Prosedur Produksi Radiofarmaka [^{18}F]FDG dan [^{68}Ga]Ga-PSMA

Rien Ritawidya

Pelatihan Petugas Keahlian Pada Fasilitas Produksi Radioisotop dan atau Radiofarmaka dari Siklotron
21 April – 8 Mei 2026
Biofarma

Direktorat Pengembangan Kompetensi BRIN

Acknowledge: Training Material Siriraj Hospitals, Thailand
IAEA Techdoc, Related Publications

Biodata

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Latar Belakang

Kebutuhan radiofarmaka PET seperti [^{18}F]FDG dan yang semakin meningkat

Mengurangi ketergantungan import radiofarmaka PET

Meningkatkan kompetensi dalam produksi radiofarmaka berbasis PET seperti [^{18}F]FDG

MANFAAT

- Mengetahui prosedur produksi radiofarmaka ^{18}F secara manual dan otomatis.
- Mengetahui prosedur produksi radiofarmaka ^{68}Ga secara manual dan otomatis.
- Mampu menjelaskan prosedur produksi radiofarmaka ^{18}F dan ^{68}Ga manual dan otomatis
- Mendapatkan wawasan tentang potensi riset dan pengembangan radiofarmaka PET

TUJUAN PEMBELAJARAN

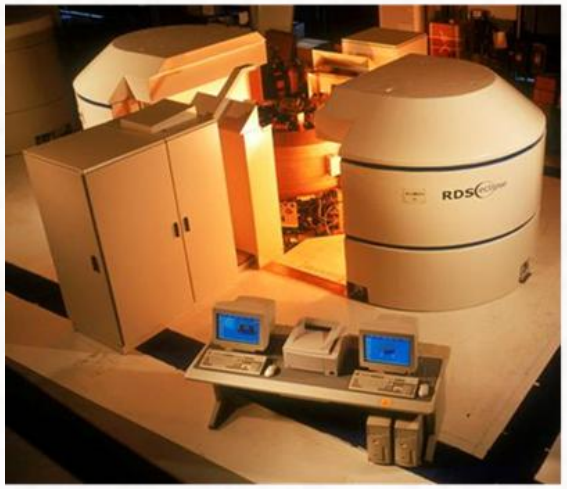
- 🎯 Kompetensi Dasar:
  - Menjelaskan berbagai prosedur produksi ^{18}F dan ^{68}Ga manual dan otomatis
  - Menjelaskan potensi riset dan pengembangan radiofarmaka PET ^{18}F dan ^{68}Ga
- 🎯 Indikator Keberhasilan:
  - Peserta dapat menjelaskan prosedur elusi generator ^{68}Ga
  - Peserta menunjukkan pemahaman melalui tanya jawab atau diskusi terkait prosedur produksi radiofarmaka ^{18}F dan ^{68}Ga manual dan otomatis

POKOK BAHASAN

- Radiofarmaka ^{18}FDG
- Workflow Produksi ^{18}FDG
- Prosedur Automatic Labeling ^{18}F
- Operating Procedures Generator Operating
- Prosedur Manual Labeling ^{68}Ga
- Prosedur Automatic Labeling ^{68}Ga

1 Radiofarmaka ^{18}FDG

Proses Produksi Radiofarmaka



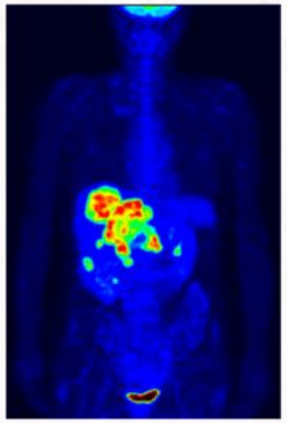
Production of Radioactive Isotopes

Synthesis of Radiopharmaceuticals

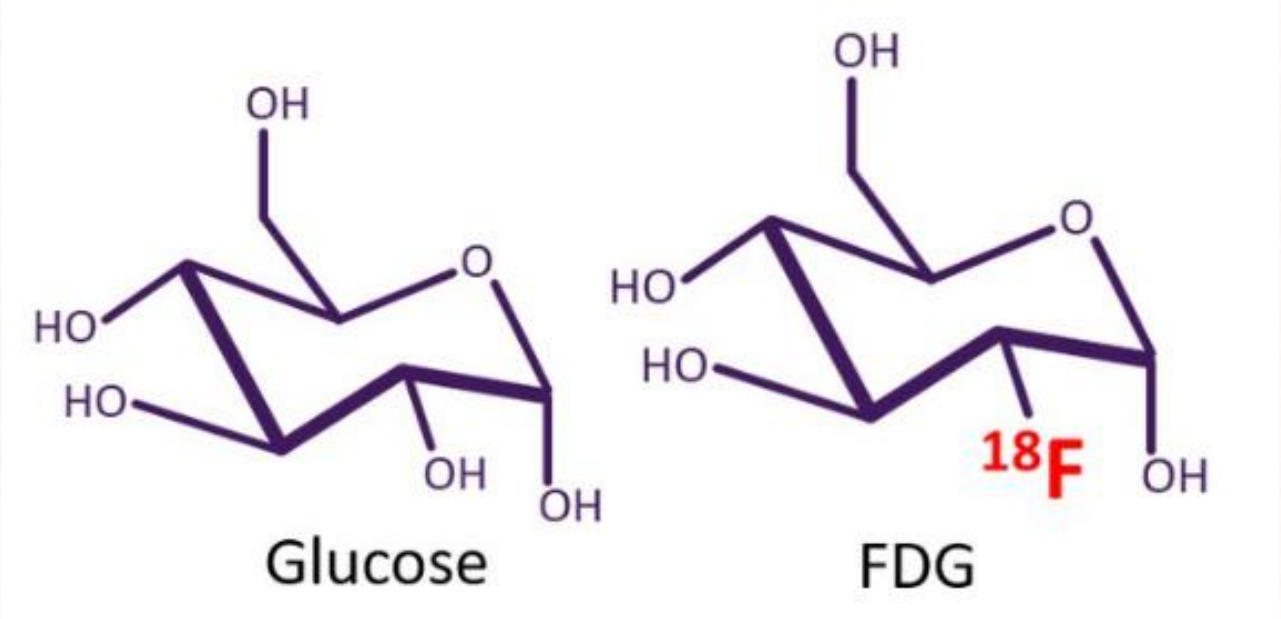
Dispensing

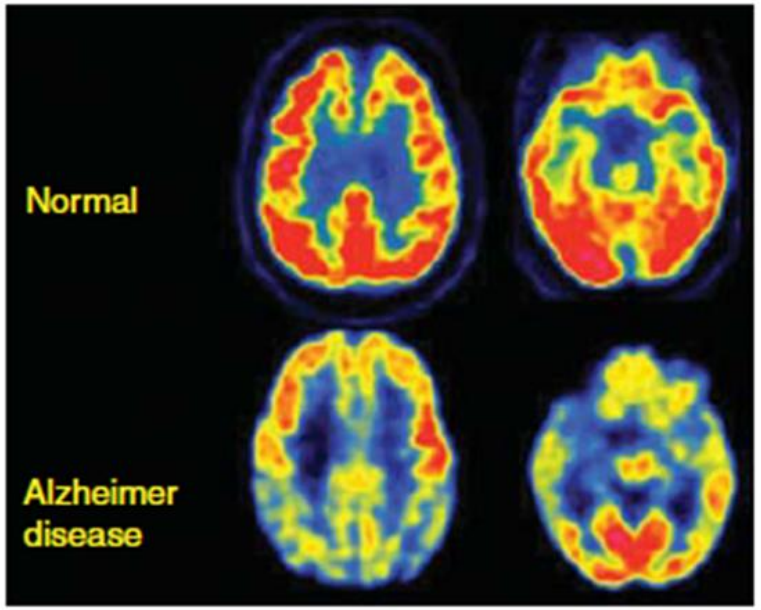
Quality Control

Distribution



Patients

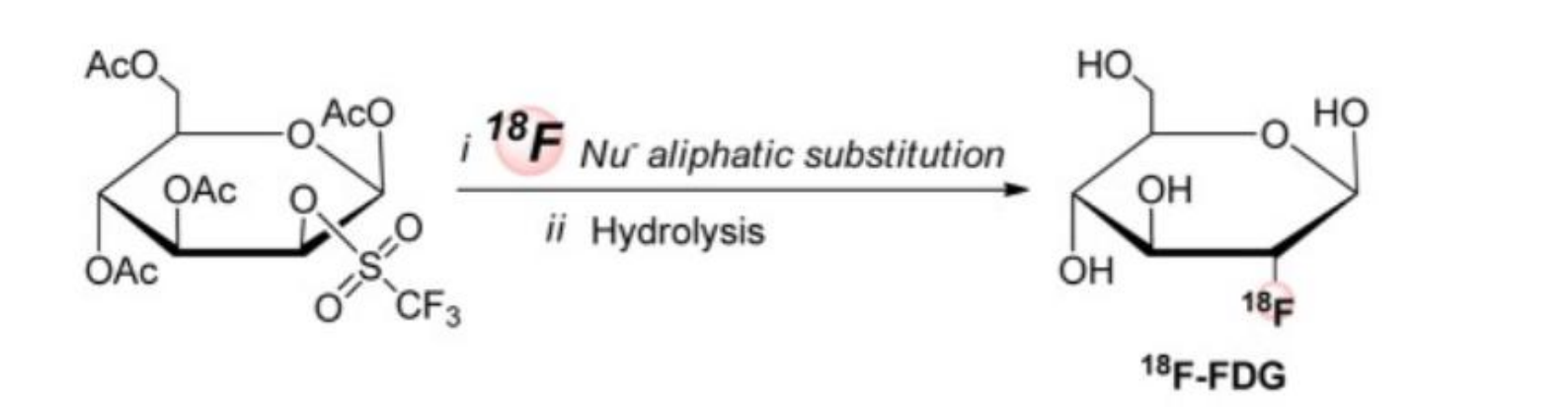




[^{18}F]Fluoro Deoxy Glucose

K.A. Johnson et al. *Cold Spring Harb Perspect* Med 2012;2:a006213

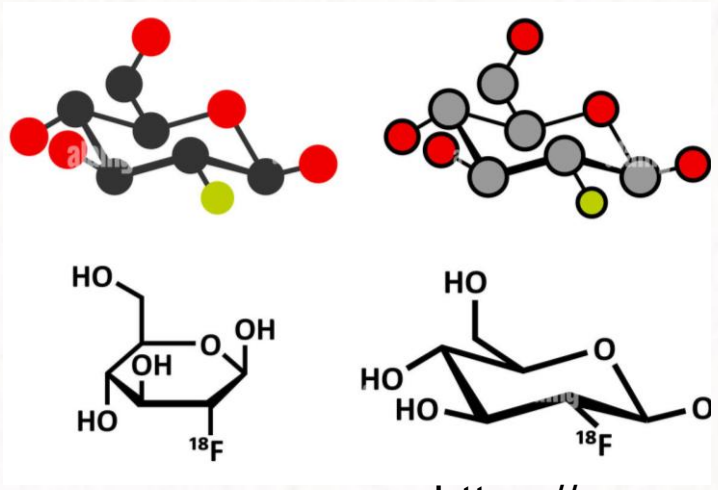
Penyiapan Radiofarmaka FDG



Prekursor

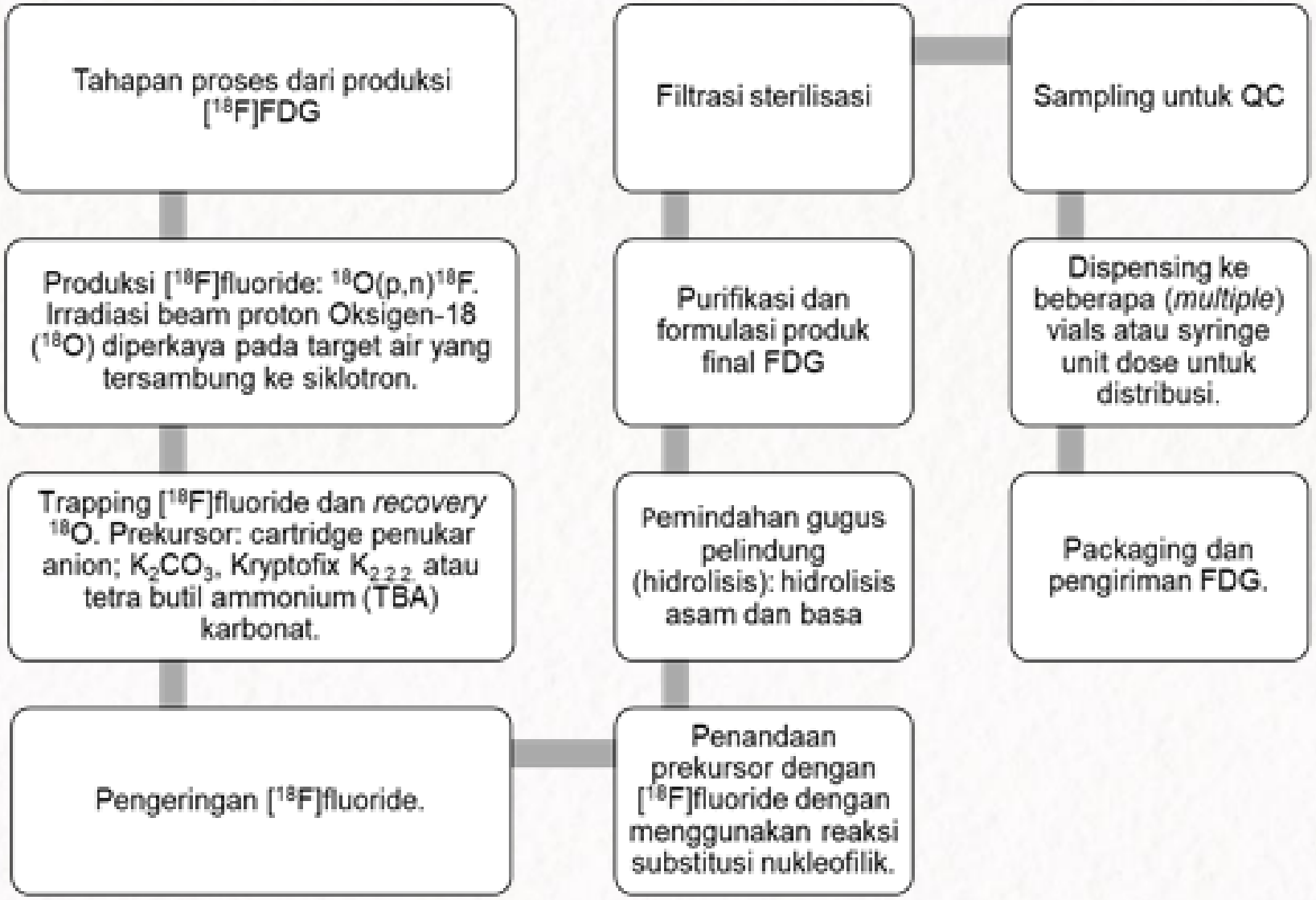
Jacobson O, Kiesewetter DO, Chen X. Bioconjug Chem. 2015; 26(1):1-18.

2 Workflow Radiofarmaka ^{18}FDG



https://www.alamy.com/

Proses Alir Produksi FDG



Tantangan produksi rutin [^{18}F]FDG

1. Kebutuhan produksi yang cepat dan andal
2. Keselamatan radiasi karena penggunaan jumlah radioaktivitas ^{18}F yang diproduksi oleh siklotron
3. Prinsip *current Good Manufacturing Practice* (cGMP) yang direkomendasikan oleh badan regulasi
4. *Cost-effective* yang harus ditanggung oleh pasien.

Modul Otomatis (*Automated Synthesis Module*)

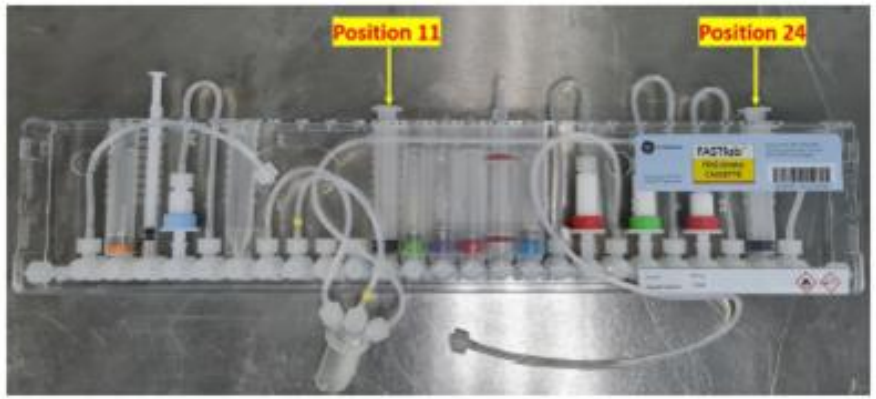
Modul otomatis adalah perangkat yang mampu melakukan secara otomatis serangkaian operasi yang dibutuhkan dalam penyiapan radiofarmasi.

Modul otomatis bisa *commercial* atau *custom made*.

Terdiri dari: *mechanical part* dan *chemistry part*.

Modul otomatis dapat berupa modul komersial atau modul yang dibuat khusus.

Kaset Tunggal (*single cassette*)
untuk Modul Sintesis Fastlab2 FDG



Todde et al. EJNMMI Radiopharmacy and Chemistry (2017) 2:8
Journal of Radioanalytical and Nuclear Chemistry, 2022

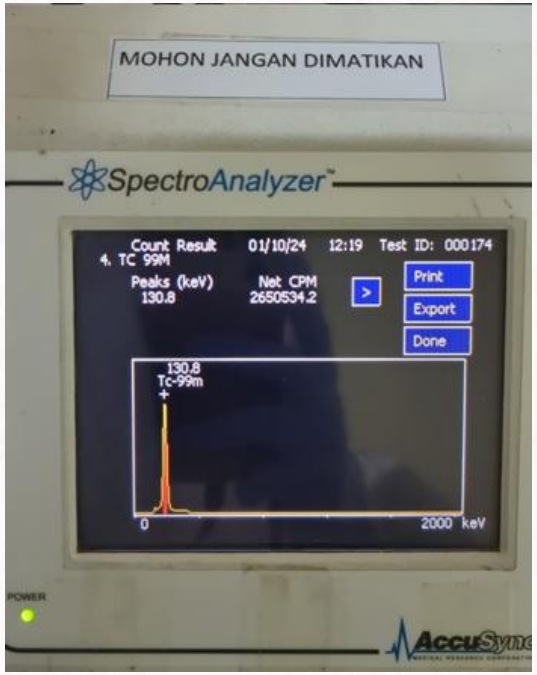
Modul Otomatis (*Automated Synthesis Module*)

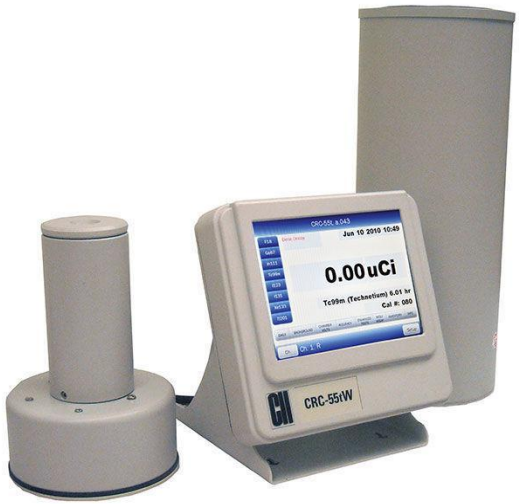
Tujuan:

- Terdokumentasi (GMP compliance) → Good Radiopharmacy Practices
- Fast
- Reliable
- Reproducible
- Pekerja terlindungi dari paparan radiasi yang besar

Modul sintesis komersial untuk produksi [^{18}F]FDG adalah Tracis ^{18}F-FDG QUAD, GE TracerLab MX, GE FASTlab, Bioscan, Inc. “F18-Plus” dan IBA Synthera, Sumitomo’s F300

Quality Control atau Kendali Kualitas Radiofarmaka ^{18}F

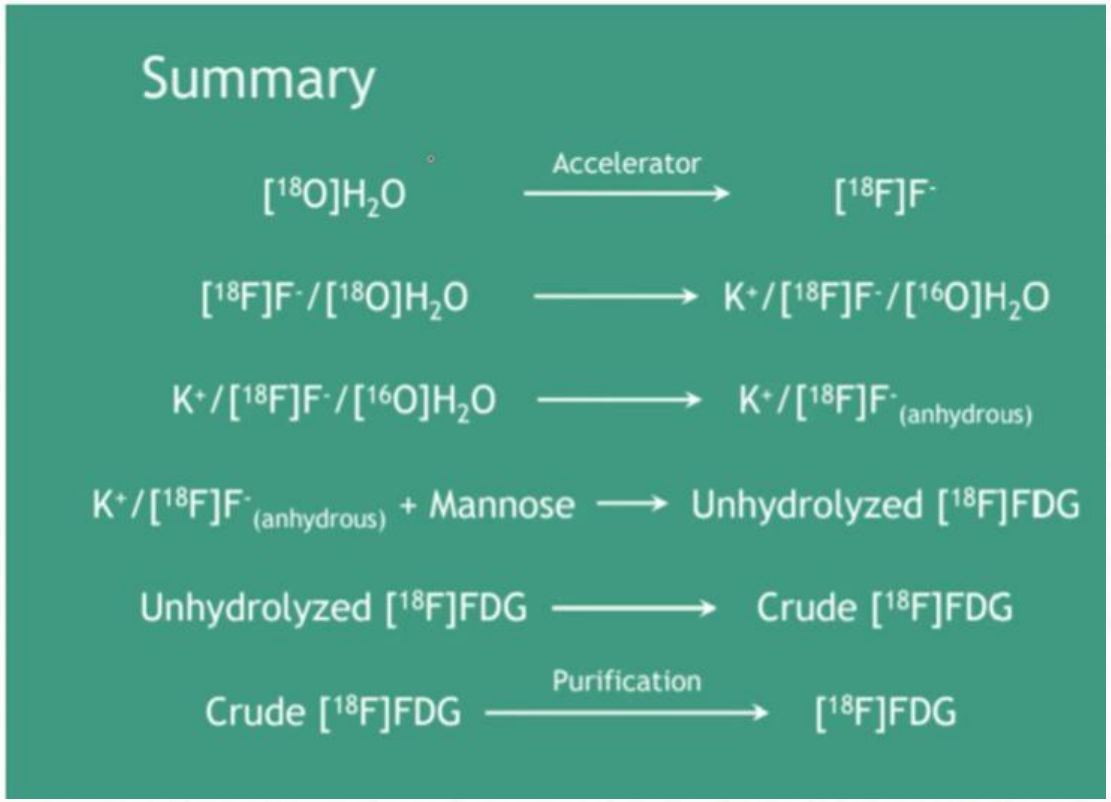




accumedi.com

Spesifikasi Kualitas dari FDG

Merujuk pada Pharmakope Internasional



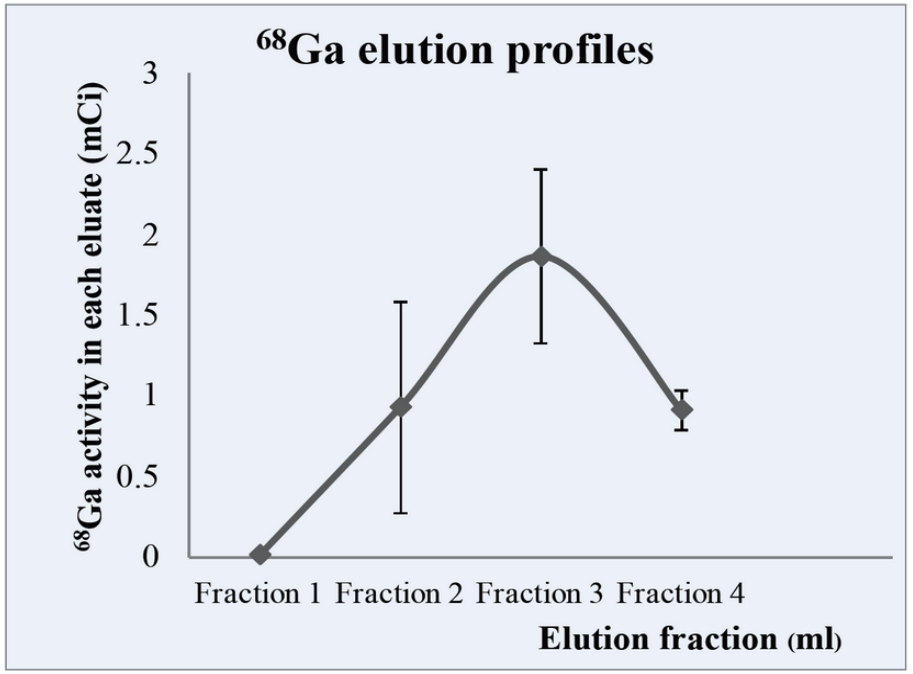
Quality parameter	Specification	Test method
Appearance	Colourless or slightly yellow solution.	Visual inspection
Identity (radiochemical and radionuclidic)	The radionuclidic and radiochemical identity are combined in the following fashion: Either tests A and C, or B and C may be applied. A. Gamma ray spectrum exhibits a major peak of 511 keV; B. The half-life is between 105–115 minutes; C. Distribution of radioactivity on a TLC strip corresponds to FDG	A. Gamma spectrum, using a gamma spectrometer B. Dose calibrator or gamma counter C. TLC with radioactivity scanner
Radionuclidic purity	Not less than 99% of total radioactivity is due to ^{18}F.	Gamma spectrometer
Radiochemical purity	Not less than 95% of total radioactivity in the test chromatogram corresponds to FDG.	TLC with radioactivity scanner
Assay of radioactivity	±10% of stated activity	Dose calibrator
pH	pH value, 4.5–8.5	pH paper (validated with pH meter)
Chemical purity: Kryptofix 2.2.2	Not more than 0.22 mg/mL*	TLC
Chemical purity: tetraalkylammonium ions	Not more than 0.275 mg/mL* Only to be measured if employed in synthesis.	HPLC
Chemical purity: 2-Chloro-2-deoxy-D-glucose	Not more than 0.05 mg/mL*	HPLC
Chemical purity: 2-Fluoro-2-deoxy-D-Glucose	Not more than 1 mg/mL*	HPLC
Residual solvents: acetonitrile and ethanol	No more than 0.04% acetonitrile and 0.5% ethanol (Based upon USP and Ph. Eur. specifications); this quality parameter is not mentioned in Ph.Int.	GC with FID detector

Techdoc IAEA IAEA RADIOISOTOPES AND RADIOPHARMACEUTICALS SERIES No. 3

3 Radiofarmaka ^{68}Ga: Generator Operating Procedure

Generator Operating Procedures

- After installation, the generator has to be eluted with a total of 30-40 mL elution medium
- Afterwards elute the generator with 4 mL elution medium.
- The elution profile was studied by collecting the eluates in fractions of 1 ml for 4 fractions. The elution yield of ^{68}Ga activity in each fraction was immediately determined in a dose calibrator.



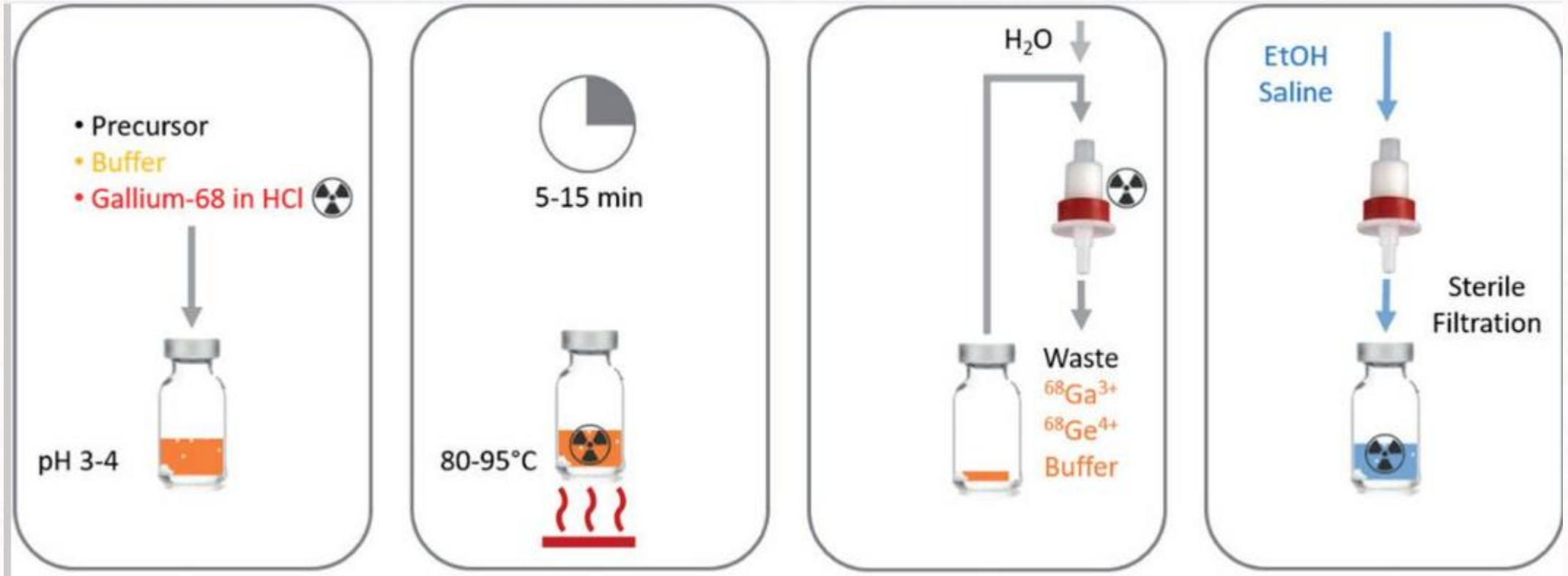
Parameter	Specification
Appearance	clear, colourless
Radionuclidic identity (half-life determination)	62 to 74 min
Radionuclidic identity (gamma-ray spectrometry)	511 + 1077 keV
Radionuclidic purity (gamma-ray spectrometry)	>99.9%
^{68}Ge breakthrough	<0.001%
Radiochemical purity (TLC)	> 95%
Microbiological quality	sterile
Bacterial endotoxins	< 175/V EU/ml
pH	<2
Iron Zinc	< 10 µg/GBq < 10 µg/GBq

Velikyan I. Molecules. 2015 Jul 16;20(7):12913-43

Sriprapa, Volume 75, No.10: 2023 Siriraj Medical Journal

4 Prosedur Manual Labeling Ga-68

Prosedur Umum Penandaan (Radiolabeling) dengan ^{68}Ga



Nelson BJB, Andersson JD, Wuest F, Spreckelmeyer S.. EJNMMI Radiopharm Chem. 2022 Oct 22;7(1):27; Meisenheimer et al, 2019

Materials

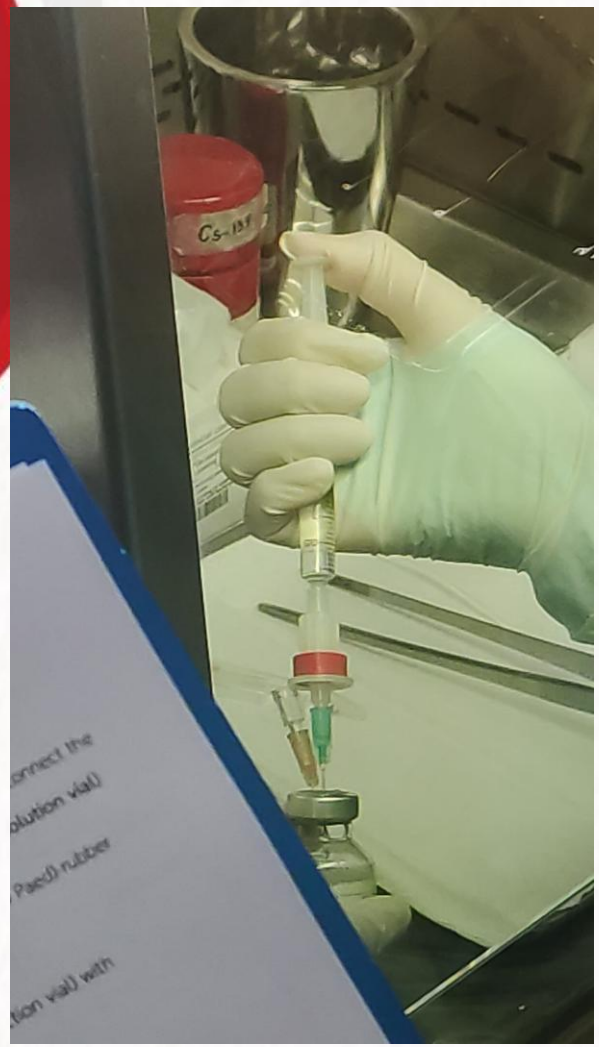
- Form/Laboratory procedure checklist

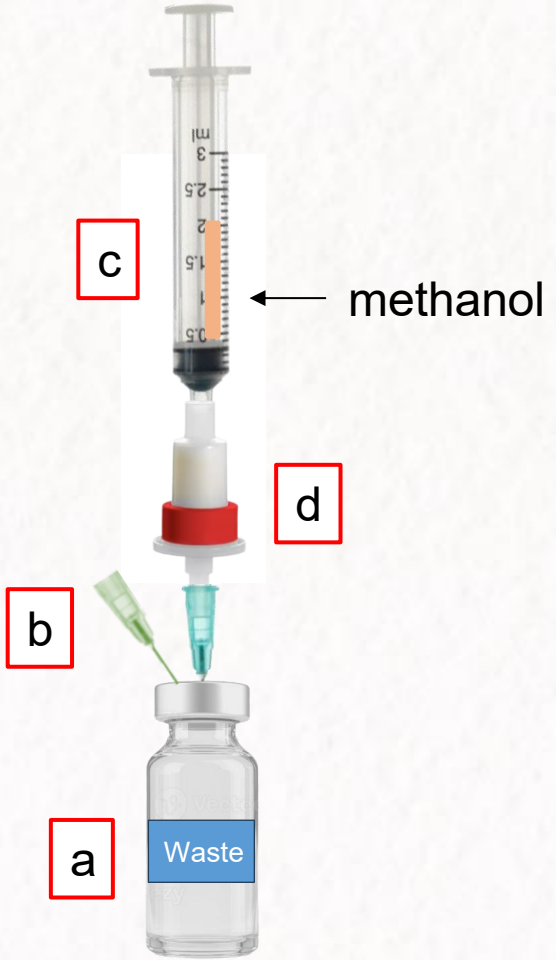
- Ga-68 generator
- Laminar air flow
- Waterbath
- Dose calibrator
- Well counter
- Container = 3

- Peptide (PSMA 11)
- Acetate buffer for PSMA 11
- Methanol
- 0.05 M HCl
- Normal saline (NSS)
- Water for injection
- Ammonium acetate
- Ethanol

- Sterile vial for Ga-68 eluate (final product)
- Vial for waste
- Vial for reaction/crude product
- C-18 cartridge = 1
- Syringe 3 ml = 3
- Syringe 5 ml = 3
- Syringe 1 ml for QC = 1
- Blue filter (0.22 µm) = 1
- Ventilation needle
- Syringe shield = 1
- pH paper
- ITL-SG Paper
- Chamber chromatography

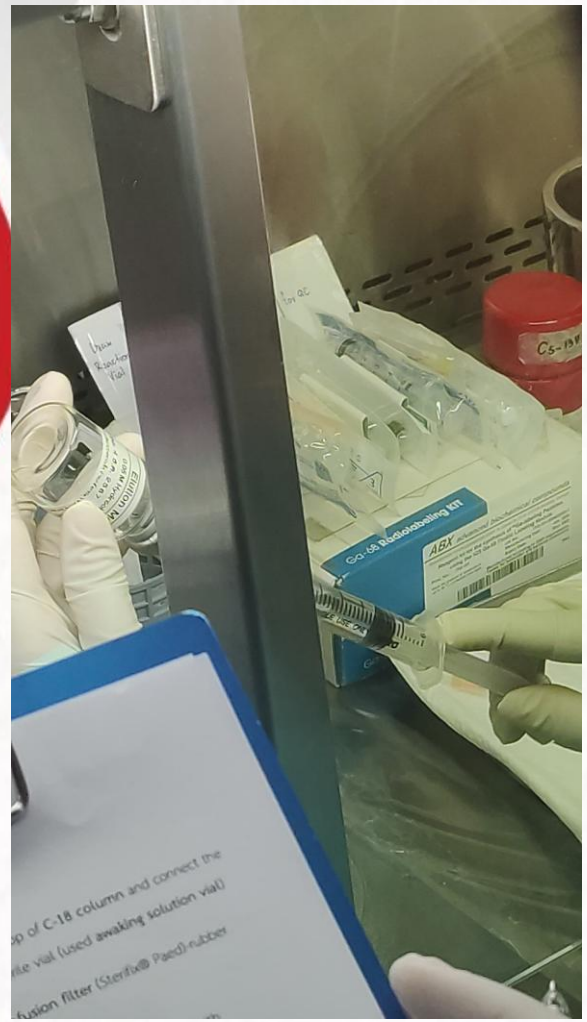
Manual Labeling of Gallium-68



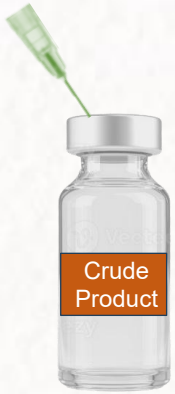


C-18 ACTIVATION

- Prepare a **waste vial** and ensure it is properly labeled **(a)**.
- Insert a **vent needle** into the waste vial to allow airflow **(b)**.
- Take a 3 mL syringe, attach a green needle, and fill the syringe with **2 mL of methanol (c)**.
- Connect the **C-18 cartridge** securely to the alcohol-filled syringe **(d)**.
- **Slowly activate the C-18 cartridge** by releasing the alcohol drop by drop, ensuring even wetting.
- Once activation is complete, set the cartridge aside and proceed with the next steps.

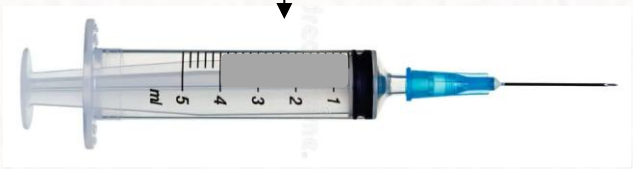


a



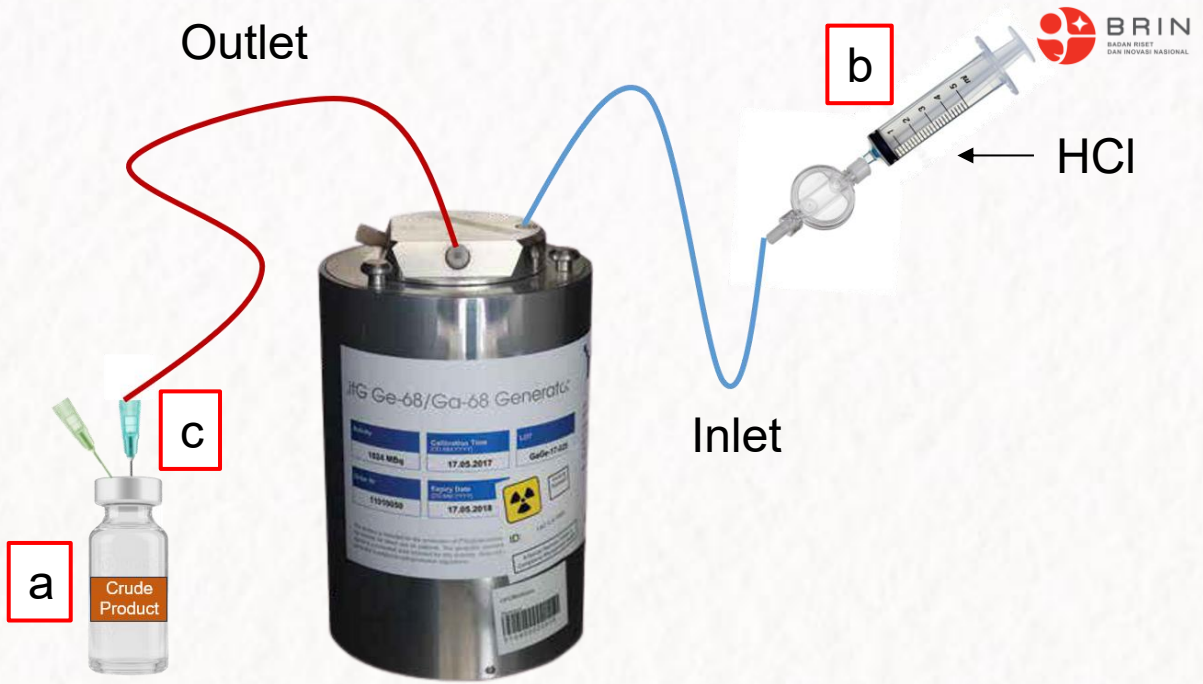
b

HCl c



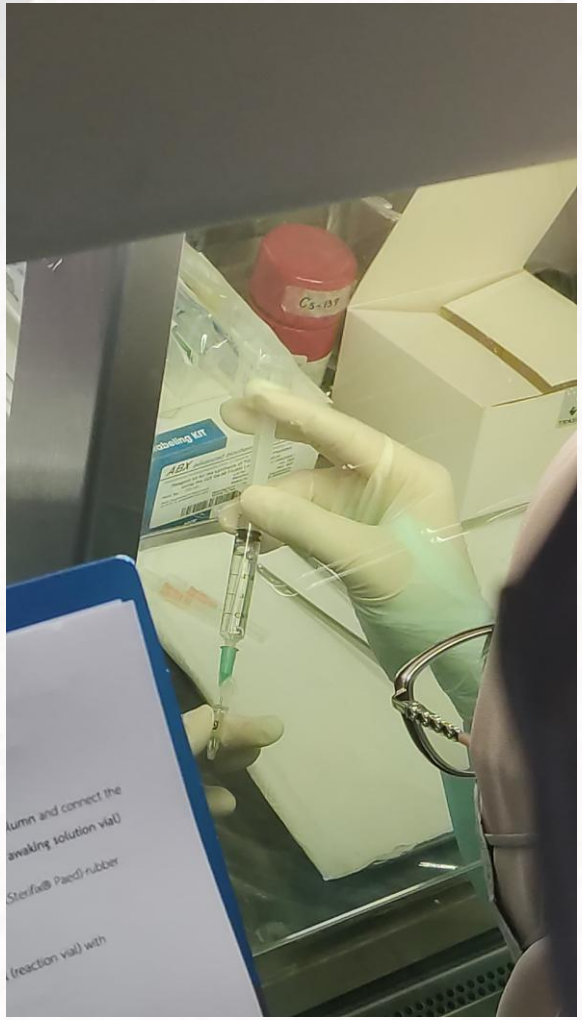
GENERATOR ELUTION PREPARATION

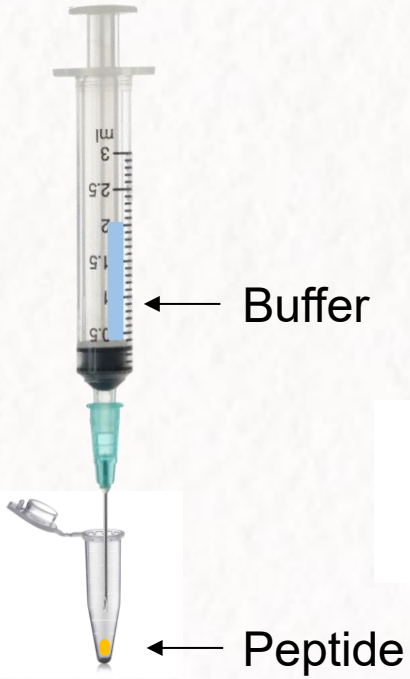
- Prepare a vial for the crude product/RNX vial and attach a vent needle **(a)**.
- Place the vial securely inside a shielded container **(b)**.
- Prepare **4 mL of HCl** (0.05 M) in a 5 mL syringe **(c)**.



ELUTION PROCESS

- Place the elution vial on the generator **(a)**.
- Connect the HCl vial to the generator inlet **(b)**.
- Insert the generator outlet needle into the crude product vial **(c)**.
- Verify that there are no leaks.
- Perform the elution process **slowly and steadily**.
- Check the **BCG activity** and **the activity of the eluted product**.

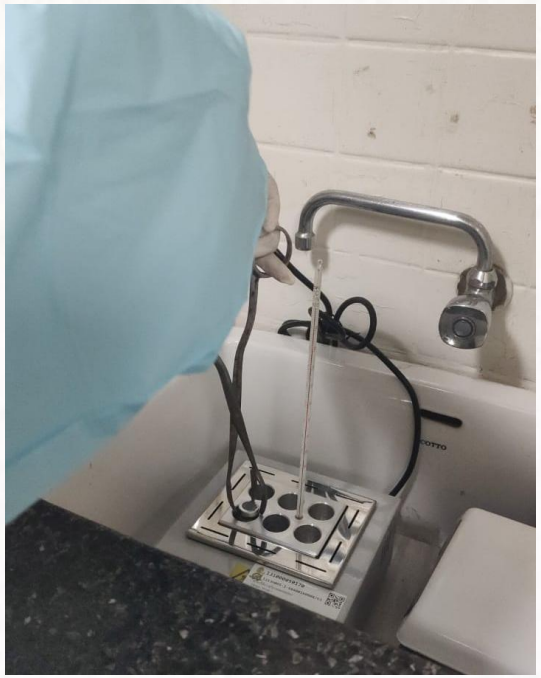


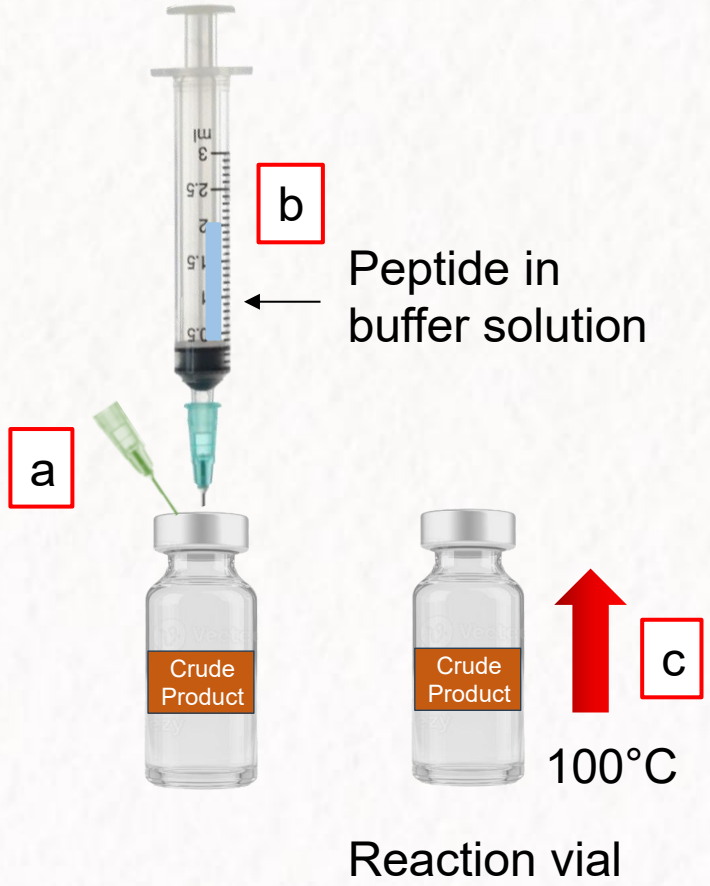


PEPTIDE PREPARATION

- Prepare **2 mL of buffer** in a 3 mL syringe.
- Draw the peptide into the syringe, then gently mix by pulling and pushing the plunger 3–4 times to ensure it is fully resuspended.

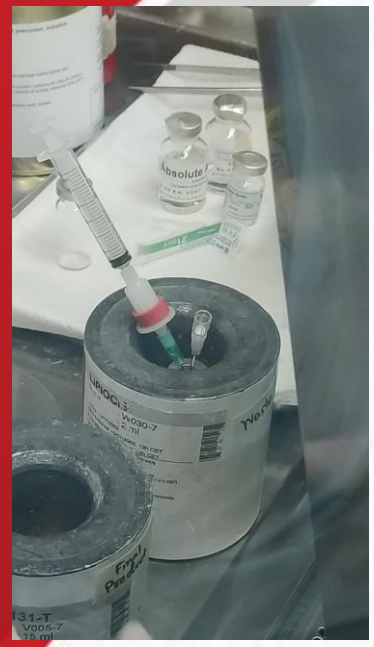
Note: Always draw the peptide first before resuspension.

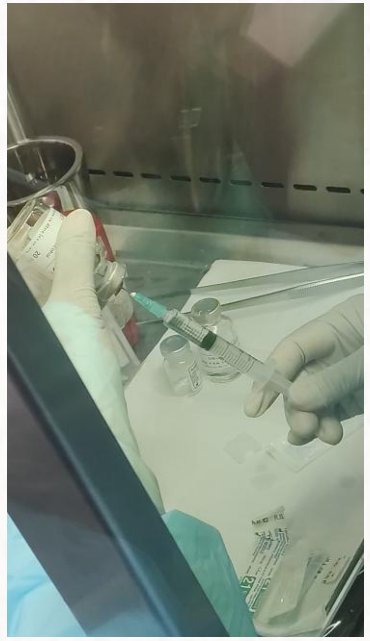


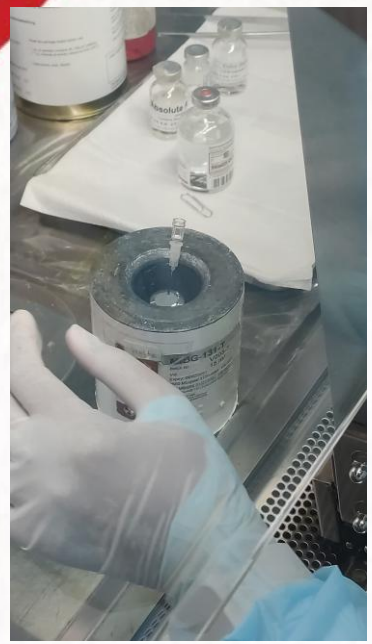


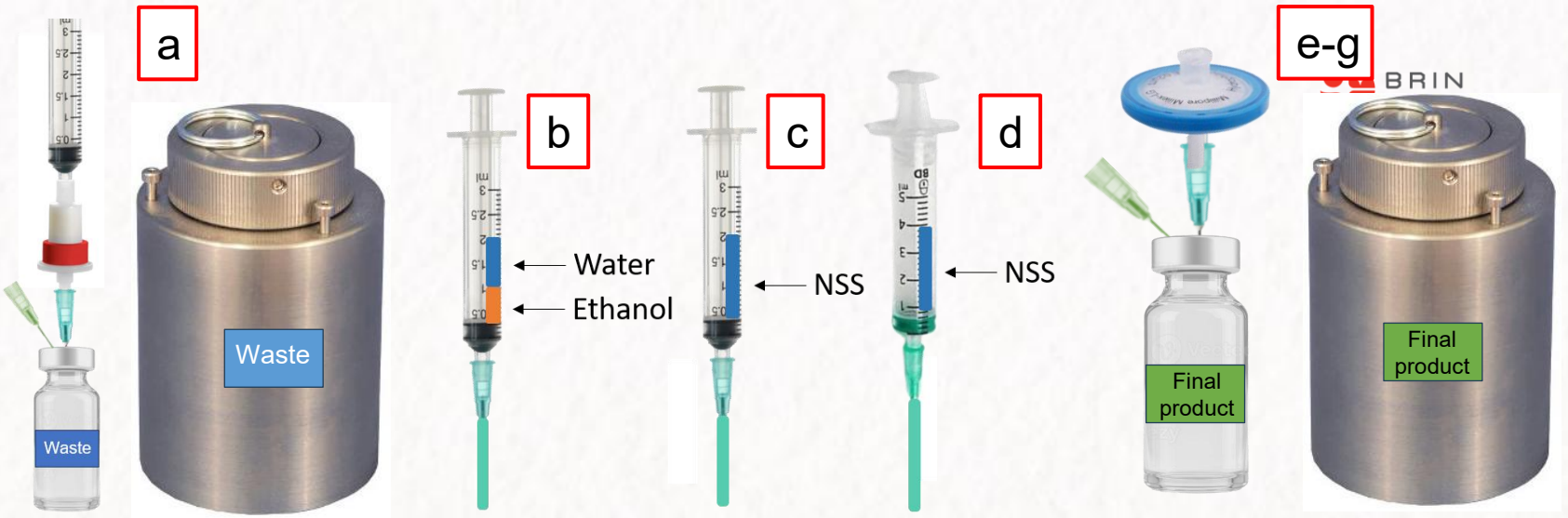
LABELING PROCESS

- Attach a venting needle to the crude product vial **(a)**.
- Add the peptide to the vial **(b)**.
- Remove the venting needle.
- Heat the vial **100°C** for **15 minutes (c)**.
- Allow the vial to cool for **5 minutes**.
- Wait for the process to be completed.



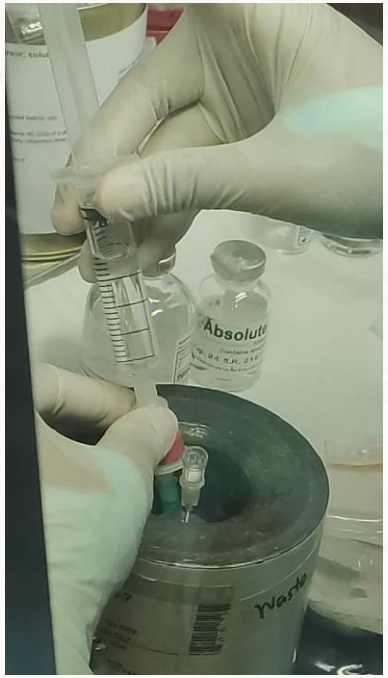


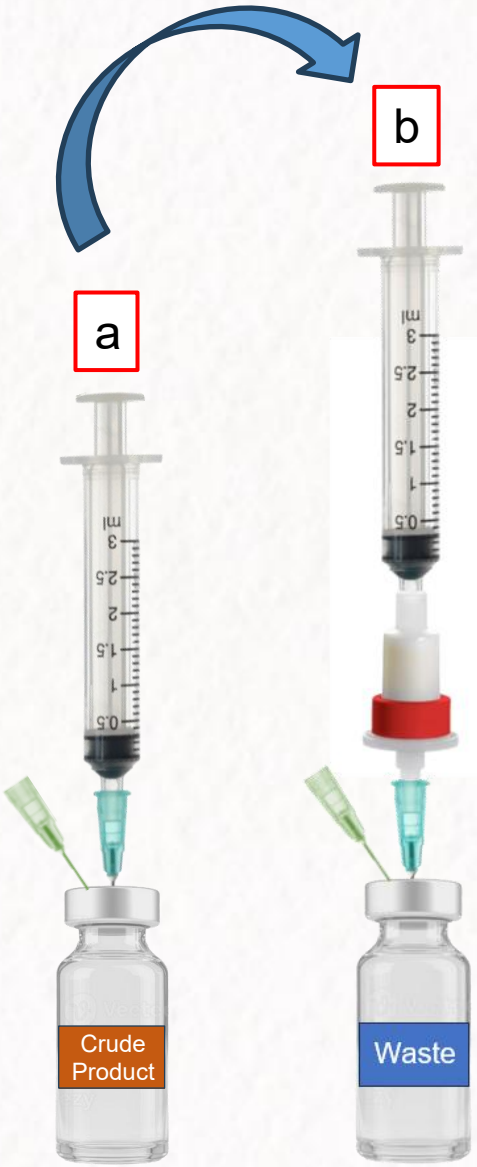




PREPARATION FOR FINAL PRODUCT

- Place the waste vial and the C-18 cartridge into the waste container **(a)**.
- Prepare a 3 mL syringe containing 1 mL of water and 1 mL of ethanol (purify product) **(b)**.
- Prepare a 3 mL syringe filled with 2 mL NSS (wash the RXN vial) **(c)**.
- Prepare a 5 mL syringe containing 4 mL of NSS **(d)**:
  - 1 mL to wash the filter.
  - 3 mL to wash the C-18 column/elute the product.
- Prepare the final product vial and its container **(e)**.
- Attach a venting needle to the final product vial **(f)**.
- Prepare a blue filter (0.22 µm) and a green needle, then insert them into the final product vial **(g)**.

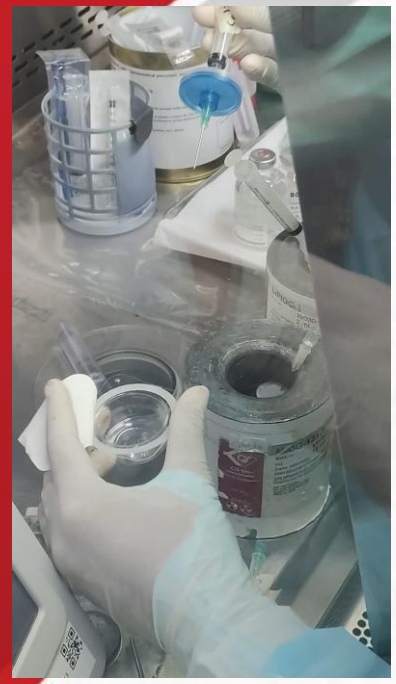


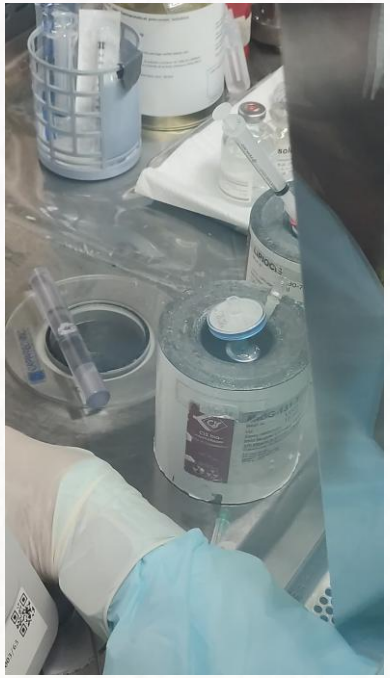


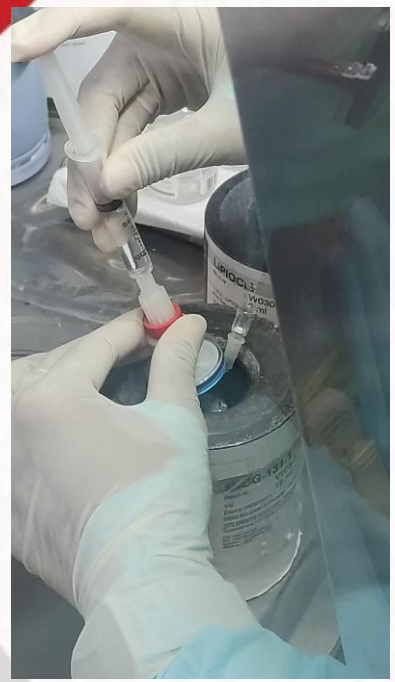
Reaction vial
(Ga 68-peptide)

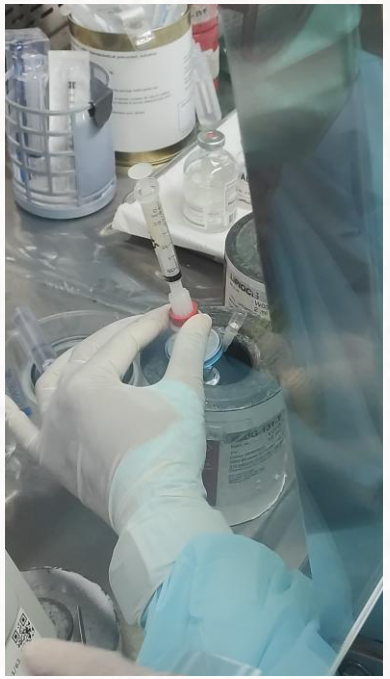
FINAL PROCESS

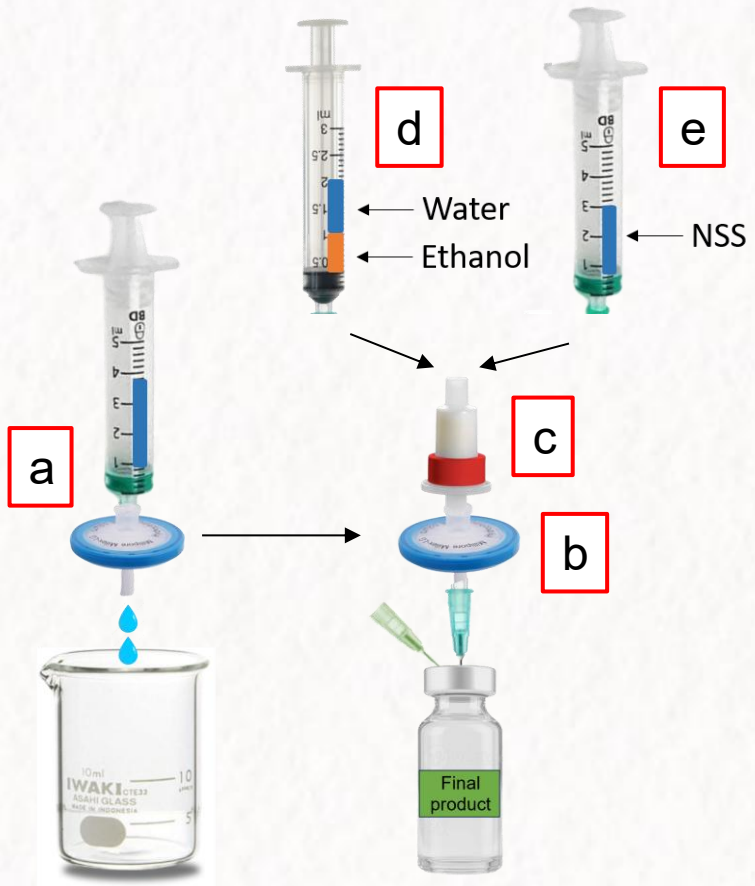
- Transfer the ^{68}Ga-peptide reaction vial (after heating and cooling) into the LAF.
- Insert a vent needle into the reaction vial.
- Withdraw all ^{68}Ga-peptide from the reaction vial and load it onto the C-18 column attached to the waste vial **(a)** (replace the syringe as needed), perform the transfer slowly, drop by drop **(b)**.
- Rinse the reaction vial containing residual ^{68}Ga-peptide with **2 ml of saline** using a syringe (ensure thorough rinsing of the vial walls and the bottom of the septum).
- Transfer the rinse back onto the C-18 column, which remains attached to the waste vial.



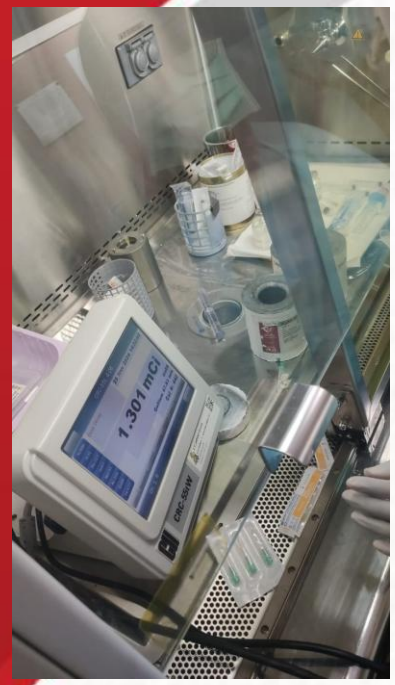


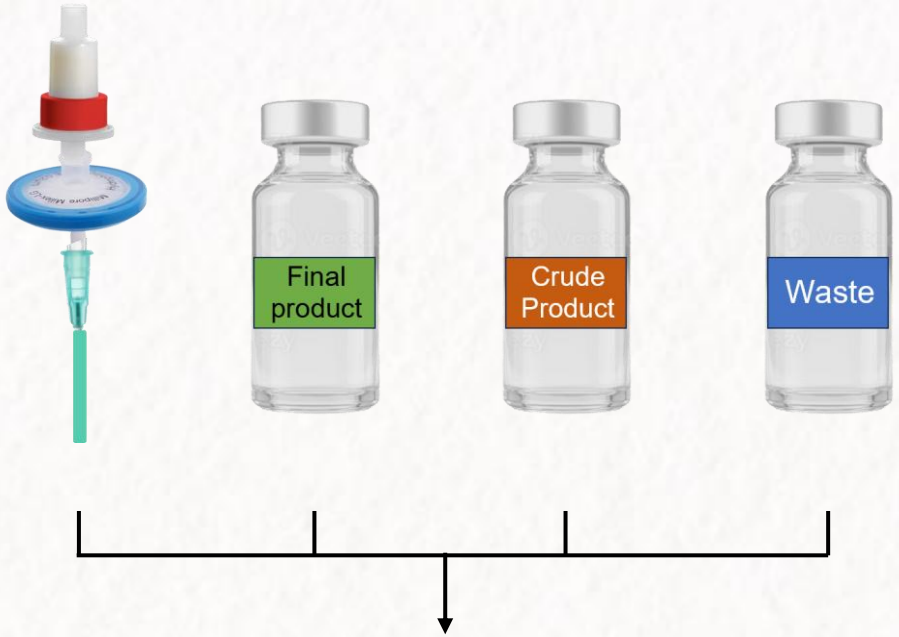






- Rinse the blue filter using a syringe filled with 4 ml of NSS (use only 1 ml at a time) as follows **(a)**:
  - Detach the blue filter from the final product vial.
  - Rinse the filter and discharge the rinsate into a separate container/waste bin.
- Reattach the blue filter and needle to the final product vial **(b)**.
- Detach the C-18 column from the waste vial and securely attach it to the blue filter on the final product vial **(c)**.
- Elute the product through the C-18 column using a syringe containing an ethanol:water mixture, ensuring no leaks **(d)**.
- Push the elution quickly to ensure the product is completely released.
- Wash with 3 ml of NSS (after 1 ml NSS has been used initially) **(e)**.

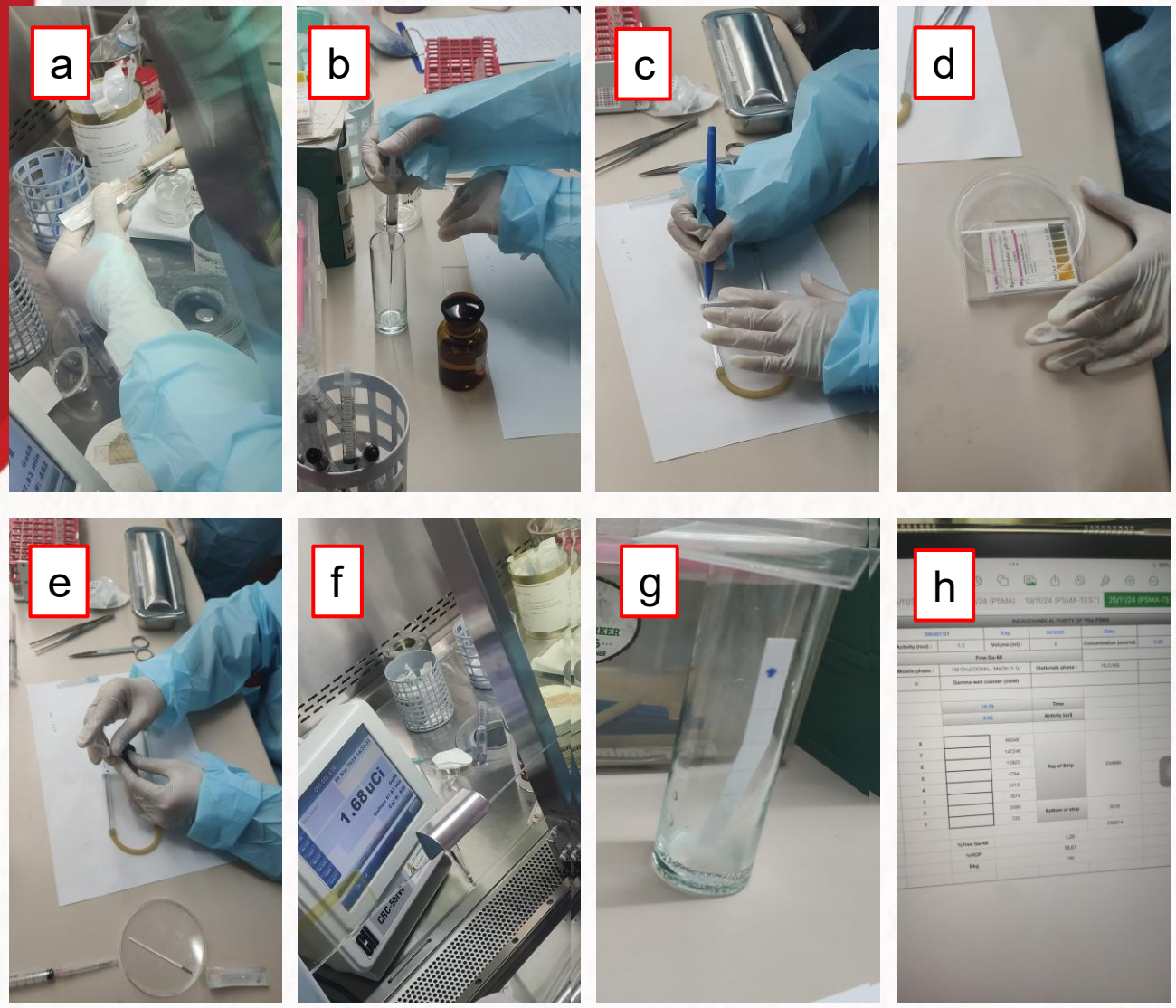




- Check the activity in the following:
  - C-18 column, filter, and needle
  - Waste vial
  - Reaction/crude product vial
  - Final product vial

Parameters	Activity
C-18 column, filter & needle	2.24 uCi
Waste vial	81 uCi
Reaction/crude product vial	0.64 uCi
Final product vial	1.301 mCi

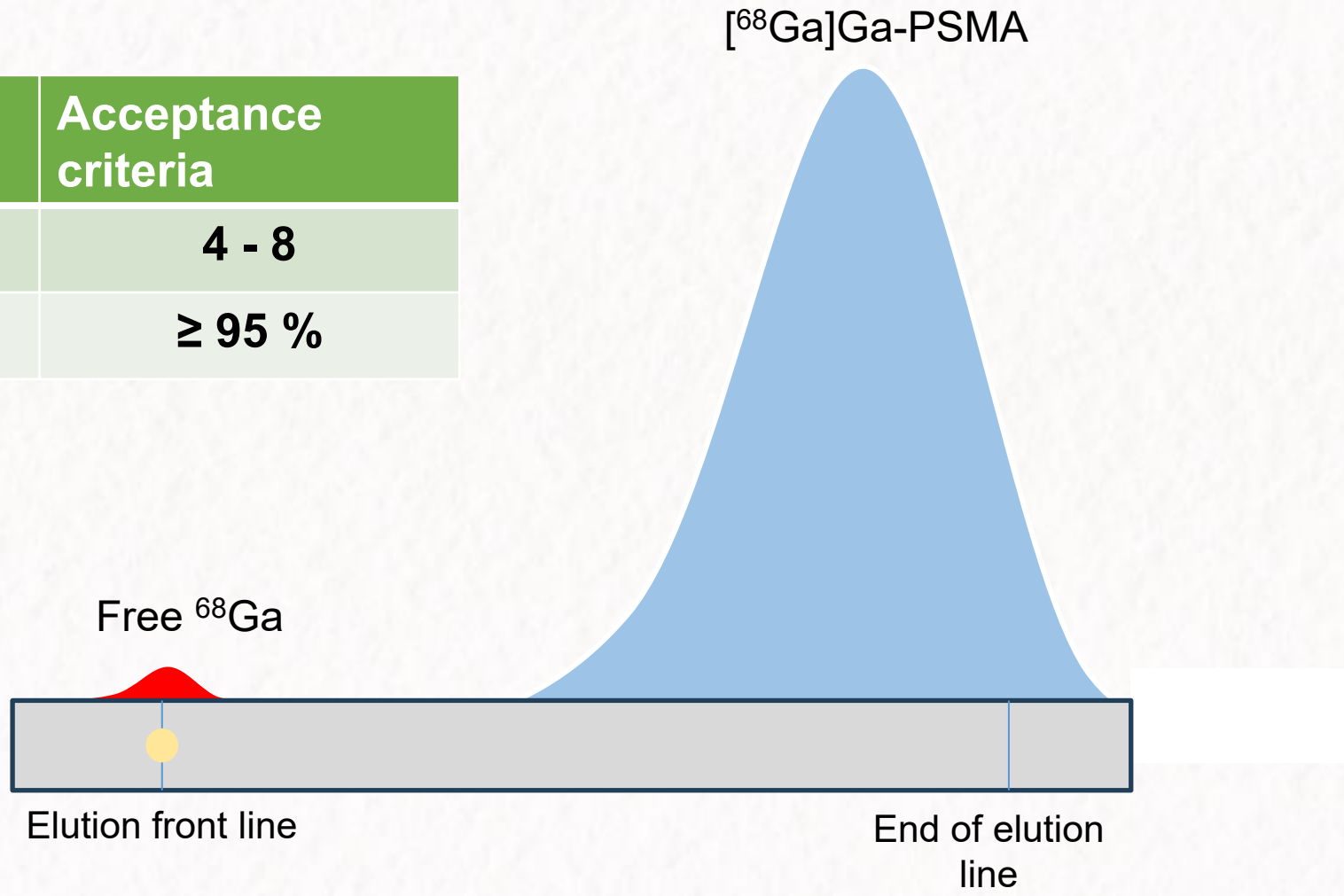
Quality Control of **Gallium-68**



- Withdraw **0.1 ml** of the product using a syringe 1 mL **(a)**.
- Shield the syringe with Pb for radiation safety.
- Prepare the elution solution, **ethanol** & **ammonium acetate** (1:1 ratio), & pour it into the elution chamber **(b)**.
- Prepare the **ITLC-SG paper** and mark the top edge with a blue pen **(c)**.
- Spot the pH paper with the sample **(d)**.
- Spot the ITLC-SG paper with the sample and measure the activity **(e-f)**.
- Perform elution by placing the ITLC-SG paper into the chamber **(g)**.
- Wait until the elution process is complete.
- Calculate the **RCP** of the product **(h)**.

Quality Control of ^{68}Ga

Parameters	Acceptance criteria
pH	4 - 8
RCP	≥ 95 %



Radiochromatogram of [^{68}Ga]Ga-PSMA

Spesifikasi ^{68}Ga[Ga]-DOTA-TOC dan ^{68}Ga[Ga]-PSMA-11

Table 4.

Specifications of [^{68}Ga]Ga-DOTA-TOC and [^{68}Ga]Ga-PSMA-11

Test	Specifications [^{68}Ga]Ga-DOTA-TOC	Specifications [^{68}Ga]Ga-PSMA-11 (In Ph. Eur. 10.4, 3044)	Method
Appearance	Clear, colourless solution	Clear, colourless solution	Visual
pH	4–8	4–8	pH strips
Endotoxins	< 175I.E./V (maximal dose in mL)	< 175I.E./V (maximal dose in mL)	
Radiochemical identity and Purity	> 91% overall purity	> 95% overall purity	TLC
	Colloidal ^{68}Ga: < 3%	Colloidal ^{68}Ga: < 3%	
	Free $^{68}GaCl_3$: < 2%	> 95% overall purity	HPLC
Radionuclidic identity	0.511 MeV, 1.077 MeV, sum peak 1.022 MeV	0.511 MeV, 1.077 MeV, sum peak 1.022 MeV	Gamma spectrometry
	62 – 74 min	61 – 75 min	Half-life
Radio nuclidic purity	^{68}Ge < 0.001%	^{68}Ge < 0.001%	Gamma spectrometry
Residual solvents	Ethanol max. 10% (V/V) or 2.5 g/dose	Ethanol max. 10% (V/V) or 2.5 g/dose	GC
Chemical Purity	Edotreotide, Galliumedotreotide, others	PSMA-11, gallium PSMA-11, others < 30 µg/V	HPLC 220 nm detection (DOTA-TOC), 280 nm (PSMA-11)
	< 50 µg/V		
	HEPES < 200 µg/V	HEPES < 500 µg/V	TLC
Sterility	Sterile	Sterile	Membrane filtration

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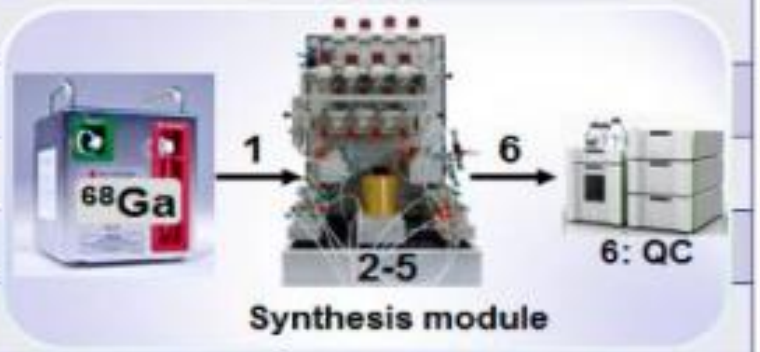
Nelson BJB, Andersson JD, Wuest F, Spreckelmeyer S. Good practices for ^{68}Ga radiopharmaceutical production. EJNMMI Radiopharm Chem. 2022 Oct 22;7(1):27. doi: 10.1186/s41181-022-00180-1

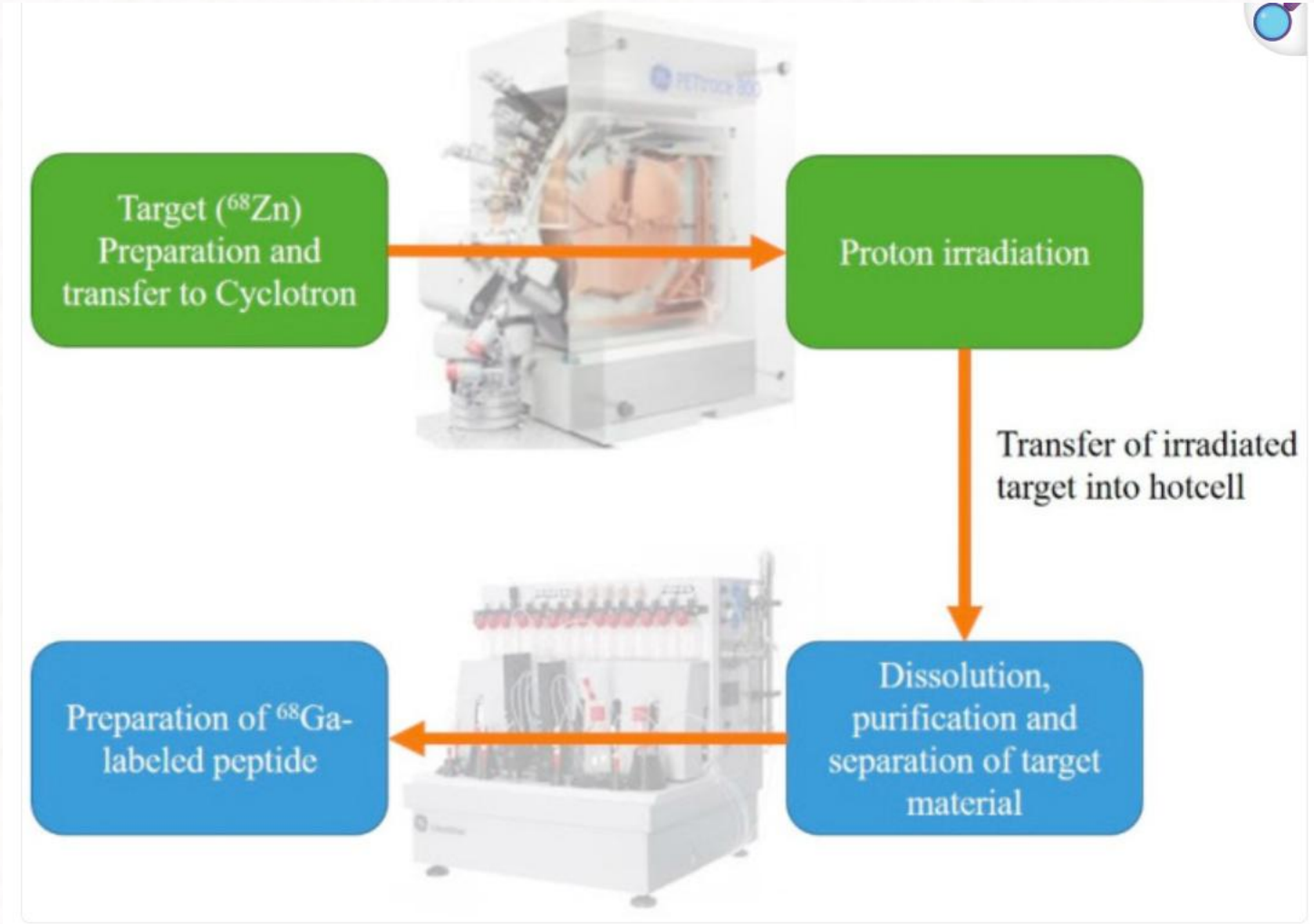
5 Prosedur Labeling Otomatis ^{68}Ga

(**Left column**) Typical preparation steps of a ^{99m}Tc-based registered radiopharmaceutical; (**Right column**) Basic steps of an automated manufacturing of a ^{68}Ga-based radiopharmaceutical.

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



Velikyan I. Molecules. 2015 Jul 16;20(7):12913-43



. Pharmaceutics. 2022 Dec 26;15(1):70.

Automatic Labeling dengan ^{68}Ga

Automation:

- Radioprotection
- High reliability
- Reproducibility
- Robustness of the production
- GMP compliance

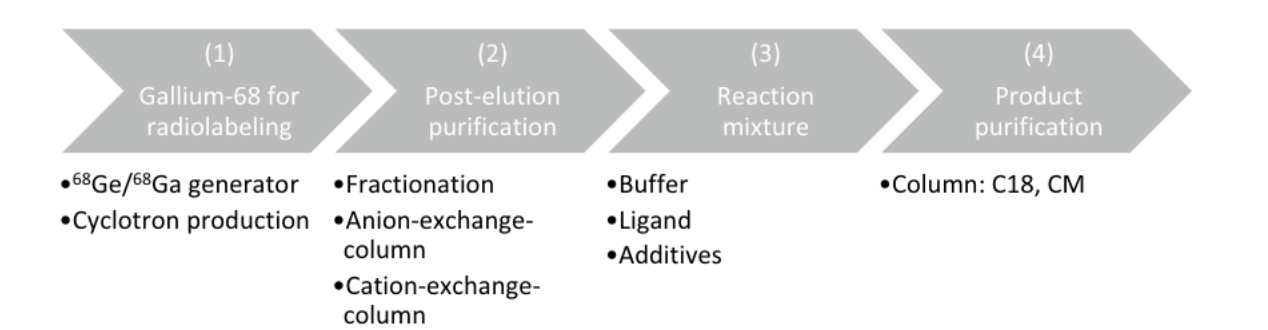


Fig. 3 Schematic overview of automated radiolabeling process

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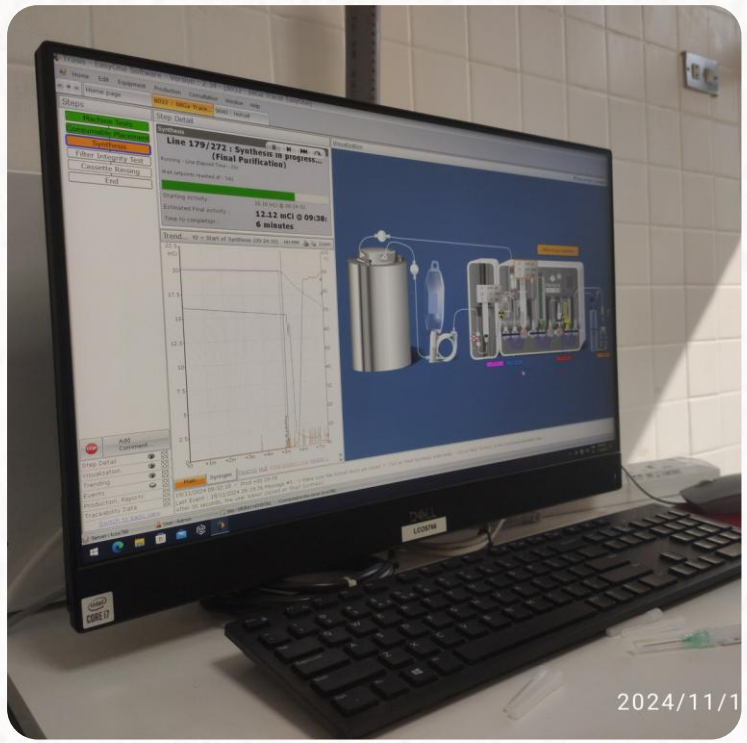
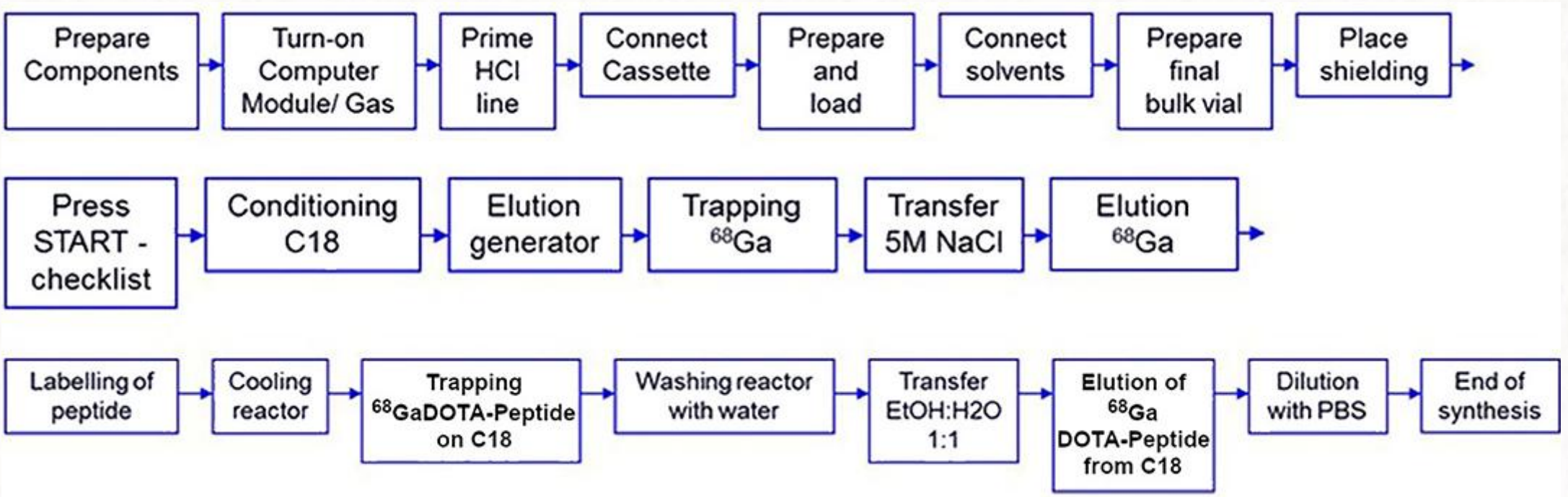


Workflow of Automation



Lepareur. Front. Med., 10 February 2022. Sec. Nuclear Medicine. Volume 9 - 2022 | https://doi.org/10.3389/fmed.2022.812050

Rangkuman

Tahapan Singkat Pembuatan ^{18}FDG

1. **Produksi ^{18}F**: Dibuat menggunakan **siklotron**, dengan menembakkan proton ke ***^{18}O-enriched water*** untuk menghasilkan **^{18}F-fluoride**.
2. **Sintesis ^{18}FDG**:

- **^{18}F-fluoride** dimurnikan menggunakan **kolom QMA**.
- Direaksikan dengan **prekursor mannose triflate** dalam kondisi anhidrat.
- Dilakukan **hidrolisis** untuk menghasilkan **^{18}FDG** yang siap digunakan dalam pencitraan PET.

3. Penyiapan radiofarmaka ^{68}Ga berbasis ligan peptida seperti DOTA-TATE dan PSMA dapat dilakukan dengan cara manual dan otomatis.

4. Generator dan sintesis modul automatis beserta prekursor tersedia secara komersial untuk produksi radiofarmaka ^{68}Ga berbasis ligan peptide.

Terima Kasih

Atas Perhatian Anda

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