

# **RADIOFARMACOLOGIE, ALLEEN ALS DE KWALITEIT GOED IS!**

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Stichting Kwaliteitsbewaking  
Medische Laboratoriumdiagnostiek

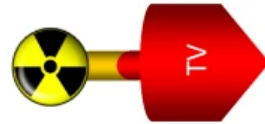
## Disclosure

De spreker heeft

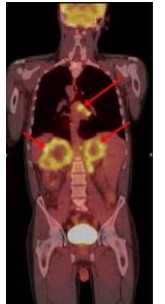
- Geen financiële banden met de IVD industrie
- Geen sponsoring door belanghebbende industrie
- Geen honoraria van belanghebbende industrie
- Geen aandeelhouder van belanghebbende industrie
- Geen andere relaties met belanghebbende industrie die gezien kunnen worden als belangenverstrengeling

# WHAT IS A RADIOPHARMACEUTICAL?

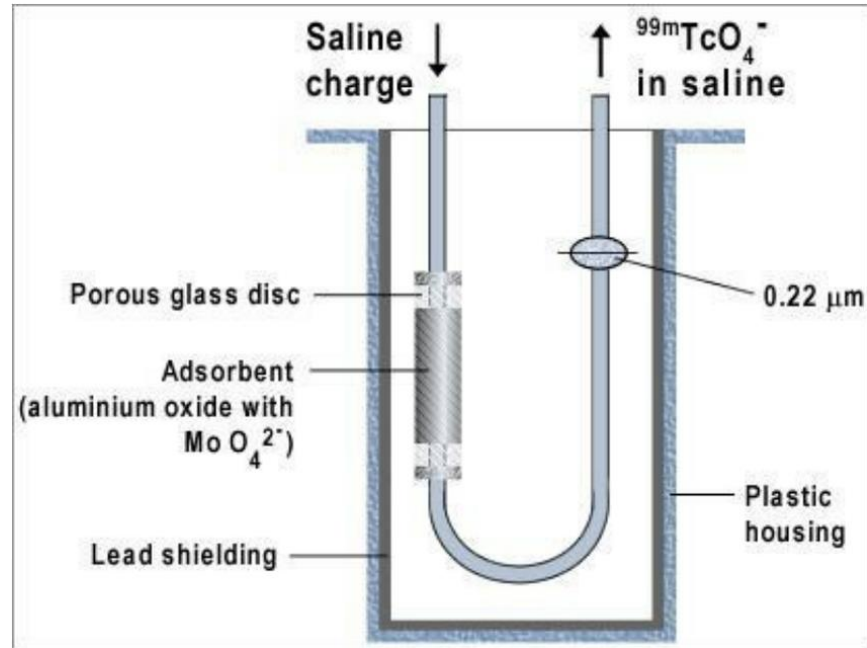
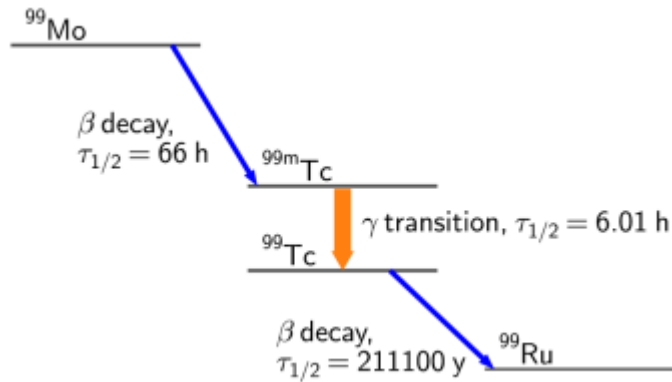
- Radiopharmaceuticals, or medicinal radiocompounds, are a group of pharmaceutical drugs containing radioactive isotopes. Radiopharmaceuticals can be used as diagnostic and therapeutic agents.



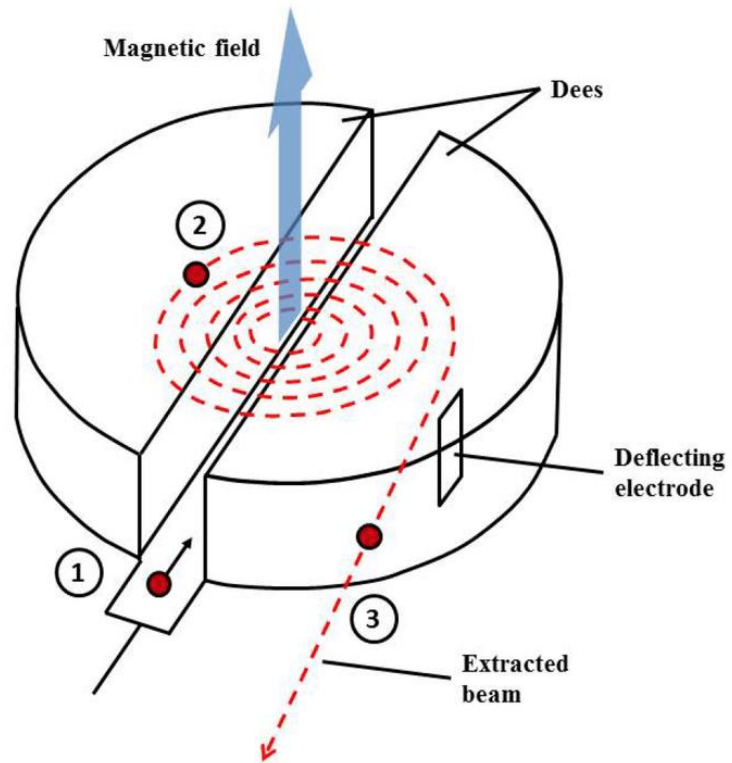
- Radiopharmaceuticals are drugs (“Wet of Geneesmiddelen”)
- Radiopharmaceuticals are part of nuclear energy law (“Kernenergiewet”)



# PRODUCTION OF MOLYBDEEN GENERATOR- RADIOPHARMANUCLIDES FOR SINGLE PHOTON EMISSION TOMOGRAPHY



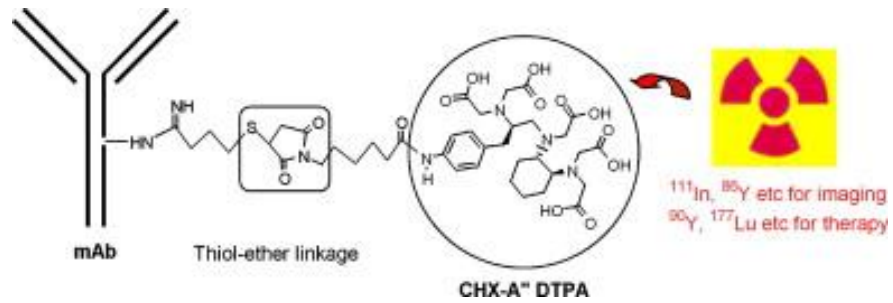
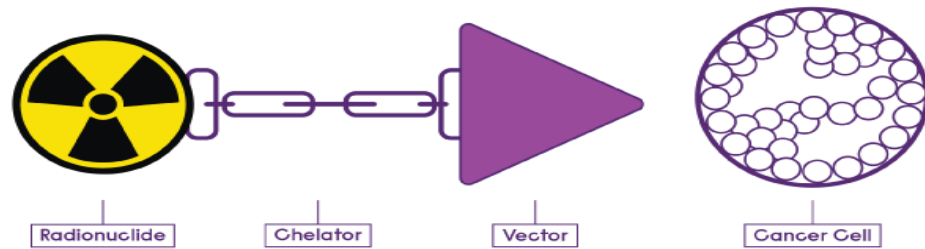
# PRINCIPLE OF CYCLOTRON



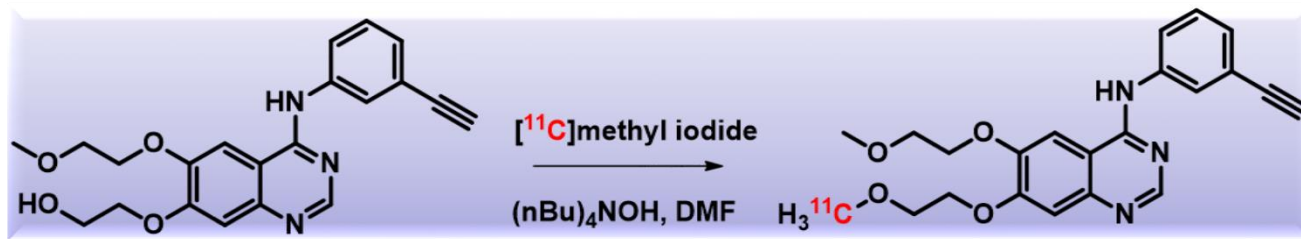
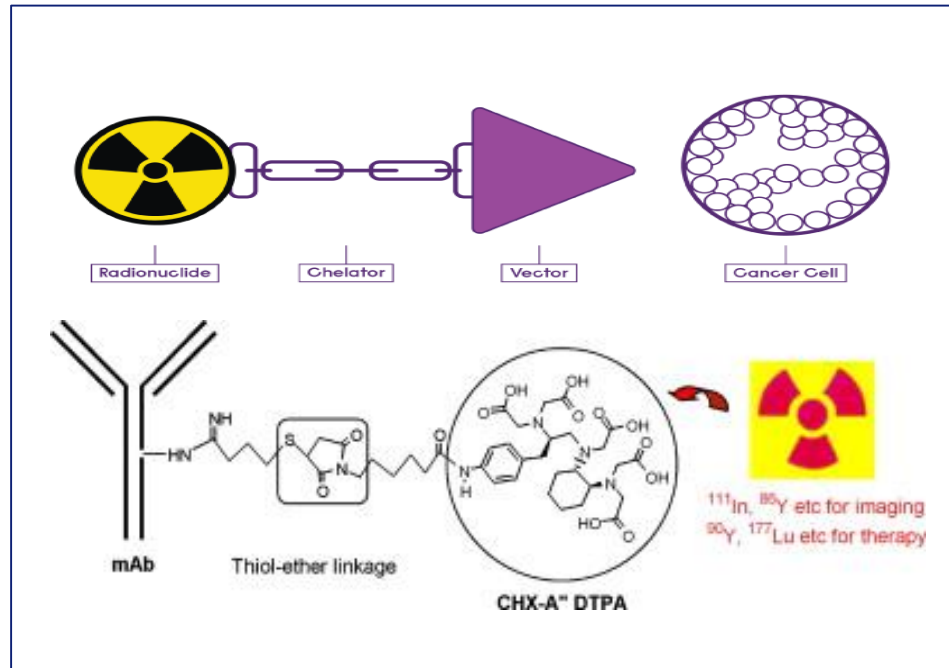
	<b>Radionuclide</b>	<b>Half-life</b>	<b>Energy</b>	<b>Decay</b>
SPECT	<sup>99m</sup> Tc	6.02 h	140 keV	IT (isomeric transition)
	<sup>131</sup> I	8.04 days	284, 364 keV	β <sup>-</sup> (beta minus)
	<sup>123</sup> I	13.22 h	159 keV	EC (electron capture)
	<sup>111</sup> In	2.83 days	171, 247 keV	EC (electron capture)
	<sup>201</sup> Tl	3.05 days	68-80 keV	EC (electron capture)
PET	<sup>18</sup> F	110 min	511 keV	β <sup>+</sup> (beta plus)
	<sup>11</sup> C	20.3 min	511 keV	β <sup>+</sup> (beta plus)
	<sup>68</sup> Ga	68 min	511 keV	β <sup>+</sup> (beta plus)
	<sup>13</sup> N	10.0 min	511 keV	β <sup>+</sup> (beta plus)
	<sup>15</sup> O	2.07 min	511 keV	β <sup>+</sup> (beta plus)

# PRODUCTION OF RADIOPHARMACON

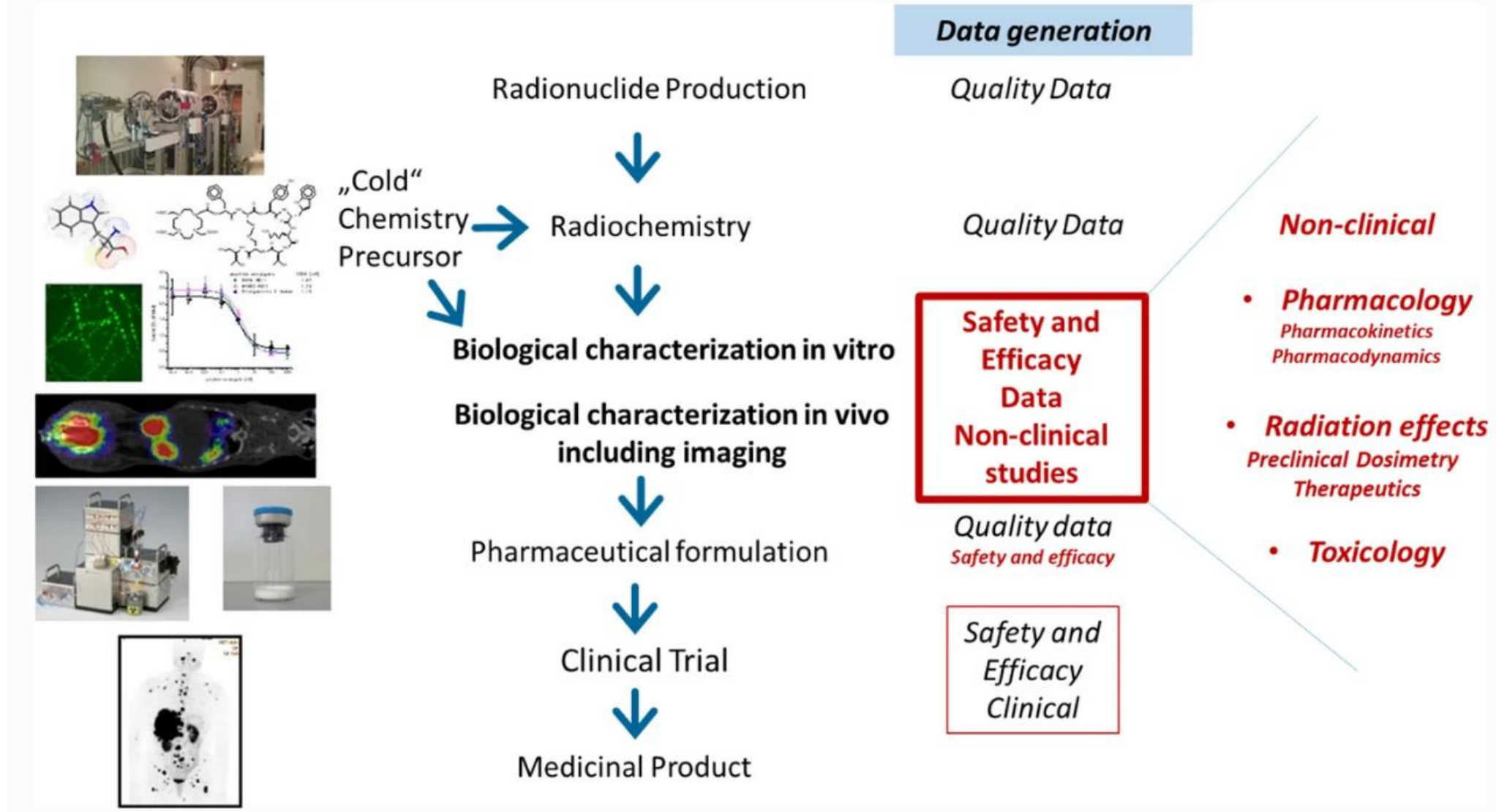
## *RADIONUCLIDES FOR POSITRON EMISSION TOMOGRAPHY*



# PRODUCTION OF RADIOPHARMACEUTICALS *FOR POSITRON EMISSION TOMOGRAPHY*

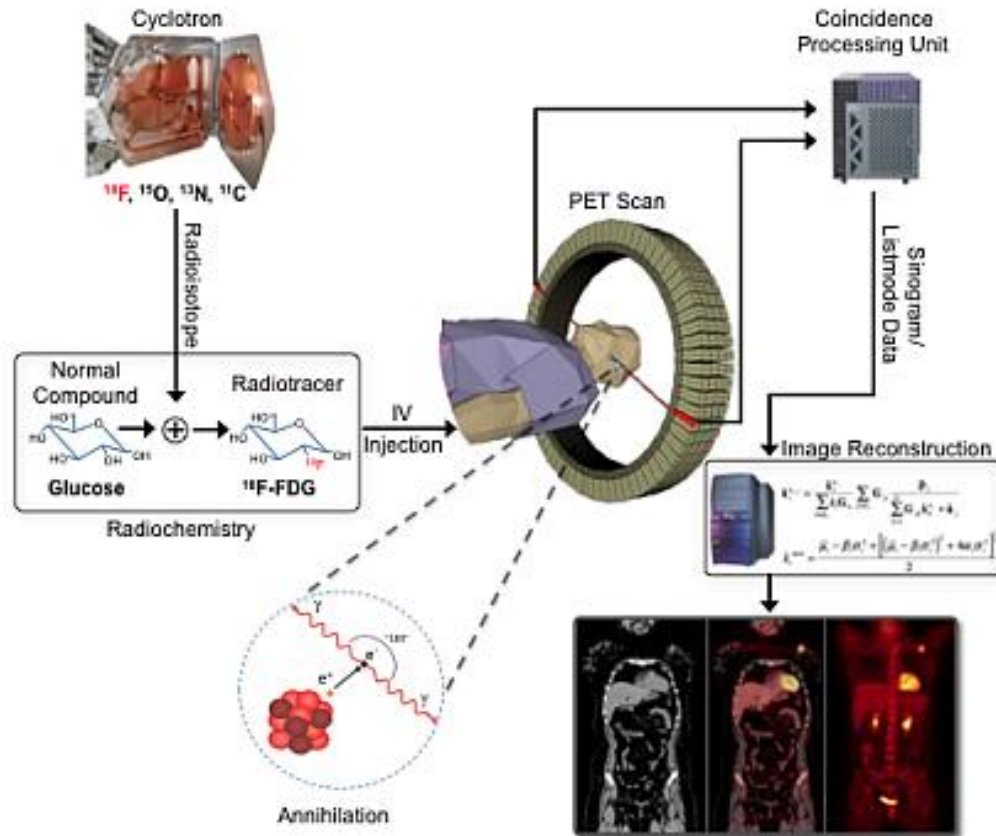






<https://ejnmmipharmchem.springeropen.com/articles/10.1186/s41181-022-00168-x>

# POSITRON EMISSION TOMOGRAPHY (PET)



# **GOOD MANUFACTURING PRACTICE**

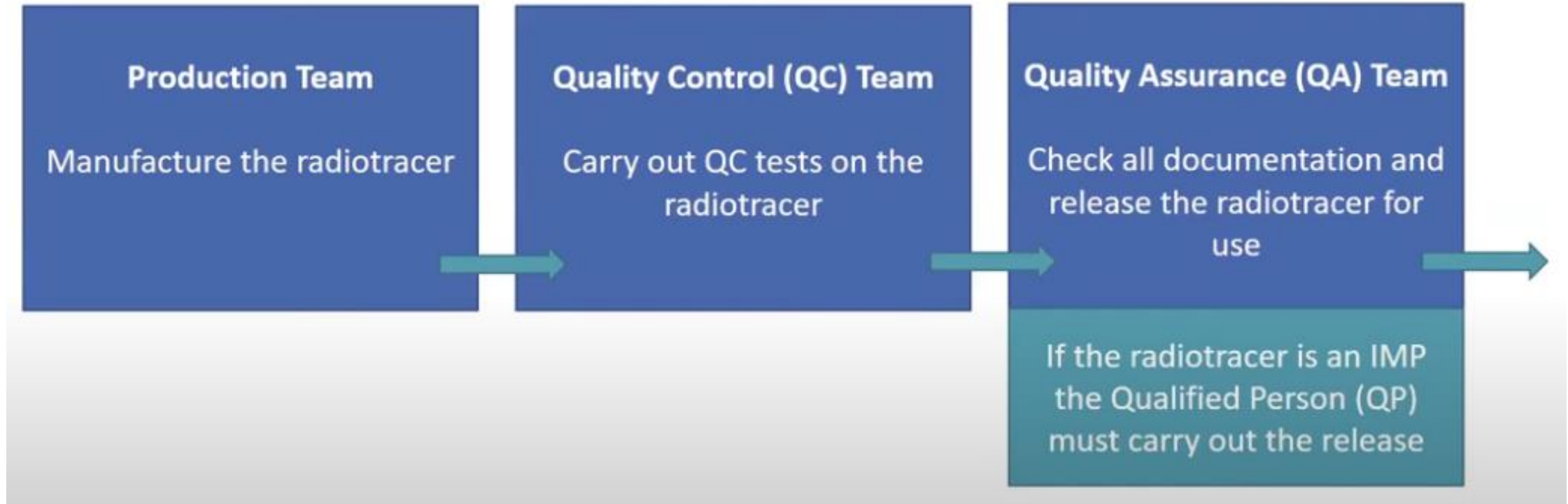
- **A system for ensuring that products are consistently produced and controlled according to quality standards**
- **Designed to minimise the risk involved in any pharmaceutical production that can not be eliminated through testing the product**

# RADIOPHARMACEUTICALS

- Considered as drugs-manufacturing according to GMP regulations
- Special aspects due to radio-active substances (“Kernenergie Wet”)
- Quality standards described in:
  - European Pharmacopeia (Ph. Eur.)
  - EU GMP Annex 3 Guideline-Manufacture of radiopharmaceuticals
  - For in-house preparations:
    - Good-Radio-Pharmacy Practice (GRPP)
    - Guidelines of the European Association for Nuclear Medicine (EANM)

# DEVELOPMENT & VALIDATION

- Screening for the right compound
  - radiopharmaceutical must bind to the right target
    - In-vitro testing in cells
    - In-vivo experiments in animals
  - attention to metabolism must be payed
  - half-life of the nuclide must be appropriate to the pharmacokinetic behaviour
  - chemistry and quality control must be done in a relative short time
  - development and synthesis must be done according to ALARA
- target-to noise ratio during imaging



# HOW TO RELEASE RADIOPHARMACEUTICALS

## Pharmaceutical quality system

- ✓ Validated proces
- ✓ Validated analytical methods
- ✓ Qualified equipment
- ✓ Qualified and trained personel
- ✓ Risk management system

## Batch documentation

- ✓ Product record
- ✓ Synthesis report
- ✓ Dispension report

First product release

## Environmental & process monitoring

- ✓ Particles
- ✓ Analytical data
- ✓ Filter integrity test

Second/final product release

## Final analytical test results

- ✓ Microbiological monitoring (2-7 days)
- ✓ Sterility testing (3-4 weeks)

# Quality Control

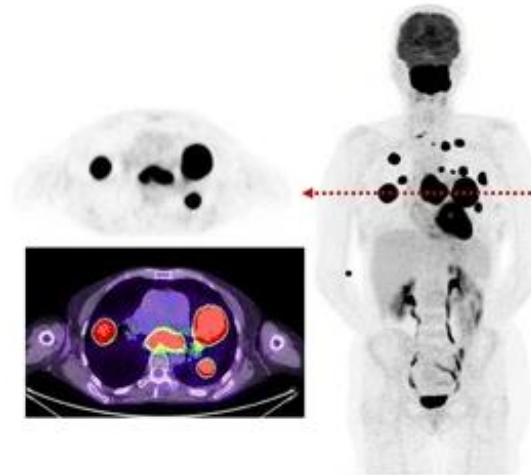
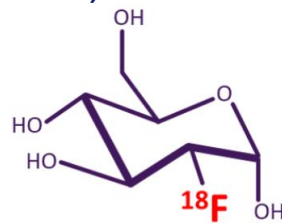
- ✓ **3 Validation runs**
- ✓ **Refer to monographs if exist (e.g. Eur. Phar.)**
- ✓ **Limited requirements**
  - ✓ **Visual inspection**
  - ✓ **Endotoxin test**
  - ✓ **pH**
  - ✓ **Sterility test**
  - ✓ **Specific activity**
  - ✓ **Filter integrity test**
  - ✓ **Radiochemical purity**
  - ✓ **Residual solvent analysis, and other toxic chemicals**



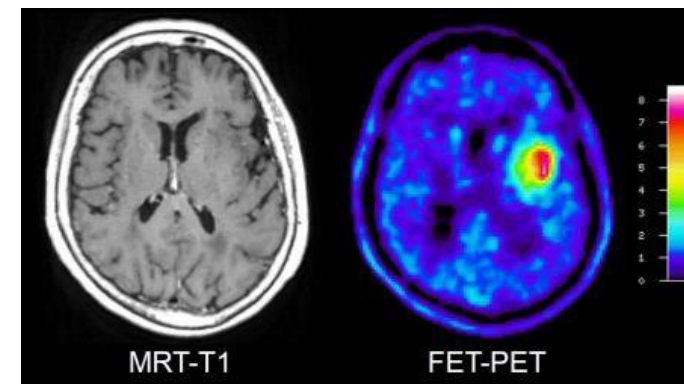
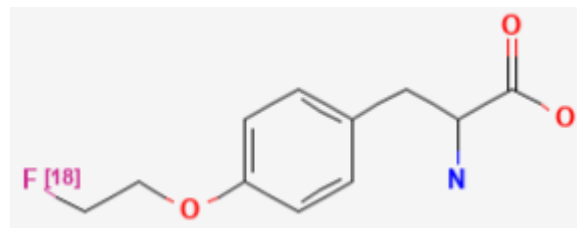


# TWO EXAMPLES

- Synthesis of Fluoro-Desoxy Glucose (FDG)  
(registered radiopharmakon)



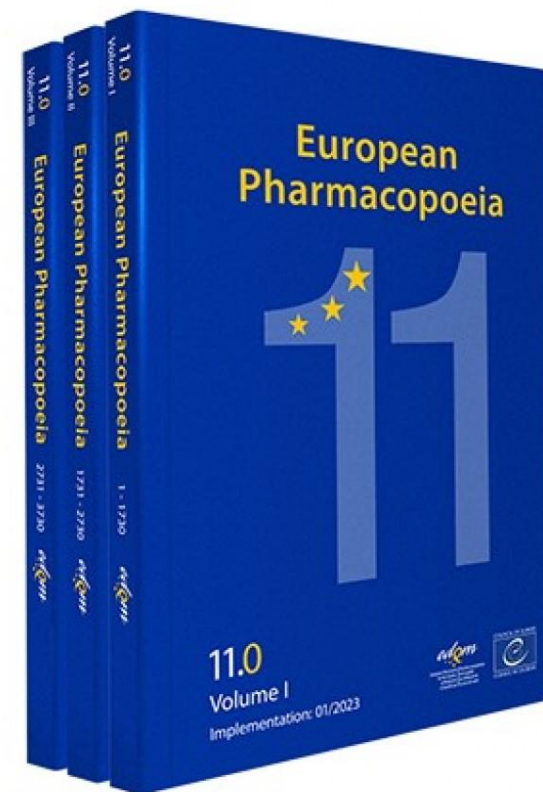
- Development of Fluoro-Ethyl-Tyrosine (FET)  
(non-registered radiopharmakon)



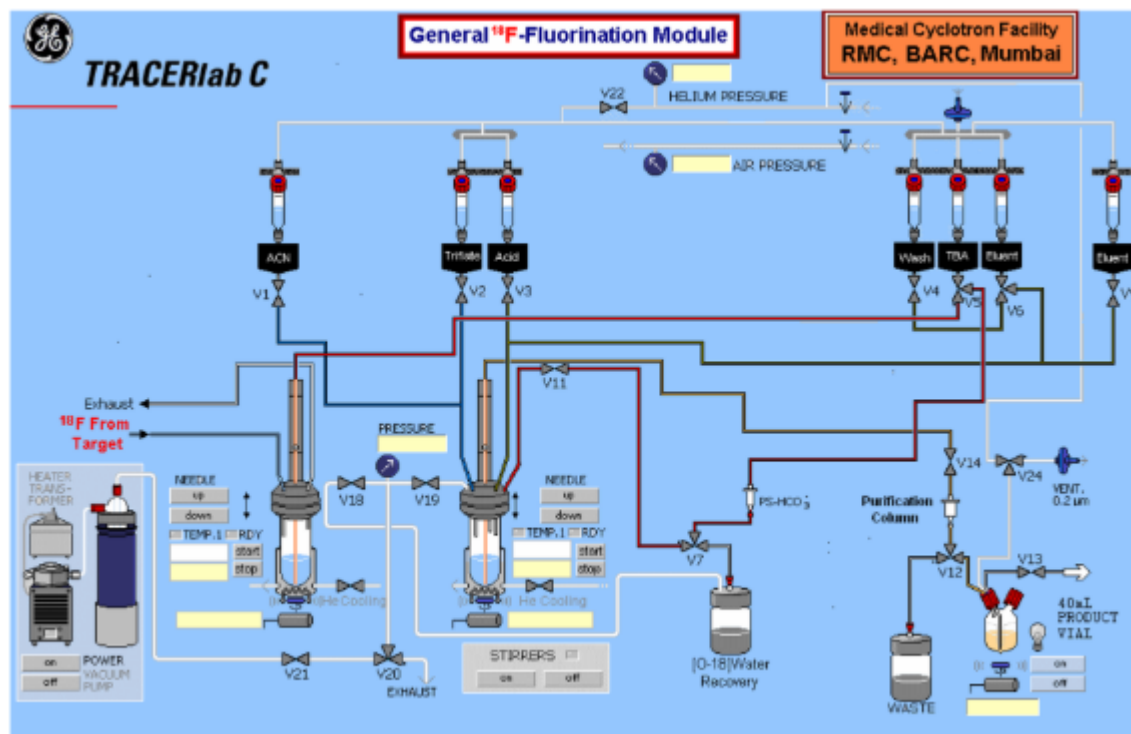
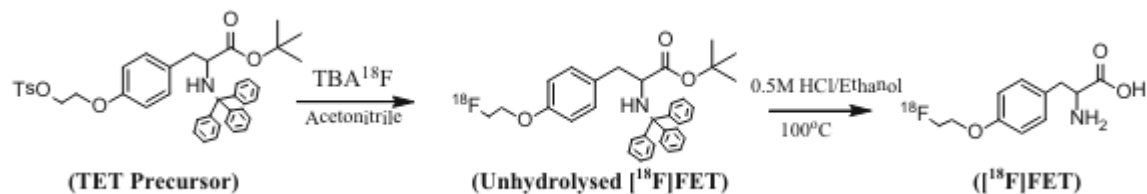
# FDG QUALITY CONTROL

**Table 1.** Specifications for  $^{18}\text{F}$ -FDG

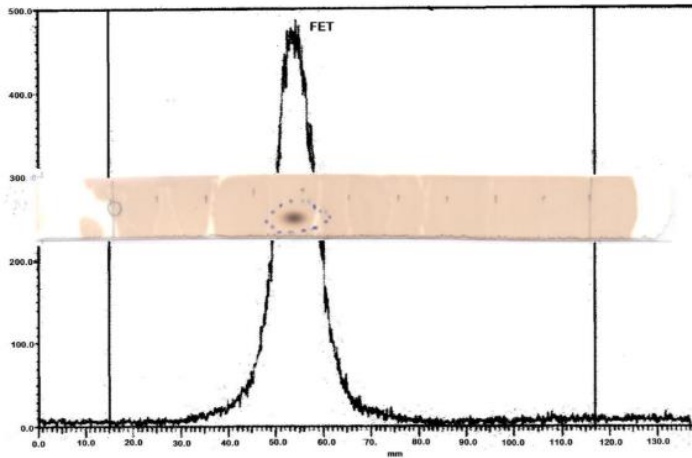
Test	Method	Specification
pH	pH paper	pH: 4.5 - 8.5
Radionuclidic purity	Half life Determination	$T_{1/2}$ : 105-115 min $T_{1/2} = (0.693 \times t) / \ln(A_0/A_t)$
	Gamma spectrometry (MCA)	There shouldn't be peak observations except 0.511MeV and 1.024MeV energy levels
Radiochemical purity and identity	HPLC analytical	$^{18}\text{F}$ FDG: $\geq 95\%$
		$^{18}\text{F}$ FDG + $^{18}\text{F}$ FDM: $\geq 95\%$
		$^{18}\text{F}$ FDM/( $^{18}\text{F}$ FDG + $^{18}\text{F}$ FDM): $\leq 10\%$ $^{18}\text{F}$ + $^{18}\text{F}$ FDG derivatives: $\leq 5\%$
Chemical purity	TLC	$\%^{18}\text{F}$ - $^{18}\text{F}$ FDG: $> 95\%$ $\%^{18}\text{F}$ - fluorine: $< 5\%$ Rf FDG standard $\pm 0.05$
	GC	Ethanol : $\leq 50$ mg/V(mL)
	GC	Acetonitril : $\leq 4.1$ mg/V(mL)
Pyrogen test	LAL tester	Kryptofix 222 : $\leq 2.2$ mg/V(mL)
		HPLC



# DEVELOPMENT/SYNTHESIS FET

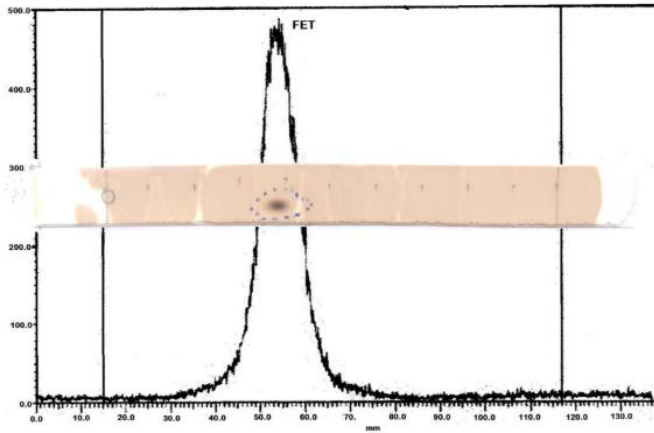


# QUALITY CONTROL FET

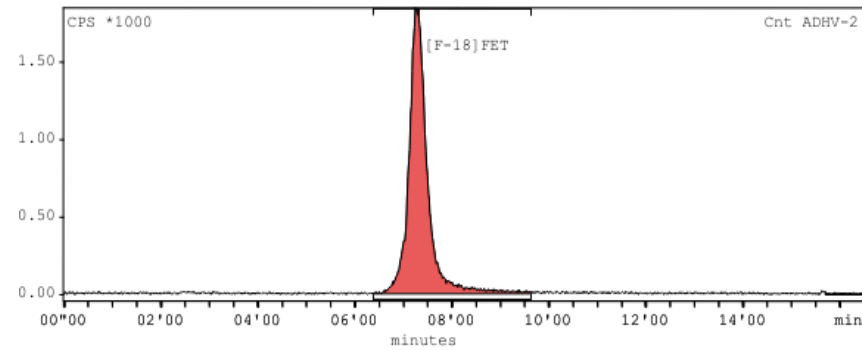
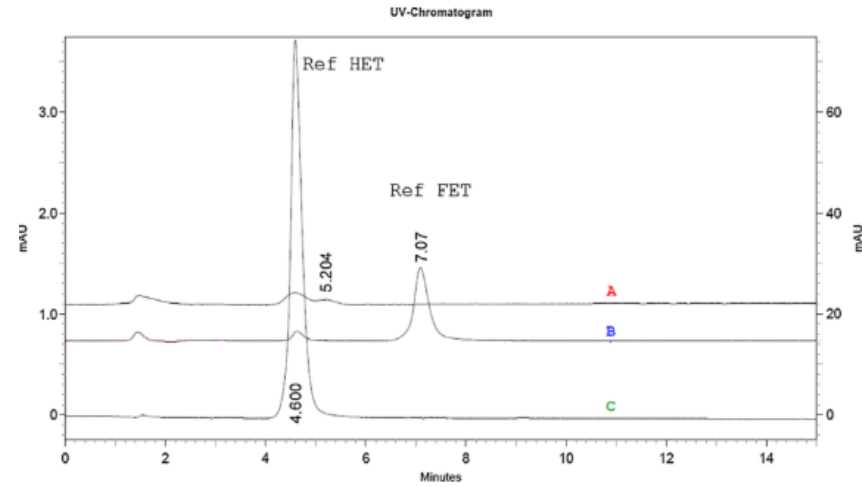


Radio-TLC of [ $^{18}\text{F}$ ]FET co-spotted with [ $^{19}\text{F}$ ]FET

# QUALITY CONTROL FET

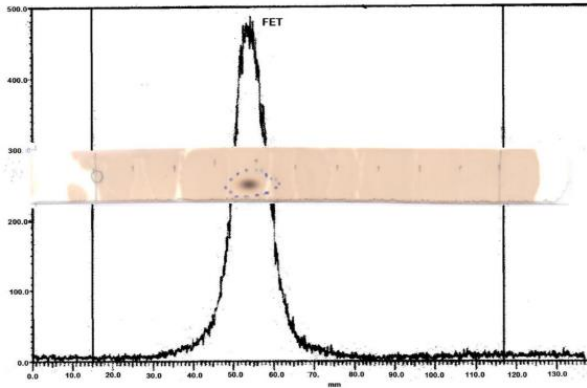


Radio-TLC of  $[^{18}\text{F}]$ FET co-spotted with  $[^{19}\text{F}]$ FET

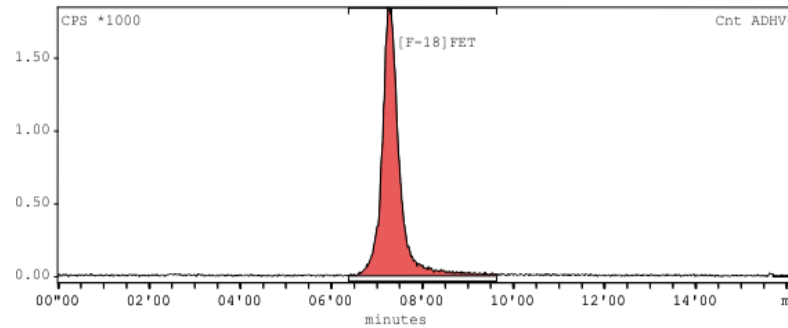
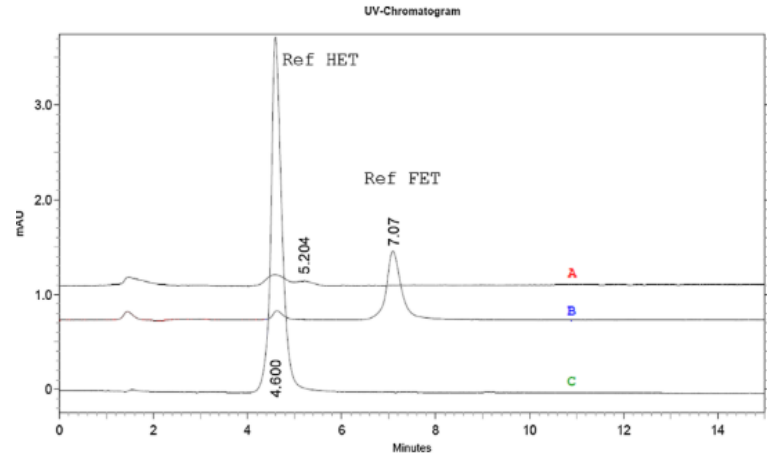


Radio-HPLC of  $[^{18}\text{F}]$ FET

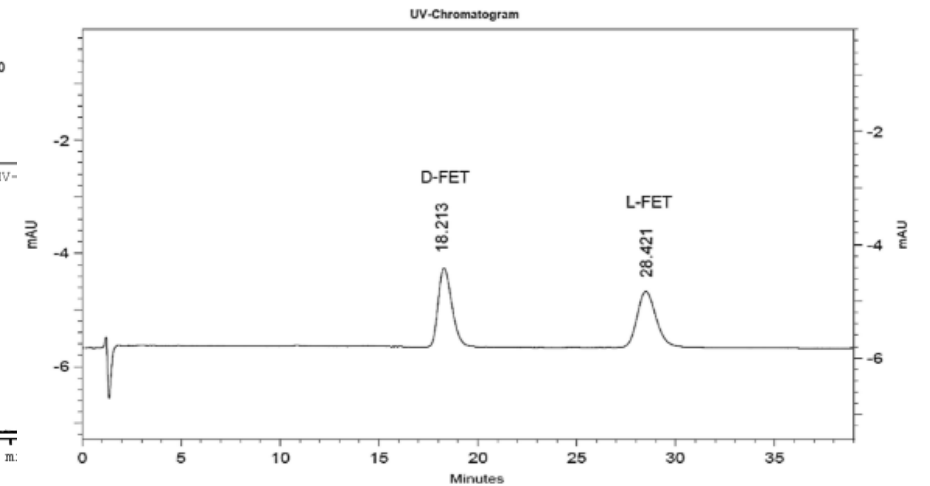
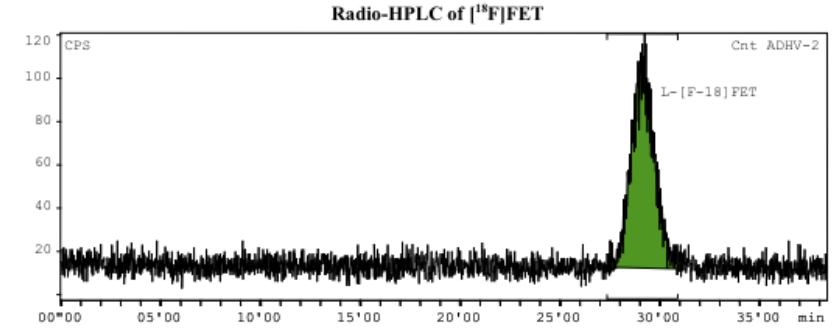
# QUALITY CONTROL FET



Radio-TLC of  $[^{18}\text{F}]\text{FET}$  co-spotted with  $[^{19}\text{F}]\text{FET}$

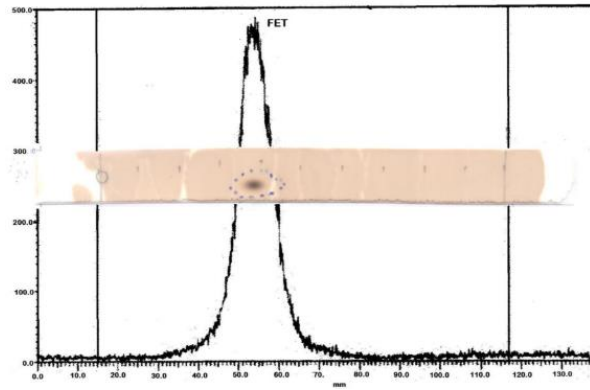


Radio-HPLC of  $[^{18}\text{F}]\text{FET}$

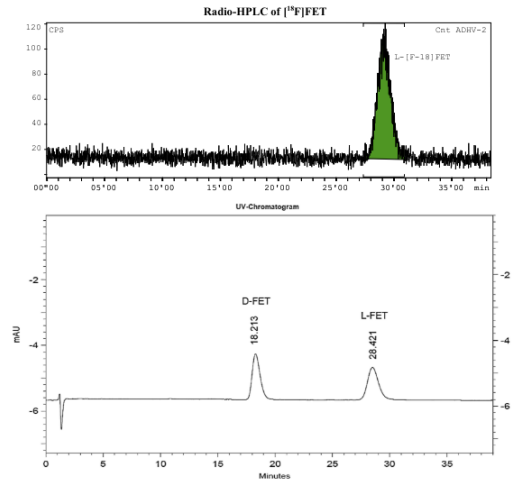


Chiral HPLC (Crownpak CR (+) column. Top: radioactive peak L-FET; bottom: UV-HPLC peak D-FET- and L-FET

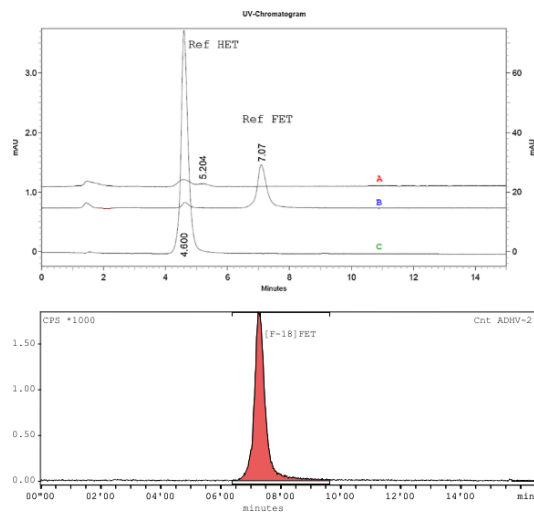
# QUALITY CONTROL FET



Radio-TLC of  $[^{18}\text{F}]$ FET co-spotted with  $[^{19}\text{F}]$ FET



Chiral HPLC (Crownpak CR (+) column. Top: radioactive peak L-FET; bottom: UV-HPLC peak D-FET- and L-FET



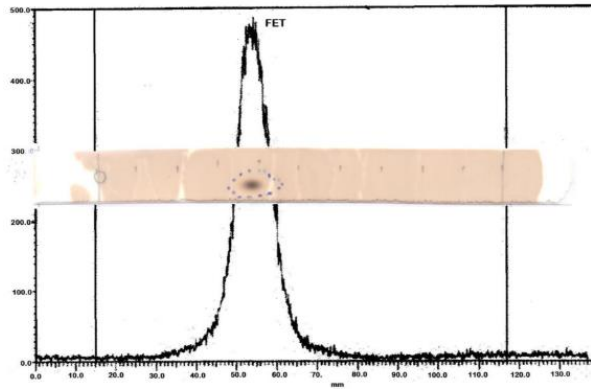
Radio-HPLC of  $[^{18}\text{F}]$ FET

## Conditional Certification Parameters

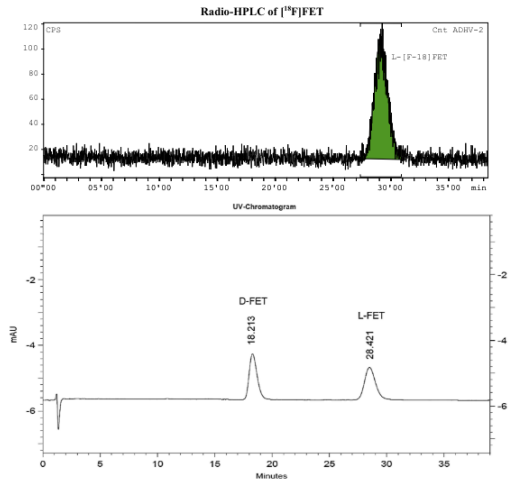
Parameter	Result	Conforms	Initials
<i>Specification</i>			
<b>Osmolality</b>	[RESULT] mOsmol/kg	[SELECT]	[INITIALS]
<i>200 - 400 mOsmol/kg</i>			
<b>pH citrate / acetate buffer</b>	[RESULT]	[SELECT]	[INITIALS]
<i>4.5 - 5.5</i>			
<b>Appearance</b>	[PICK RESULT]	[SELECT]	[INITIALS]
<i>Clear, colourless solution</i>			
<b>pH Formulated product</b>	[RESULT]	[SELECT]	[INITIALS]
<i>4.0 - 7.0</i>			
<b>Radiochemical purity according to HPLC</b>	[RESULT]%	[SELECT]	[INITIALS]
<i>≥ 95.0%</i>			
<b>Radiochemical identity according to HPLC</b>	[PICK RESULT]	[SELECT]	[INITIALS]
<i>ΔRt product - reference ± 10%</i>			
<b>Chemical purity according to HPLC</b>	[PICK RESULT]	[SELECT]	[INITIALS]
<i>Chromatogram similar to that of matrix in SST. Carrier on same Rt as reference</i>			
<b>Chemical purity HPLC: concentration of each unknown peak</b>	[PICK RESULT]	[SELECT]	[INITIALS]
<i>Concentration of each unknown peak ≤ 0.22 pmol/μL</i>			
<b>Chemical purity HPLC: sum of concentrations of all unknown peaks</b>	[PICK RESULT]	[SELECT]	[INITIALS]
<i>Sum of concentrations of unknown peaks ≤ 0.88 pmol/μL</i>			
<b>Bubble point 0.22 μm GV filter</b>	[RESULT] bar	[SELECT]	[INITIALS]
<i>≥ 3.45 bar</i>			
<b>Bubble point 0.22 μm FG filter</b>	[RESULT] bar	[SELECT]	[INITIALS]
<i>≥ 0.90 bar</i>			
<b>Endotoxin content assay - Sample value</b>	[RESULT] EU/mL	[SELECT]	[INITIALS]
<i>≤ 2.5 EU/mL</i>			



# QUALITY CONTROL FET



Radio-TLC of  $[^{18}\text{F}]$ FET co-spotted with  $[^{19}\text{F}]$ FET

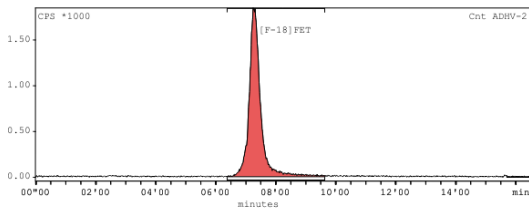
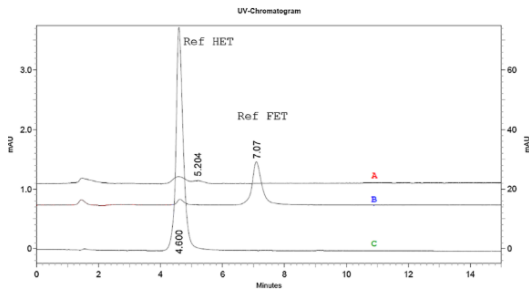


Chiral HPLC (Crownpak CR (+) column. Top: radioactive peak L-FET; bottom: UV-HPLC peak D-FET- and L-FET

## Final Certification Parameters

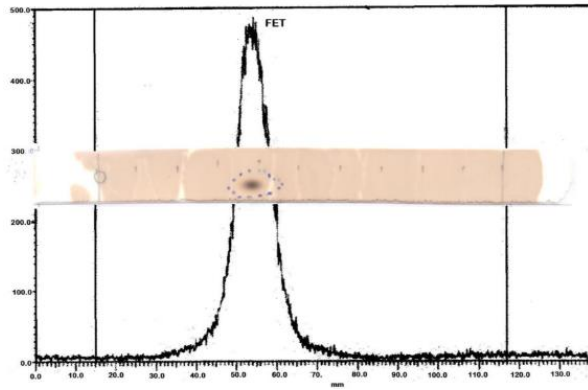
Parameter	Result	Conforms	Initials
<i>Specification</i>			
Sterility	[PICK RESULT]	[SELECT]	[INITIALS]
<i>Sterile</i>			
Acetone concentration in ppm	[RESULT] ppm	[SELECT]	[INITIALS]
$\leq 50$ ppm			
Acetonitrile concentration in ppm	[RESULT] ppm	[SELECT]	[INITIALS]
$\leq 50$ ppm			
Ethanol concentration in ppm	[RESULT] ppm	[SELECT]	[INITIALS]
$\leq 1000$ ppm			

Chemical purity HPLC: concentration of each unknown peak $\leq 0.22$ pmol/ $\mu$ l	[RESULT]%	[SELECT]	[INITIALS]
Sum of concentrations of unknown peaks $\leq 0.22$ pmol/ $\mu$ l	[PICK RESULT]	[SELECT]	[INITIALS]
Bubble point 0.22 $\mu$ m GV filter	[PICK RESULT]	[SELECT]	[INITIALS]
$\geq 3.45$ bar			
Bubble point 0.22 $\mu$ m FG filter	[PICK RESULT]	[SELECT]	[INITIALS]
$\geq 0.90$ bar			
Endotoxin content assay - Sample value	[RESULT] bar	[SELECT]	[INITIALS]
$\leq 2.5$ EU/mL	[RESULT] EU/mL	[SELECT]	[INITIALS]

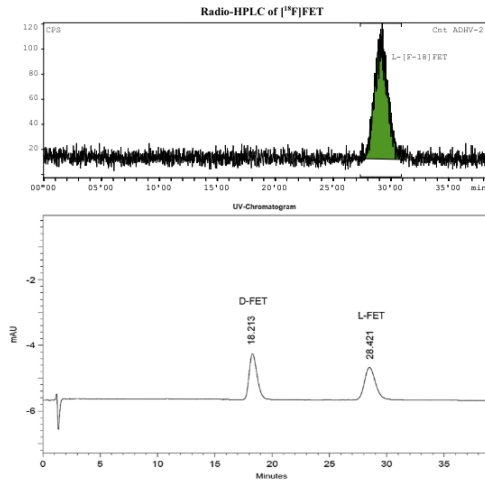


Radio-HPLC of  $[^{18}\text{F}]$ FET

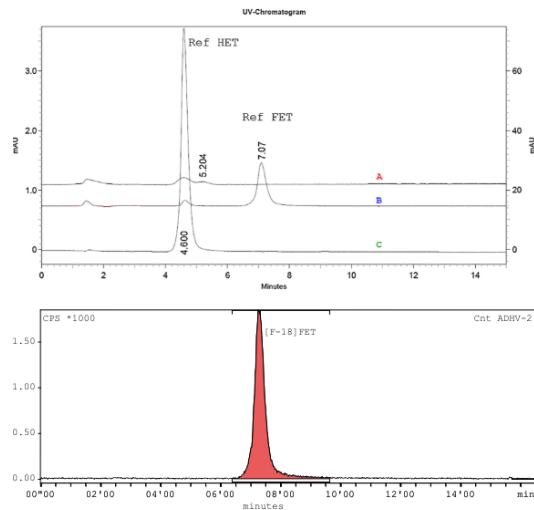
# QUALITY CONTROL FET



Radio-TLC of  $[^{18}\text{F}]$ FET co-spotted with  $[^{19}\text{F}]$ FET



Chiral HPLC (Crownpak CR (+) column. Top: radioactive peak L-FET; bottom: UV-HPLC peak D-FET- and L-FET



Radio-HPLC of  $[^{18}\text{F}]$ FET

## Non-Certification Parameters

Parameter	Result	Conforms	Initials
<i>Specification</i>			
HPLC SST - System equilibration	[PICK RESULT]	[SELECT]	[INITIALS]
<i>Equilibration chromatogram stable</i>			
HPLC SST - Duplicate reference runs	[PICK RESULT]	[SELECT]	[INITIALS]
<i>Difference in duple &lt; 0.4 min (Rt 2.4–2.8 min)</i>			
HPLC SST - Blank formulation solution	[PICK RESULT]	[SELECT]	[INITIALS]
<i>Similar to matrix master chromatogram</i>			
Molar activity on ART	[RESULT] GBq/ $\mu\text{mol}$	[SELECT]	[INITIALS]
<i>For information only</i>			
Endotoxin content assay - Sample rxn time CV	[RESULT]%	[SELECT]	[INITIALS]
<i>&lt; 25.0%</i>			
Endotoxin content assay - Spike rxn time CV	[RESULT]%	[SELECT]	[INITIALS]
<i>&lt; 25.0%</i>			
Endotoxin content assay - Spike recovery	[RESULT]%	[SELECT]	[INITIALS]
<i>Between 50% and 200%</i>			

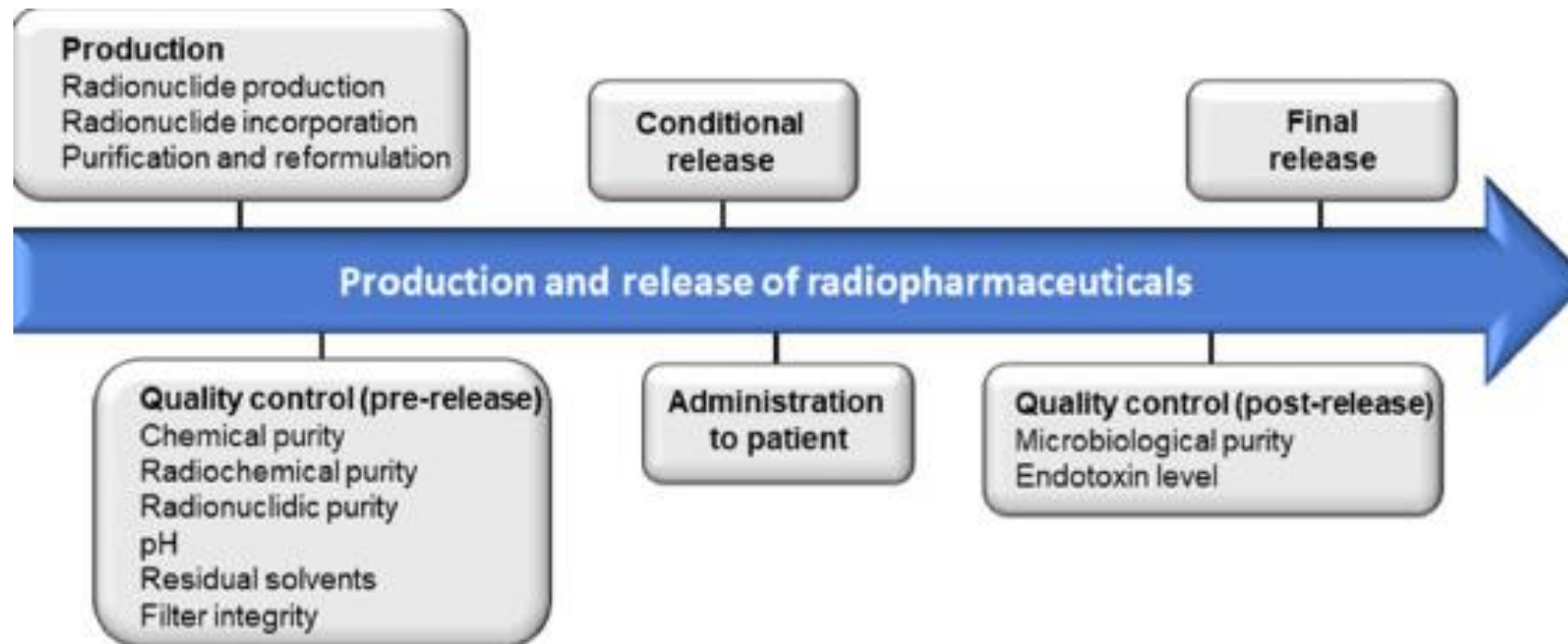
Acetone  $\leq 50$  ppm  
 Acetonitrile concentration  $\leq 50$  ppm  
 Ethanol concentration in ppm  $\leq 1000$  ppm

[PICK RESULT] [SELECT] [INITIALS]  
 [RESULT] bar [SELECT] [INITIALS]  
 [RESULT] bar [SELECT] [INITIALS]  
 [RESULT] EU/mL [SELECT] [INITIALS]  
 [SELECT] [INITIALS]

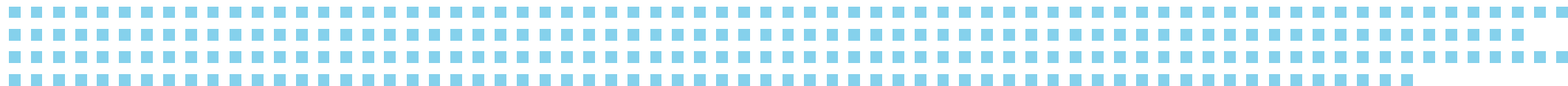
# IMPURITIES IN RADIOPHARMACEUTICALS

- **Artifact formation:** mimic or obscure pathological findings
- **False positive findings:** increase of radioactivity in regions, not related to physiological or pathological processes
- **False negative findings:** decrease of radioactivity in regions, related to physiological or pathological processes
- **Quantitative errors:** affect the quantitative analyses, e.g. alteration of measured uptake in tumors or kinetic parameters
- **Inconsistent image quality:** difficulty to compare images made at different time points, leading to misdiagnosis according to response on treatment

# VALIDATION, PRODUCTION, QUALITY CONTROL AND RELEASE OF RADIOPHARMACEUTICALS



**RADIOFARMACOLOGIE, ALLEEN ALS DE KWALITEIT GOED IS!**



# QUESTIONS

