The kit is supplied as a single-dose kit for preparing a single-dose injection
- The kit has a shelf life of 12 months at 25°C (room temperature)
- To be reconstituted in accordance with Aseptic Procedure (elution under LFH)

Kit for the preparation of Ga 68 dotatate - CMC

- The kit has to be used in combination with a solution of Ga 68 in HCl provided by the Eckert & Ziegler GalliaPharm® Ge-68/Ga-68 generator
 - Essential factors for the patient safety and its appropriate medicinal use for PET
 - European Union and EU Countries: Registered as a medicinal product
 - USA: A Type II Drug Master File (DMF No. 28741) was filed with the FDA
 - meets requirements of the relevant EU pharmacopoeia monograph
 - Sterility over the entire one-year shelf-life
 - Ge 68 breakthrough limit (< 0.001%)
- It has to be reconstituted in accordance with aseptic procedure (elute under LFH)
- Ga 68 dotatate solution can be used up to 4 hours after reconstitution.
- The recommended activity to be administered for PET imaging in adults is 2 MBq/kg of body weight (0.054 mCi/kg), up to 200 MBq (5.4 mCi).

Kit for the preparation of Ga 68 dotatate - CMC

- This kit allows a simple Ga 68 labelling procedure based on direct reconstitution of a pre-formulated kit with no requirement for any processing of the eluate or any additional filtration or purification step
- Because of the GMP quality of the product, a complete list of validated analytical controls is applied at the production site before release of the kit (see next slide)
- This leaves to the final user's responsibility only few confirmatory quality tests, similarly to the ones routinely performed with existing ^{99m}Tc -based kits. These tests are meant to verify the correctness of the reconstitution procedure.

QC to be performed by the end-user on the reconstituted product prior to patient administration

Test	Method
Appearance	Visual inspection
pH	pH strips
Labeling efficiency	Thin layer chromatography

Kit for the preparation of Ga 68 dotatate - CMC

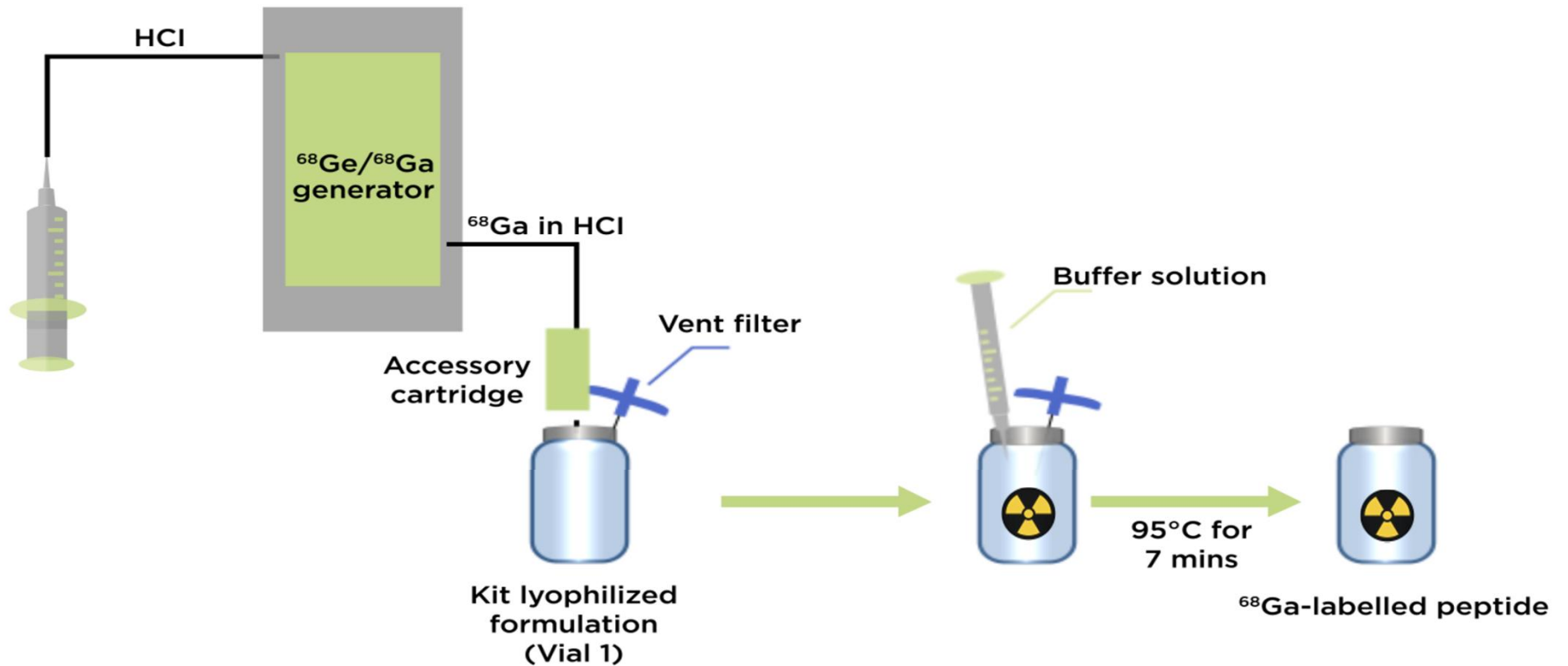
QC testing performed on the kit Vial 1 before release

Test	Reference
Appearance	In house
Container-closure integrity test	In house
Particulate matter	USP<788>
Residual moisture	USP <731>
Uniformity of dosage unit	USP <905>
Dotatate identification and assay	In house
Excipients identification and assay	In house
Sterility	USP <71>
Bacterial endotoxin	USP <85>
Radiochemical purity by HPLC and ITLC	In house

QC testing performed on the kit Vial 2 before release

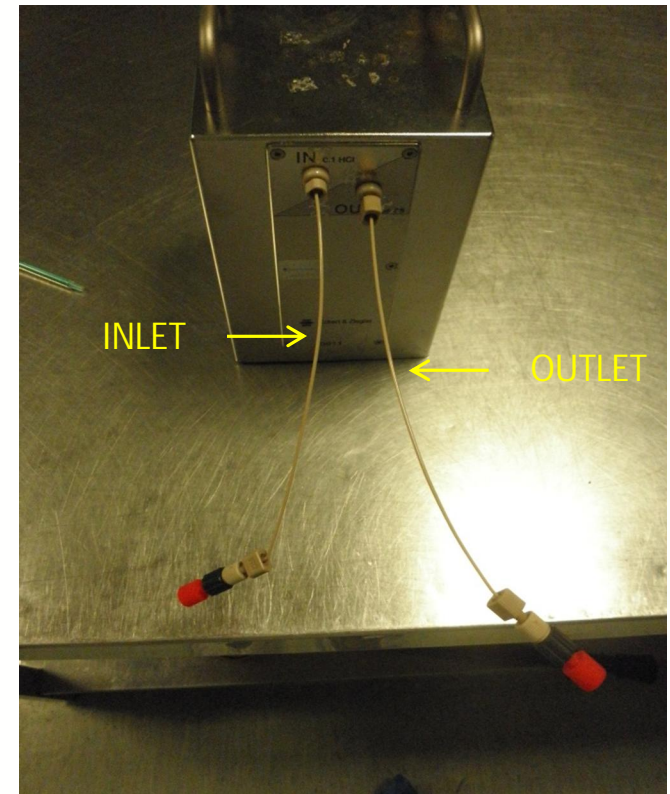
Appearance	In house
Container-closure integrity test	In house
Particulate matter	USP<788>
Buffer identification and assay	In house
pH of reconstituted solution	USP <791>
Sterility	USP <71>
Bacterial endotoxin	USP <85>

Reconstitution Procedure



E&Z Generator Elution Procedure

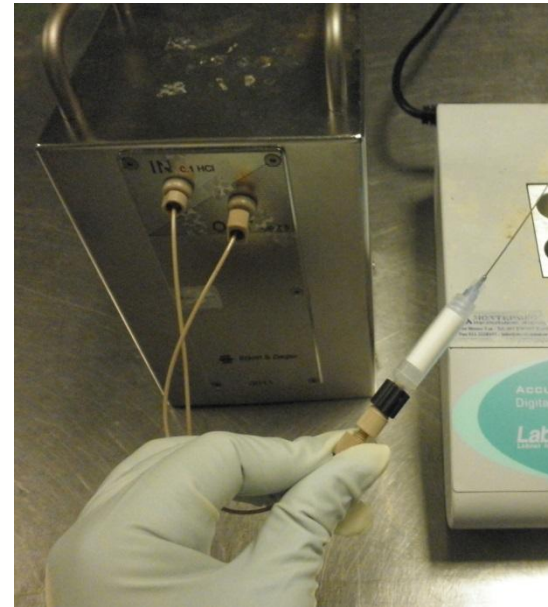
- Generator is supplied with a stopcock manifold to be assembled for the elution
- The final configuration of the assembled generator here



- As per Manufacturer recommendation proper testing of the Ga 68 chloride eluate for Ge 68 breakthrough may be required.

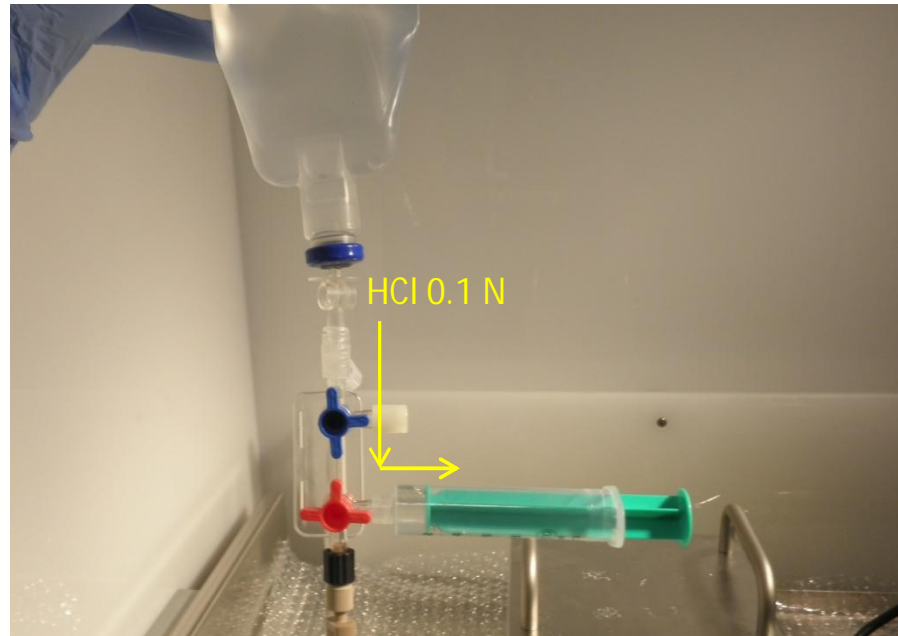
Method of reconstitution

- Connect the top of the cartridge to the male luer of the outlet line of the $^{68}\text{Ge}/^{68}\text{Ga}$ generator and the bottom of the cartridge with a sterile needle.
- Connect the Vial-1 to the outlet line of the generator by pushing the needle through the rubber septum and
- Place the vial in a lead shield container
- Elute the generator directly into Vial-1 through the cartridge, and the needle according to the instructions for use of the generator.
The elution can be performed either manually or by mean of a pump



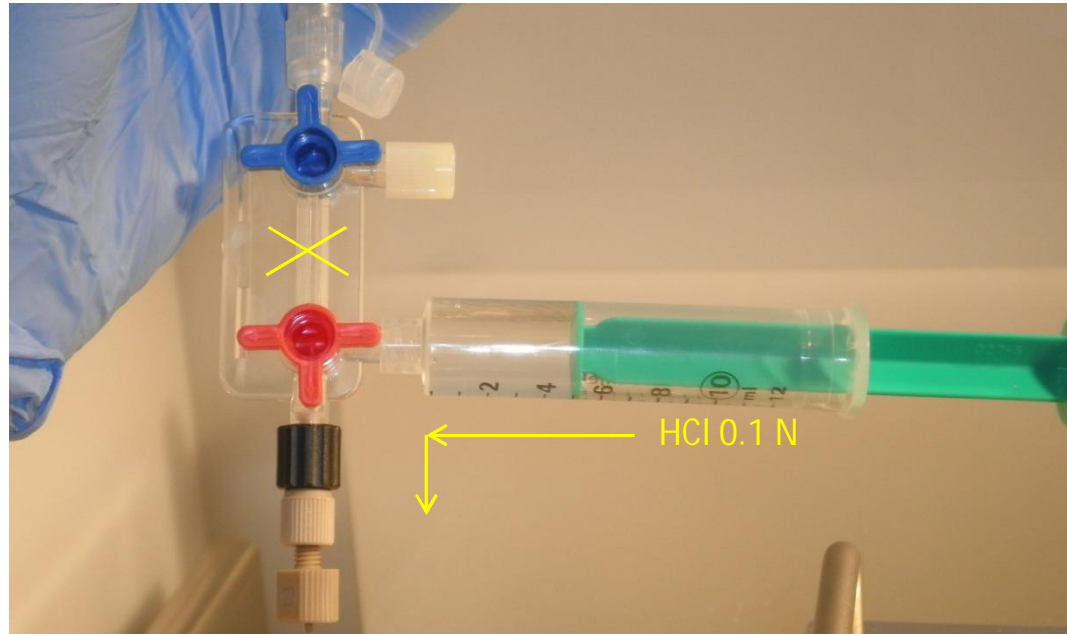
E&Z Generator Elution Procedure

- Galliapharm E &Z generator is supplied with Hydrochloric Acid (HCl) 0.1 N
- As shown below, the syringe is loaded with the required volume (5 ml) of HCl 0.1 N: Use a stopcock valves as shown in the picture below and withdraw the HCl by pulling the syringe plunger



E&Z Generator Elution Procedure

- Close the connection between the syringe and the bag of HCl and turn the red valve toward the inlet port of the generator
- Push the syringe plunger to start the elution. Manufacturer may recommend additional techniques



Method of Reconstitution

- Flip off the cap from the Vial-1.
- Pierce the Vial-1 with a 0.2 mm sterile air venting filter in order to stabilize atmospheric pressure within the vial during the reconstitution process
- Flip off cap from Vial-2
- With a low dead space 1 ml sterile syringe carefully withdraw the adequate volume of the reaction buffer
- Buffer volume is calculated in ml by multiplying the volume of HCl used for the elution of the generator in ml by its molarity
- $\text{buffer volume (ml)} = \text{HCl volume (ml)} \times \text{HCl molarity}$
 - For the E&Z generator $5 \text{ [ml]} \times 0.1 \text{ [N]} = 0.5 \text{ ml of buffer}$



Method of reconstitution

- At the end of the elution, disconnect the generator from Vial 1 removing the needle from the rubber septum and immediately add the kit buffer previously dosed in the 1 ml sterile syringe
- Withdraw the syringe and the 0.2 mm sterile air venting filter and then move the vial to the heating hole of the dry bath and leave it at 203 °F (+95 °C) for at least 7 minutes (do not exceed 10 minutes heating) without agitation or stirring.
- After 7 minutes, remove the vial from the dry bath, place it in an appropriately labelled lead shield and let it cool down at room temperature for approximately 10 minutes.



Specifications & Quality Controls

Thin layer chromatography: Material

- Varian ITLC SA pre-cut to 1 cm x 12 cm strips. Marked with a pencil 1 cm from each end
- Mobile phase: Ammonium acetate 1M: Methanol (1:1 V/V)
- Developing tank
- Radiometric ITLC scanner

Thin layer chromatography: Sample Analysis

- Developing tank: mobile phase - 3 to 4 mm & cover the tank
- A drop of the Ga 68 dotatate solution on a pencil line
- The strip placed in the developing tank → 10 cm from the point of application
- Scan the ITLC with a radiometric ITLC scanner

- The retention factor (Rf) specifications are as follows:
 - Non-complexed Ga 68 species = 0 to 0.1
 - Ga 68 dotatate = 0.6 to 0.8

Specifications & Quality Controls

Test	Acceptance Criteria	Method
pH	3.2 – 3.8	pH-indicator strips
Labelling Efficiency	≥ 92% and other Ga 68 species ≤ 5%	Thin layer chromatography (ITLC)
Appearance	clear solutions, particulate free	Visual inspection

- DO NOT USE if RCP less than 92%
- Need Visual inspection of final solution prior to use.
- Store final solution in a leaded container, at a temperature below 77 °F (+25 °C)
- Final solution is stable for up to 4 hours after preparation.

Conclusion

- Lyophilized Ga 68 dotatate Kit meets GMP standards
- Reconstitution is performed under aseptic environment according to pharmacy guidelines
- First PET drug to have commercial availability as a cold kit formulation
- Availability for institutions
 - Unit dose via radiopharmacy network
 - Cold Kits
- Serves unmet medical needs in the US