



Agenda

- **PET characteristics**
- **Manufacturing of radiopharmaceuticals**
- **Good Manufacturing Practice**
- **Radiopharmaceutical Production Site — process management and design**
- **Applications**

Agenda

- PET characteristics
- Manufacturing of radiopharmaceuticals
- Good Manufacturing Practice
- Radiopharmaceutical Production Site — process management and design
- Applications

Contemporary diagnostics modes

Anatomy

Physiology

Metabolic

Molecules

X-ray

MRI

USG

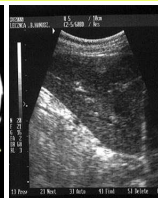
Positron Tomography PET



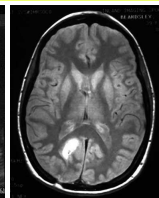
RTG



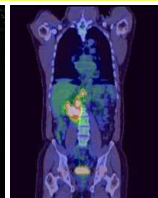
CT



USG



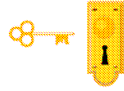
MRI



PET

Some definitions

Radiotracer - chemical compound consists of:

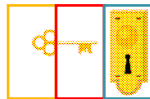


Radioisotope: a radionuclide with physical data suitable for external measurement

Linker : a molecule with suitable pharmacokinetics, and high concentrations in the target organ or process

Some definitions

Radiotracer - chemical compound consists of:

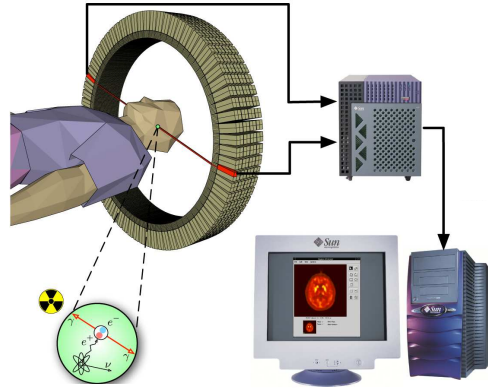


Radioisotope: a radionuclide with physical data suitable for external measurement

Linker : a molecule with suitable pharmacokinetics, and high concentrations in the **target organ or process**

PET Characteristics

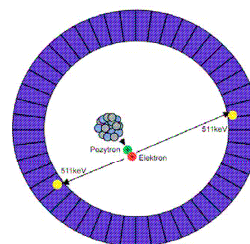
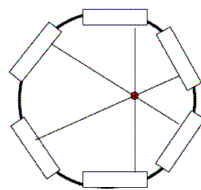
- 3D imaging mode with β -isotopes



PET Characteristics

Linear resolution in clinical imaging [mm]:

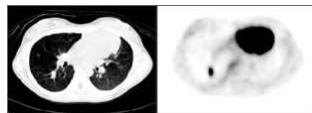
- CT: 0.5-1.0
- MRI: 0.2-
- USG: 0.1-1
- PET: 3-6



PET Characteristics

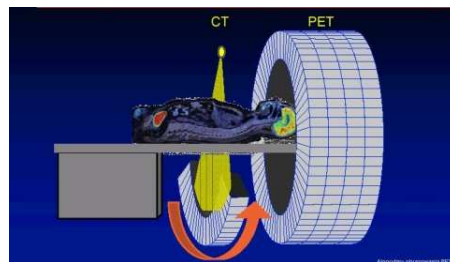
Linear resolution in clinical imaging [mm]:

- CT: 0.5-1.0
- MRI: 0.2-
- USG: 0.1-1
- PET: 3-6



PET Characteristics

- Coupling PET with anatomic imaging modes



Agenda

- PET characteristics
- **Manufacturing of radiopharmaceuticals**
- Good Manufacturing Practice
- Radiopharmaceutical Production Site — process management and design
- Applications

PET Radioisotopes

Useful radionuclides

- | | | |
|---------------------|-----------|----------|
| • ^{18}F — | half-life | 110 min. |
| • ^{11}C - | half-life | 20 min. |
| • ^{15}O - | half-life | 2 min. |
| • ^{13}N - | half-life | 10 min. |

Radionuclide scissiors

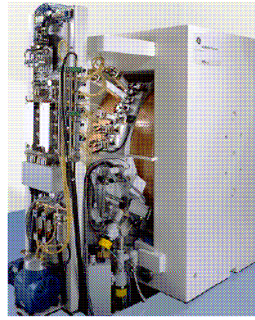
- Shorter half-life — radiation exposure
- Longer half-life — clinical availability

Isotopes production

Cyclotrone



Cyclotrone IBA 18/9

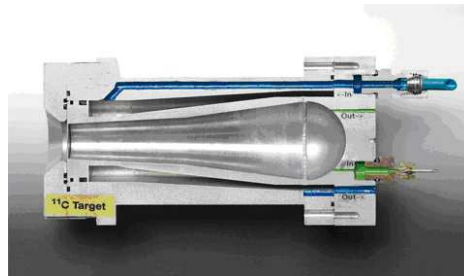


Cyclotrone GE PETrace 8

Targets



Target for liquids



Target for gases

^{18}F Production



Target for liquids

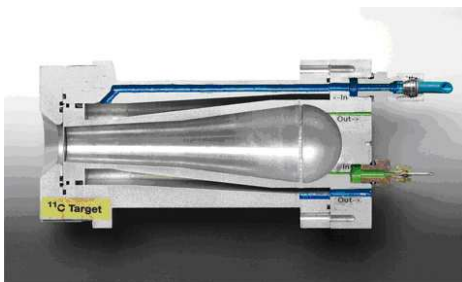
Production ^{18}F :

Reaction: $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$

Target: H_2^{18}O c, 95% ^{18}O

Product: $^{18}\text{F}^-$

^{18}F Production



Target for gases

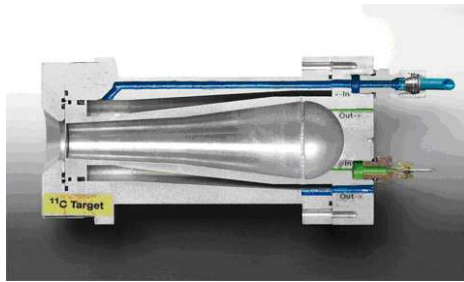
Production ^{18}F :

Reaction : $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$

Target : ^{18}O g, 95% ^{18}O

Product : F_2 ($^{18}\text{F}^{19}\text{F}$)

¹¹C Production



Target for gases

Production ¹¹C :

Reaction : $^{14}\text{N}(p,\alpha)^{11}\text{C}$

Target : 99,6% ¹⁴N (0,1-5% H₂)

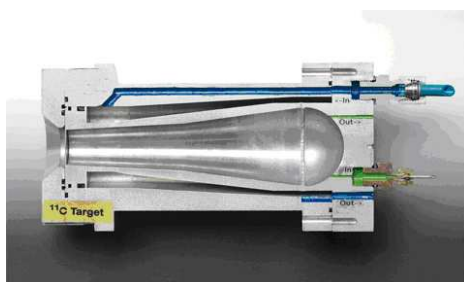
Product : HCN, CH₄

or

Target : ¹⁴N (O₂)

Product : CO, CO₂

¹⁵O Production



Target for gases

Production ¹⁵O :

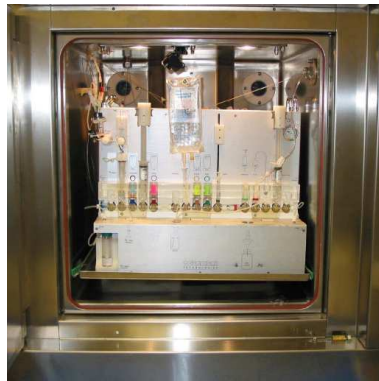
Reaction : $^{14}\text{N}(d,n)^{15}\text{O}$

Target : 99% nat N₂ + 1% ¹⁶O₂

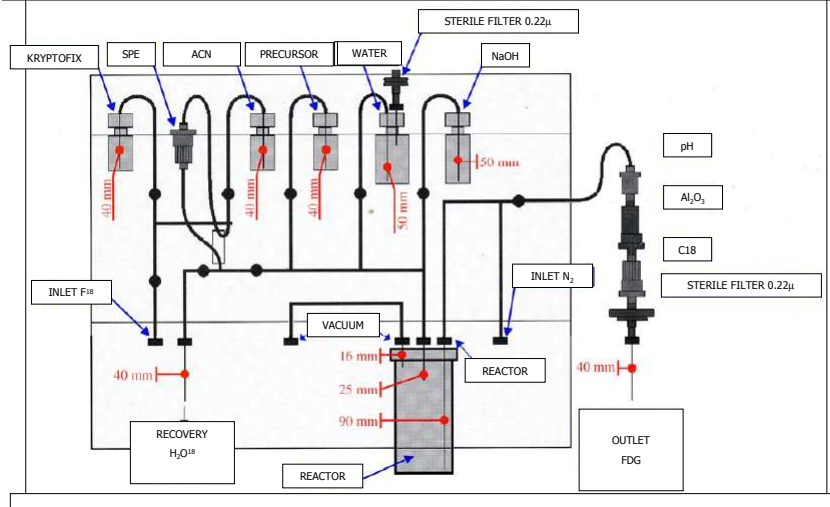
Product : ¹⁵O¹⁶O

Radiopharmaceuticals manufacturing

Automatic units



Radiopharmaceuticals manufacturing

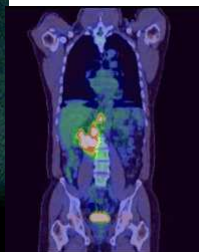


Radiopharmaceuticals manufacturing

Dispensing



Radiopharmaceuticals manufacturing



Agenda

- PET characteristics
- Manufacturing of radiopharmaceuticals
- **Good Manufacturing Practice**
- Radiopharmaceutical Production Site — process management and design
- Applications

GMP

Type of manufacture	Non - GMP	GMP parts I & II (Increasing) including relevant annexes			
Radiopharmaceuticals Precursors (Long-lived)	Reactor Production	Chemical synthesis	Purification steps	Processing, formulation and dispensing	Aseptic or final sterilization
PET-radiopharmaceuticals Precursors (Short-lived)	Cyclotron Production	Chemical synthesis	Purification steps	Processing, formulation and dispensing	Aseptic or final sterilization
Radionuclide Generators	Reactor Production	Processing			

GMP

Type of manufacture	Non - GMP	GMP parts I & II (Increasing) including relevant annexes			
Radiopharmaceuticals Precursors (Long-lived)	Reactor Production	Chemical synthesis	Purification steps	Processing, formulation and dispensing	Aseptic or final sterilization
PET-radiopharmaceuticals Precursors (Short-lived)	Cyclotron Production	Chemical synthesis	Purification steps	Processing, formulation and dispensing	Aseptic or final sterilization
Radionuclide Generators	Reactor Production	Processing			

Manufacturing regulations



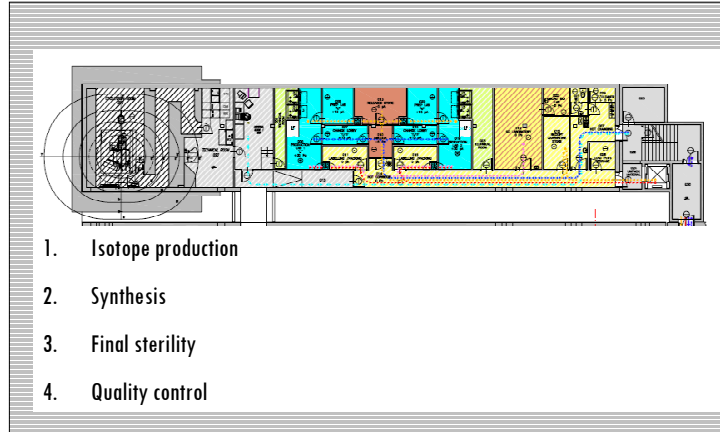
EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

ANNEX 1
MANUFACTURE OF STERILE MEDICINAL PRODUCTS

ANNEX 3
MANUFACTURE OF RADIOPHARMACEUTICALS

Radiopharmaceutical site structure



Cleanrooms

Clean room classes by PIC:

class	Terminal filter-effectivity	Air renewal/h	Max. particles allowed/m ³ 0,5µm	Max. particles allowed /m ³ 5 µm	Max. viable microorganisms allowed/m ³
A	99.997	vertical flow 0,3m/s Horizontal flow 0,45m/s	≤3500	0	<1
B	99.995	5-20	≤3500	0	5
C	99.95	5-20	≤350000	≤2000	100
D	95.0	5-20	≤3500000	≤20000	500

Cleanrooms

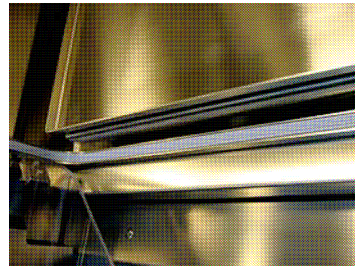
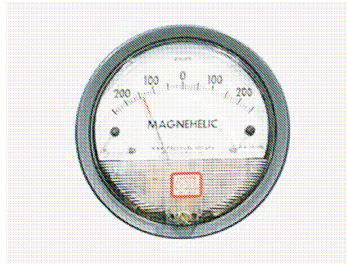
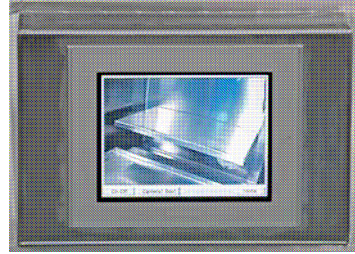
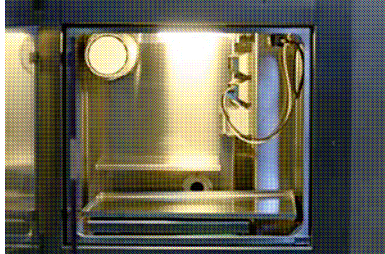
	Microorganisms
Fingertip	20-100/cm ²
Hand	1000-6000
Saliva	10 ⁸ -10 ⁹ /ml
Nasal discharge	10 ⁶ -10 ⁷ /ml
1 x Sneezing	10 ⁴ -10 ⁶



Cleanrooms



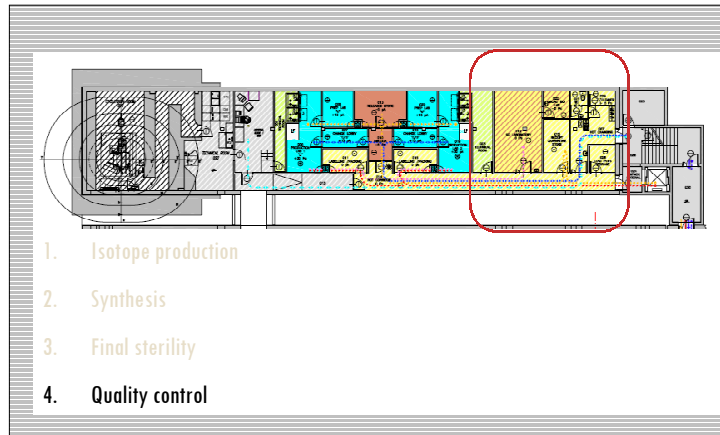
Isolator safety features



Dispensing unit



Quality control

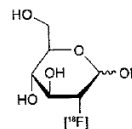


Quality control

01/2005:1325

FLUDEOXYGLUCOSE (^{18}F) INJECTION

Fludeoxyglucosi (^{18}F) solutio iniectionabilis



DEFINITION

Fludeoxyglucose (^{18}F) injection is a sterile solution of 2- ^{18}F fluoro-2-deoxy-D-glucopyranose (2- ^{18}F fluoro-2-deoxy-D-glucose) for diagnostic use. The injection contains not less than 90.0 per cent and not more than 110.0 per cent of the declared fluorine-18 radioactivity at the date and time stated on the label. Not less than 95 per cent of the radioactivity corresponds to fluorine-18 in the form of 2- ^{18}F fluoro-2-deoxy-D-glucose and 2- ^{18}F fluoro-2-deoxy-D-mannose, with the 2- ^{18}F fluoro-2-deoxy-D-mannose fraction not exceeding 10 per cent of the total radioactivity. Not less than 99.0 per cent of the radioactivity corresponds to fluorine-18. The content of 2-fluoro-2-deoxy-D-glucose is not more than 10 mg per maximum recommended dose of injection.



Application in medicine and science

Oncology

Tumor diagnostics:

- Evaluation of the nature of the change
- Diagnosis and staging of cancer
- Monitoring during and after treatment
- Radiotherapy planning

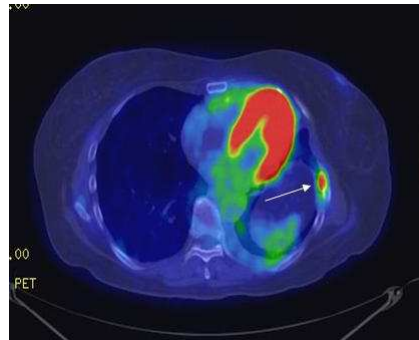
Application in medicine

Oncology

Evaluation of the the change



CT

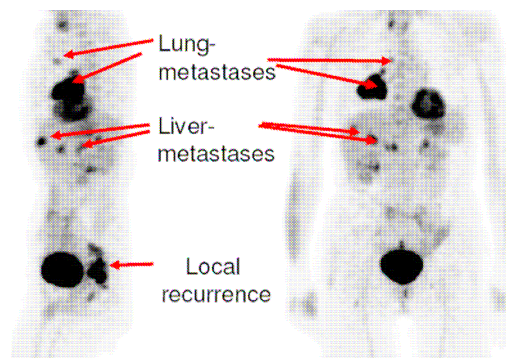


PET

Application in medicine

Oncology

Diagnosis and staging of cancer

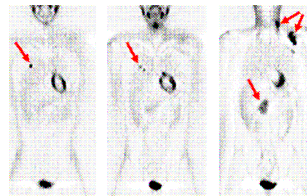


Application in medicine

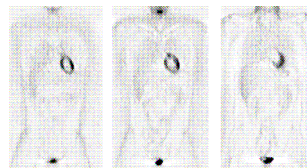
Oncology

Monitoring during and after treatment

Before



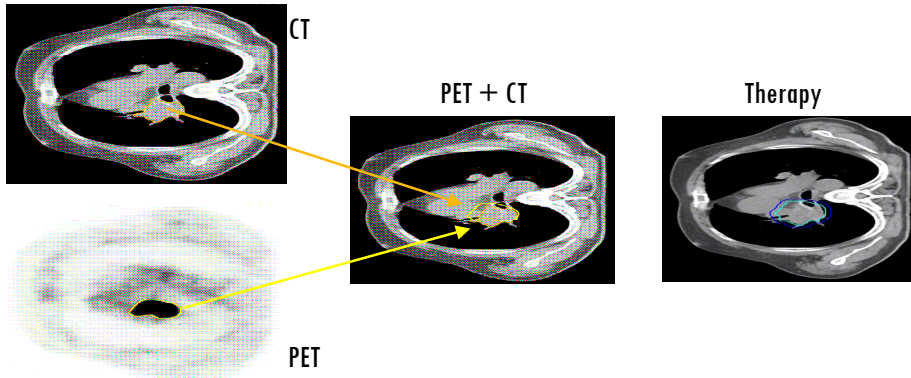
After



Application in medicine

Oncology

Radiotherapy planning :



Application in medicine

Oncology

Principles:

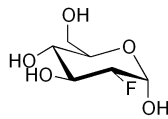
- increased glycolysis in tumor cells — *Warburg phenomenon* — 20-30-times higher glucose metabolism
- increased permeability of biological membranes of tumor cells
- increased protein synthesis
- specific reactions

Application in medicine

Oncology

Principle:

- increased glycolysis in tumor cells – *Warburg phenomenon* – 20-30-times higher glucose metabolism



^{18}F -FDG (2-Deoxy-2-fluoro-D-glucose)

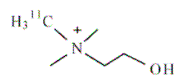
Standard radiopharmaceutical in clinical practice: diagnosis of most cancers

Application in medicine

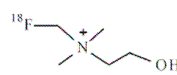
Oncology

Principle:

- increased permeability of biological membranes of tumor cells



^{11}C -choline



^{18}F -choline

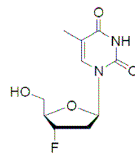
Diagnosis of prostate cancer

Application in medicine

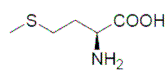
Oncology

Principle :

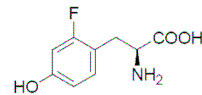
- increased protein synthesis



¹⁸F -thymidine



¹¹C -methionine



¹⁸F-methyltyrosine

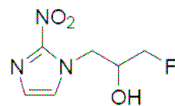
Brain cancer, others as supplementary tracers

Application in medicine

Oncology

Principle:

- Specific reactions



¹⁸F-MISO

Diagnosis of hypoxia

Application in medicine

Neurology

- Brain cancer diagnostics
- Diagnosis and staging of dementia (AD) and movement disorders (PD)
- Neuroactivation

Cardiology

Diagnosis and evaluation of heart : $^{13}\text{NH}_3$, $^{18}\text{F-FDG}$, $^{11}\text{C-palmitate}$

Application in science nad R&D

AnimalPET

- Drug discovery
- Clinical studies

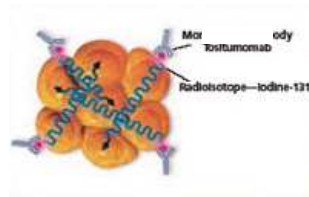


Application in science nad R&D

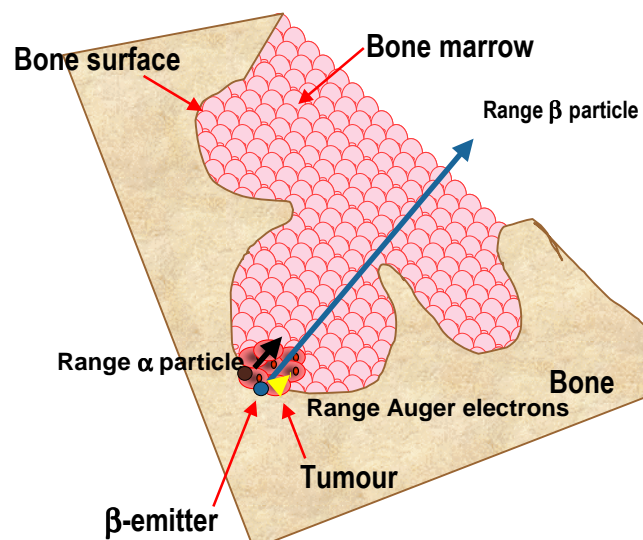
ImmunopET

^{124}I , ^{89}Zr – PET radiotracers ($t_{1/2}$ ca 80-100h), labelling MAB (monoclonal antibodies)

^{211}At – alfa emitter for treatment



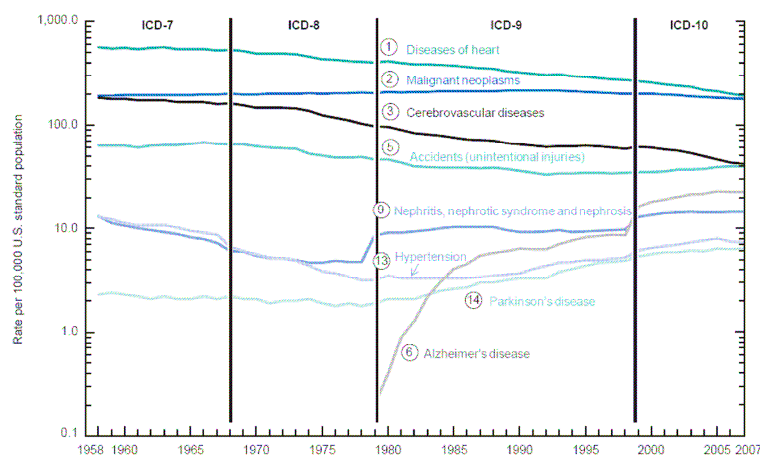
Application in science nad R&D



Summary

- PET characteristics
- Manufacturing of radiopharmaceuticals
- Good Manufacturing Practice
- Radiopharmaceutical Production Site — process management and design
- Applications

Concluding remark



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality.

A photograph of a PET scanner gantry, showing the circular opening and the patient bed inside. The text is overlaid on the image.

Radiopharmaceuticals for Position Emission Tomography (PET)

Krzysztof Kilian

University of Warsaw, Heavy Ion Laboratory
