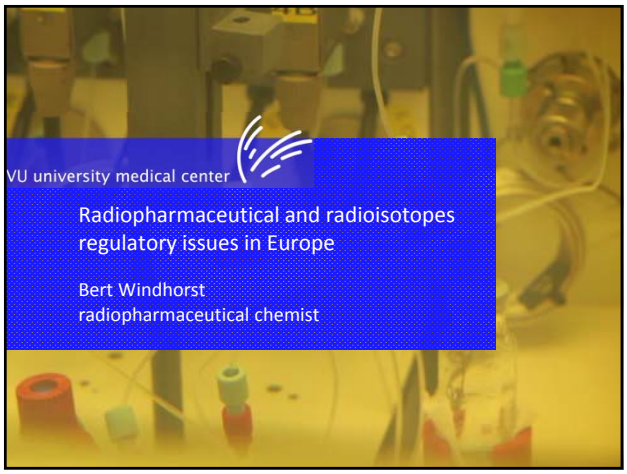


Outline

VUmc

Regulations EU

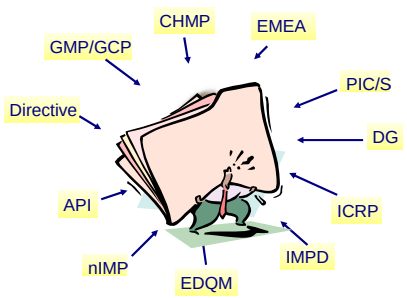
Quality control

2

EU regulations

VUmc

There are many !



3

Regulatory documents

Directive 2001/20/EC → "Clinical Trial Directive"

Directive 2001/83/EG → Qualified Person,...

Directive 2003/94/EC → GMP

Directive 2004/27/EC → API according to GMP

Directive 2005/28/EC → GCP / Authorization for IMP

CHMP/SWP/28367/2007 → First in human clinical trial guideline (EMEA)

Regulation (EC) No 1394/2007 → Advanced therapy regulation

The current challenge for radiopharmaceutical development are pharmaceutical regulations, not radiation safety issues

4

Eudralex

The Rules Governing Medicinal Products in the European Union

Vol 1: Medicinal Products for Human Use

- **Directives**
  - **2001/83/EC**: Community code relating to medicinal products for human use (amended by directives 2002/98/EC, 2004/24/EC y 2004/27/EC)
  - **2003/94/EC:** laying down the principles and guidelines of (GMPs)
- **Regulations**
  - **1394/2007:** advanced therapy medicinal products (amends also dir. 2001/83)

Vol 4: GMPs

- **Part I:** Basic Requirements for Medicinal Products
- **Part II:** Basic Requirements for Active Substances used as Starting Materials
- **Annexes**

Vol 10: Clinical Trials

5

Manufacture license

6

EU GMP directive

Regulations to be found at EU website

EUDRALEX 4

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

7

GMP directive : chapters

1. Quality Management
2. Personnel
3. Premises and equipment
4. Documentation
5. Production
6. Quality Control
7. Contract Manufacture & analysis
8. Complaints and Recall
9. Self inspection

8

GMP directive : Annexes

19 in total, detailed information

Here important :
Annex 1 : Manufacture of sterile products
Annex 3 : Manufacture of radiopharmaceuticals
Annex 15 : Qualification and validation

9

Annex 1

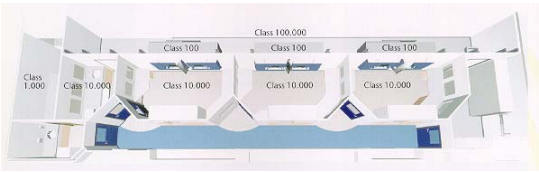
Describes specifications of premisis, personnel

Important : aseptic or end sterilization

Grades for cleanroom : A, B, C or D

10

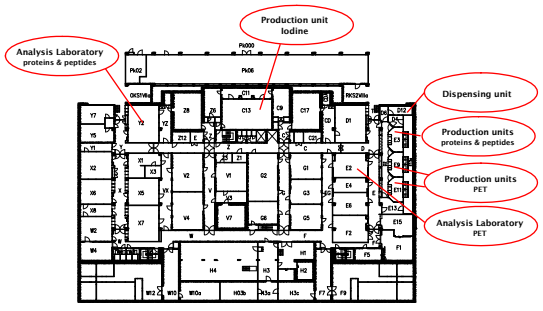
GMP cleanroom design



VUmc, Amsterdam

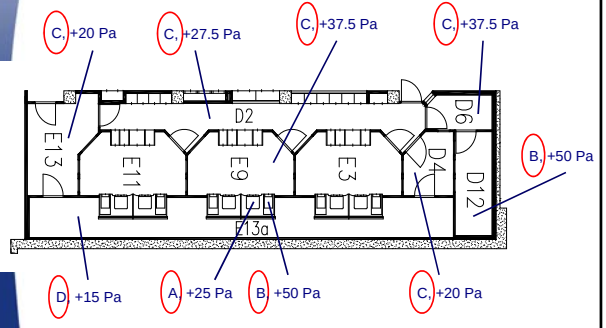
11

Lab



12

GMP cleanroom



13

GMP cleanroom

14

GMP cleanroom

15

Hot lab considerations

Get in touch with experienced companies in an early stage

Visit other sites

Research and routine in one lab possible, but requires high discipline of personnel

16

Annex 3

Added to handouts

17

Annex 15

Qualification and Validation

Validation Master Plan, VMP

(a) validation policy;
(b) organizational structure of validation activities;
(c) summary of facilities, systems, equipment and processes to be validated;
(d) documentation format: the format to be used for protocols and reports;
(e) planning and scheduling;
(f) change control;
(g) reference to existing documents.

18

Validation

VMP, Validation Master Plan

19

Site Master File, SMF

Most important document. Describes the site, personnel, general procedures and responsibilities

Nowadays there is a guidance for SMF:

20

To make life more easy

Purification with prep HPLC, often required

Advantage: everything before HPLC can be considered ‘chemistry’, everything after HPLC ‘pharmacy’

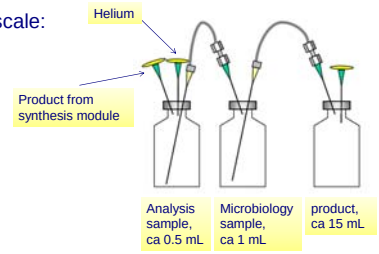
21

To make life more easy

Dispending is often an issue.

Automate? Commercial devices available.

Small scale:



22

Heat sterilization

If possible, gives additional guarantee

20' @ 121 ºC (40 min) or 6' @ 134 ºC (15 min)

Sometimes used for ^{18}F products

23

GMP summary

GMP is a burden, but also a necessity

GMP will help you with external partners

GMP will help you getting things organized

Takes a dedicated person to manage it

Responsibility towards the product is in the chemist, not in the SOP

24

Quality Control

Not specific

Product dependency

Therefor difficult to determine what specification must be met

Annex 3: Qualified Person is responsible

Quality assurance

9. Quality assurance is of even greater importance in the manufacture of radiopharmaceuticals because of their particular characteristics, low volumes and in some circumstances the need to administer the product before testing is complete.

25

Regulations

Pharmacopeia is leading!

http://www.edqm.eu/en/european-pharmacopoeia-publications-1401.html

A monograph describes the specifications to be met for a certain medicine, also radiopharmaceutical.
If a monograph is available, one should comply to it

Full list to be found in Eur Pharm ed 7.

26

Specifications

What specifications to define?

General: all that are of importance for the quality of the product and safety of the patient

For product: active ingredient and excipients
- Control on what has been made: characterization
- Control on quality: purity, specific activity
- Control on manufacturing process: pH, sterility

What specification for preliminary release and which one not?

Set of specifications different for every radiopharmaceutical
common sense and agreement of pharmacist and chemist

27

Specifications

Obvious:

- Sterility
- Residual solvents
- pH
- radiochemical purity
- chemical purity
- endotoxins

28

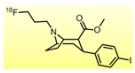
Specifications

What about these:

- Specific activity
- Osmolarity
- Buffer
- radionuclidic identity and purity
- Bottle
- Chemicals used in manufacture
- Excipients

29

Specifications examples

[^{18}F]FP-β-CIT 

Dopamine transporter ligand: SA important? ✔

Dissolve in 10% ethanol in buffer, osmolality? ✘

Buffer: citrate/acetate pH 4.5

Home brew: ✔

Pharmacy: ✘

Radionuclidic purity / identity ? ✔ ✘

30

Specifications

VUmc

[^{18}F]FP-β-CIT

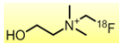
3. **SPECIFICATIES**

ALGEMEEN	EISEN	VRIJGIFTE SPECIFICATIE
Uiterlijk	Helder en kleurloze vloeistof	Ja
pH	4 – 7	Ja
Radiochemische zuiverheid (HPLC)	≥ 98 %	Ja
Specifieke Activiteit (ART)	≥ 18,5 GBq/µmol	Ja
Integriteit filter	Luchtweerstand steriel filter > 2,0 bar	Ja
Aceton	≤ 50 ppm	Nee
Acetonitril	≤ 50 ppm	Nee
Dimethylformamide	≤ 50 ppm	Nee
Diisopropylamine	≤ 50 ppm	Nee
Diisopropylethylamine	≤ 50 ppm	Nee
Ethanol concentratie	8 – 12 %	Nee
Halfwaardetijd	105-115 minuten	Nee
Steriliteit	Steriel	Nee
Bacteriele endotoxine gehalte	≤ 2.5 EU/ml (V_{max} = 70 ml)	Nee
Radionuclidische zuiverheid	≥ 99.9%	Nee
Radionuclidische identiteit dmv gammaspectrum	0.511 MeV	Nee
Radiochemische identiteit	R_t = 6 – 8 min (HPLC)	Nee
Chemische zuiverheid	Naast injectiepiek en FP-CIT geen andere	Ja

31

Specifications examples

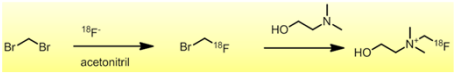
VUmc

[^{18}F]fluormethylcholine 

To study uptake in tumor, especially prostate cancer

Specific activity important? ✗

Cartridge purification, precursor? ✓



Dibromomethane is toxic, synthesized in first step with intermediate purification, analyze? ✓

32

Specifications

VUmc

[^{18}F]fluormethylcholine

3. **SPECIFICATIES**

Algemeen	Eisen	Vrijgifte Specificatie
Uiterlijk	Helder, kleurloze vloeistof	Ja
HPLC (System suitability test): - Systeem gequilibreerd (SST) - Blanco formuleringsbuffer (SST)	Equilibrerings-chromatogram stabiel Identiek aan masterchromatogram	Ja Ja
HPLC Analyse: - Radiochemische zuiverheid - Radiochemische identiteit - Chemische zuiverheid	≥ 98 % Rt van product 5 – 7 min Naast injectiepiek, geen andere UV pieken dan in blanco	Ja Ja Ja
Integriteit filter	Luchtweerstand steriel filter > 2 bar	Ja
pH	4 – 8	Ja
Dibroommethaan	≤ 50 ppm	Ja
N,N-Dimethylaminoethanol	≤ 1000 ppm	Ja
Ethanol concentratie	≤ 2 %	Nee
Aceton	≤ 50 ppm	Nee
Acetonitril	≤ 50 ppm	Nee
Steriliteit	Steriel Extern: Autoclaafgegevens: printstrook temperatuur ≥ 134°C printstrook overdruk ≥ 3,0 bar	Nee (Intern) Ja (Extern)
Bacteriële endotoxine gehalte	Sample value ≤ 2,5 EU/ml (V_{max} = 70 ml)	Nee

33

Methods

VUmc

Purity / identity: HPLC

Design of HPLC method

If you have a HPLC purified product: HPLC for QC must be different (stationary phase and eluent)

Prior to analysis: system suitability test
- inject blanc + reference on HPLC for analysis before QC of product

Be sure that QC HLC is quantitative: check for compounds sticking on HPLC column: gradient of validate

34

Methods

VUmc

HPLC continued

Chemical purity difficult.

- What to measure
- What to define as impurity
- Quantification of impurities
- Known and unknown impurities

Often: defined as 'no irregular signal in UV chromatogram'
Or 'total of impurities less than 10% of UV of product'

In case of known impurities: quantitative analysis, eg stavudine in [^{18}F]FLT synthesis

35

Methods

VUmc

Purity / identity : TLC or ITLC

Comes from radiometals and works excellent: large difference between bound and unbound.

In general make sure that product runs on TLC and unbound does not: good analysis

For fluor-18 chemistry products TLC is not preferred.
- possible to identify unreacted [^{18}F]fluoride
- not possible to identify product

Use of TLC in chemistry development: fast and reliable

36

Methods

Measure pH:

Electronically, preferably with print-out. Saves copying raw data with extra signature, makes life in GMP more easy.

Paper can be applied, but less accurate and no print out possible (photo is!)

37

Methods

Residual solvents:

Several method possible, packed columns and capillary columns

Head space injection or solution

Internal standard methods

Preferably not a first release specification, but a validated one

38

Sterility

Microbiological testing of product according to Eur. Pharm.
Can be done yourself or at dedicated lab

Sterility filter: test afterwards if filter was intact by 'bubble point' test.

First release: filter, indicative for sterility

Final release: including the microbiological test. Final and definitive proof of sterility

If you can: do heat sterilization!

39

Methods

Endotoxins

Can be determined within 20 min after synthesis with commercially available analyzer (Charles Rivers PTS100)

Alternative methods are possible, but far more laborious

Disadvantage: PTS100 cartridge is expensive (ca 50 euro)

40

Further reading

Molecular Imaging: radiopharmaceuticals for PET and SPECT
by Shankar Vallabhajosula

Chapter 13

41