Radiation Protection and Nuclear Safety in a PET-Radiopharmaceuticals Production Site

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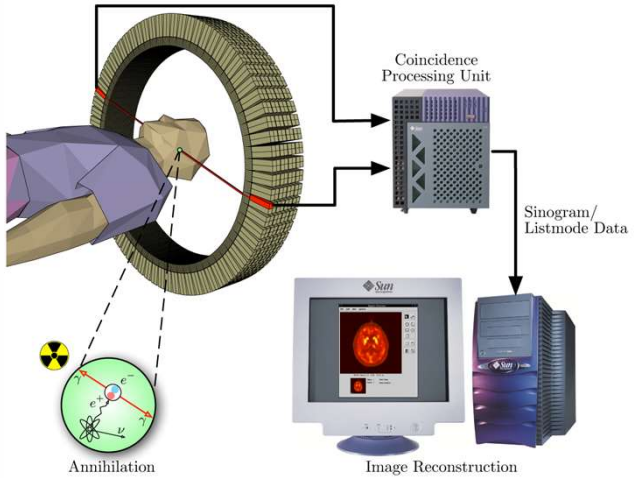
PET-radiopharmaceutical production site?

- Production of positron-emitting radiopharmaceuticals!
- PET-imaging in diagnostic nuclear medicine
  - Early diagnosis and follow of treatment of many diseases
  - Wide applications in oncology



Positron-emitting radiopharmaceuticals (1)

- Mainly (very) short lived radionuclides
- Wide range of radiopharmaceuticals

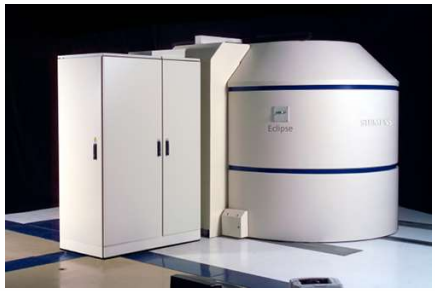
Radionuclide	Half-life	(Common) Production routes	Radiopharmaceuticals
^{18}F	110 min	$^{18}O(p,n)^{18}F$	^{18}FDG, ^{18}FET, $Na^{18}F$, ^{18}F-PSMA,…
^{15}O	2 min	$^{15}N(p,n)^{15}O$	$C^{15}O_2$, $^{15}O_2$,…
^{11}C	20 min	$^{14}N(p,\alpha)^{11}C$	$^{11}CO_2$, ^{11}C-methionine,…
^{13}N	10 min	$^{16}O(p,\alpha)^{13}N$	^{13}N-ammonia
^{68}Ga	68 min	$^{69}Ga(p,2n)^{68}Ge \rightarrow {}^{68}Ga$ $^{68}Zn(p,n)^{68}Ga$	^{68}Ga-dotatoc, ^{68}Ga-dotatate, ^{68}Ga-PSMA,…
^{64}Cu	12.7 h	$^{64}Ni(p,n)^{64}Cu$	^{64}Cu-ATSM ,^{64}Cu-SARTATE,…
^{82}Rb	1.2 min	$^{85}Rb(p,4n)^{82}Sr \rightarrow {}^{82}Rb$	$^{82}RbCl$,…
^{124}I	100 h	$^{124}Te(p,n)^{124}I$	$Na^{124}I$,…
^{89}Zr	78 h	$^{89}Y(p,n)^{89}Zr$	^{89}Zr-DFO,…

Positron-emitting radiopharmaceuticals (2)

- Cyclotron production of radionuclides!
- Practical issues short-lived radionuclides
  - Radionuclide production close to radiopharmaceutical labelling
  - Radiopharmaceutical labelling close to clinical application
- Radiation protection issues short-lived radionuclides
  - Rapid decay of sources ☺
  - Large activities have to be produced to enable clinical use e.g. the entire day 😳
- Nowadays still dominated by ^{18}F and ^{18}FDG

A production site at a glance

Cyclotron



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(GMP)-Radiopharmacy

Good Manufacturing Practice!

Belgian license classification

- Art 3.1 and 3.3 RD 20/07/2001
  - Institutions with particle accelerators designated for the production of radionuclides

  or

  - Institutions with a monthly production > 500 000 exemption level (500 GBq ^{18}F)

Class IIA installation!

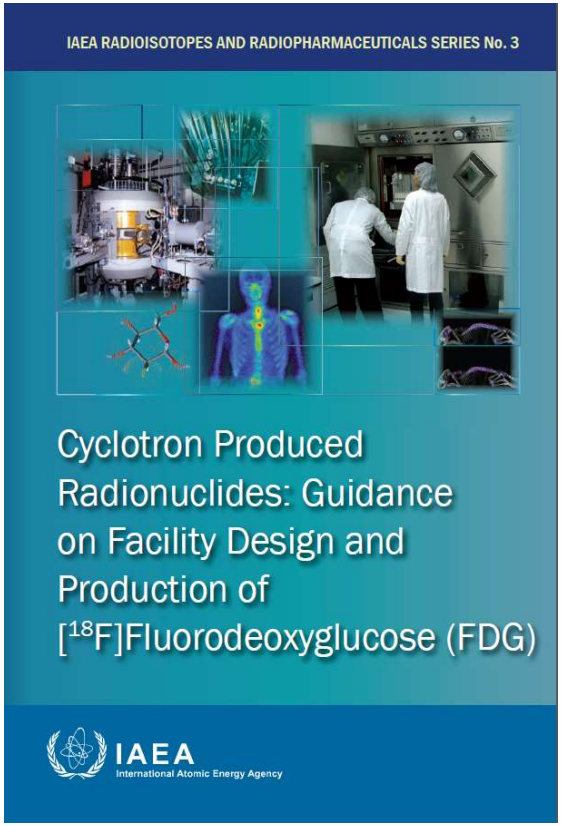
Safety report of class IIA

- Art 7.2/1 RD 20/07/2001: license of class IIA subjected to safety report
- Content specified in RD
  - Description of the institution
  - Site characteristics
  - Infrastructure
  - Risk analyses
  - Description of safety systems
  - Waste management

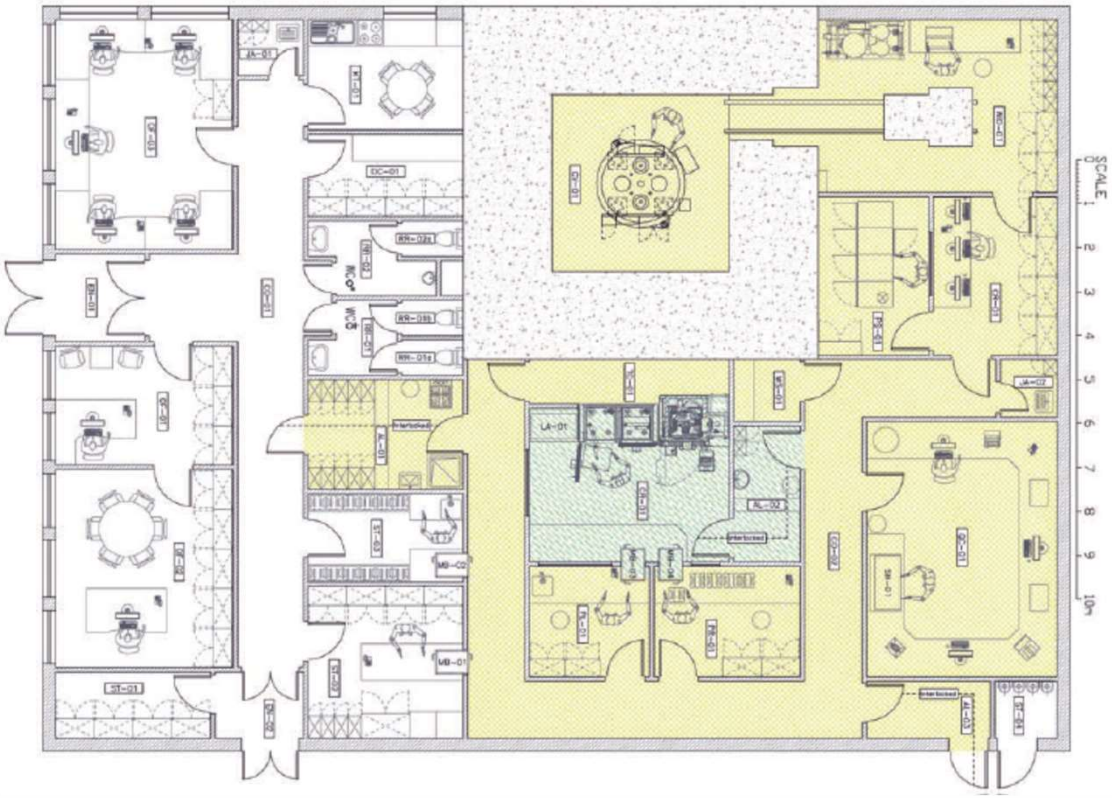
  - Radiation protection
  - Internal organisation
  - Technical specifications
  - Decommissioning
  - Emergency plans
- To be updated for each modification and at least yearly (transfer to FANC)

Facility design

- Appropriate design!
  - Product quality
  - Safety
- Result of risk analyses will impact design and vice versa!
  - Compromises to be made
  - Each site has unique characteristics
  - To fulfil both GMP and radiation protection / nuclear safety requirements
  - Some design details can simplify / complicate future working procedures

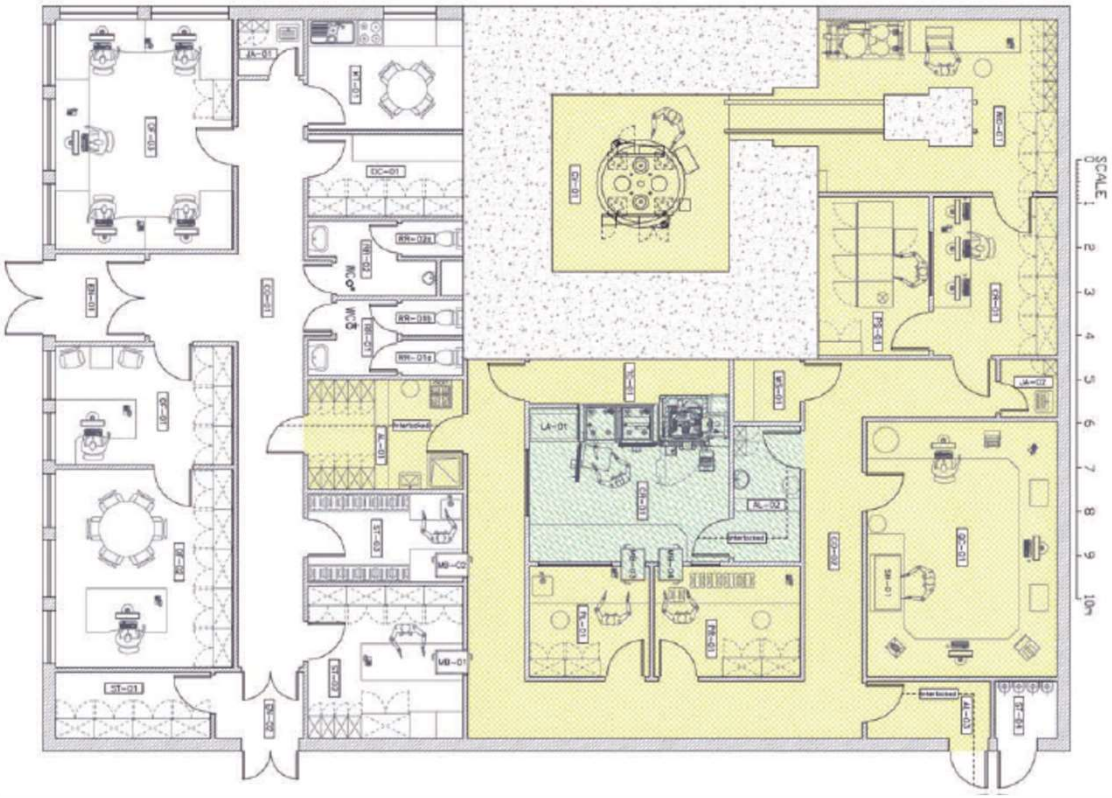


Main components (zones) of a generic facility



- Controlled areas
  - Cyclotron vault and control room
  - Hotlab for production of radiopharmaceuticals
  - QC-lab: Quality Control of radiopharmaceuticals
  - Packing / shipment zone
  - Technical installations including waste storage, ventilation system, chimney
- Other areas
  - Offices
  - Storage of consumables
  - …

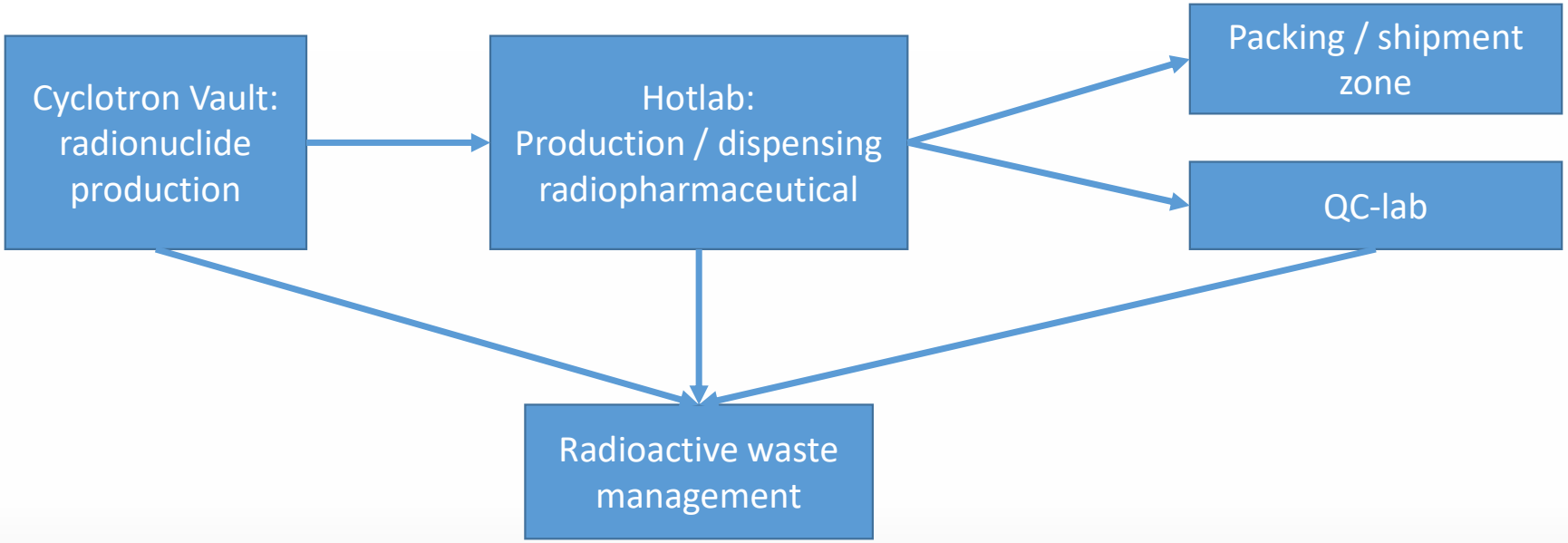
Pressure cascade



- GMP ↔ Radiation Protection
  - RP: protect the worker and the environment from radioactive contamination (rooms in negative pressure)
  - GMP: protect the radiopharmaceutical from bacteriological contamination from the environment (rooms in positive pressure)
- Compromises
  - Use negative pressure in areas with the highest radioactive contamination risk
  - Fulfil the requirements of the GMP classification of areas (class A-B-C-D) and use positive pressure were needed

The daily road of radiation sources

- Each step of the production process: proper risk analysis
- Not limited to individual areas, also transfer of sources
- Proper attention to nuclear safety issues

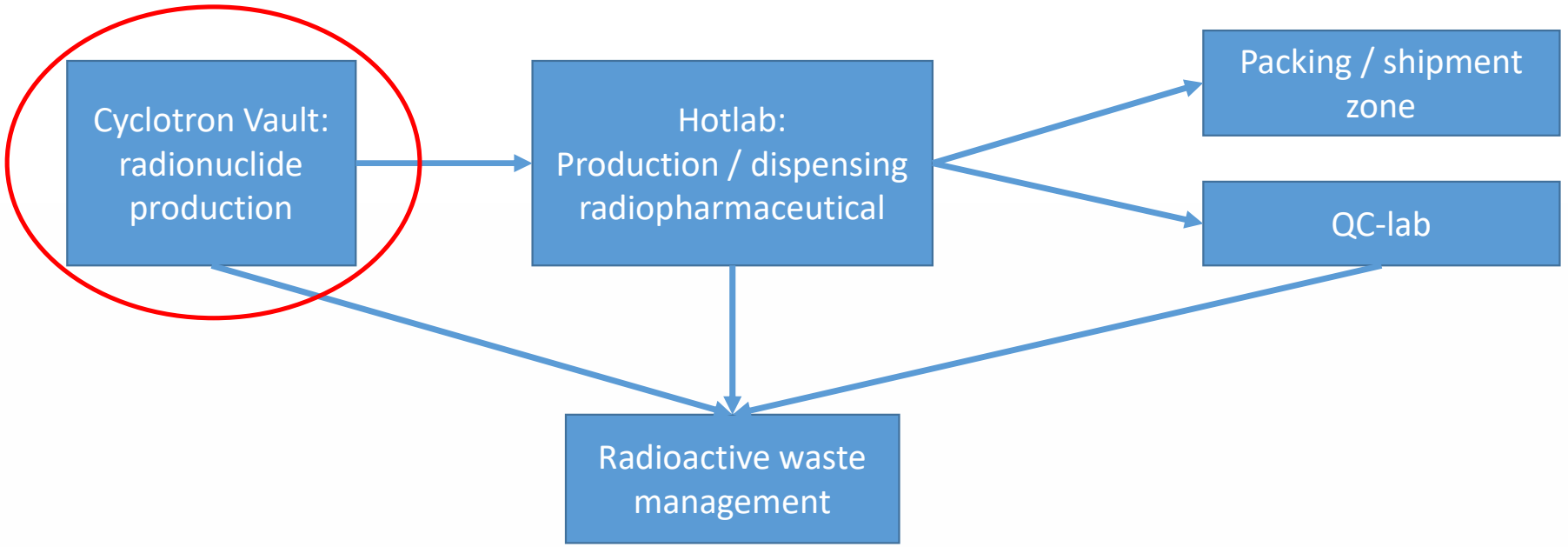


Nuclear safety

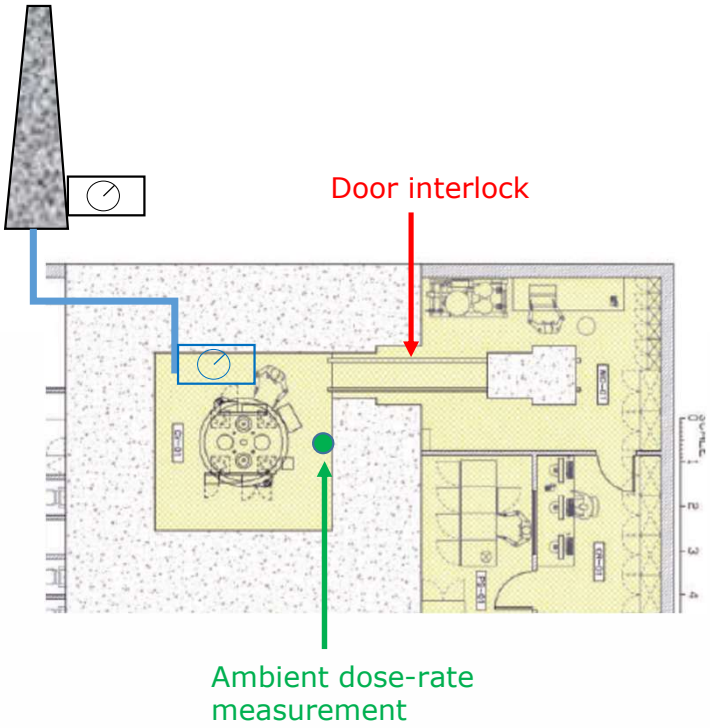
- Why?
  - Equipment involving high dose rates (cyclotron)
  - Relatively large activities being produced / handled
- How?
  - Foresee proper operating conditions
  - Avoid accidents
  - Limit impact of potential accidents / anomalies
- Ensure protection
  - Workers
  - Public
  - Environment

When everything runs smoothly…

The daily road of radiation sources

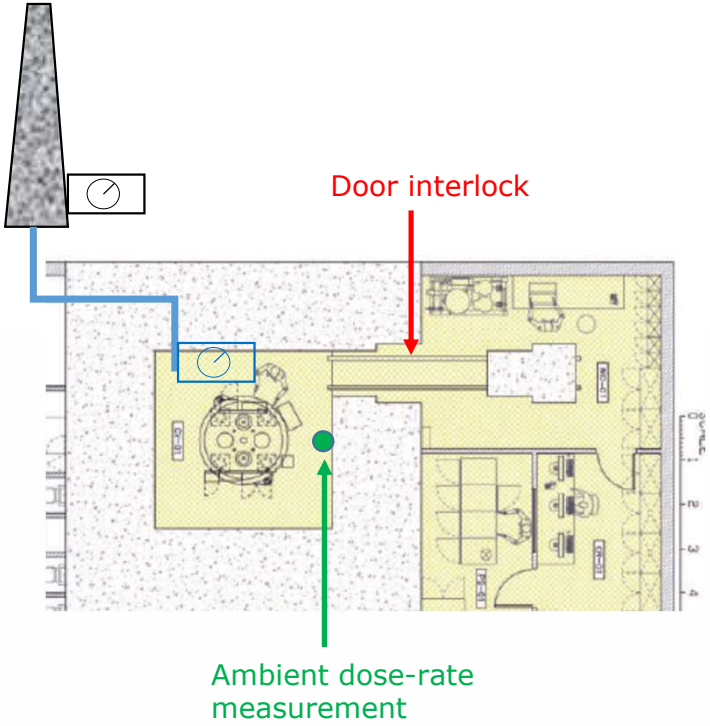


Radionuclide production (1)



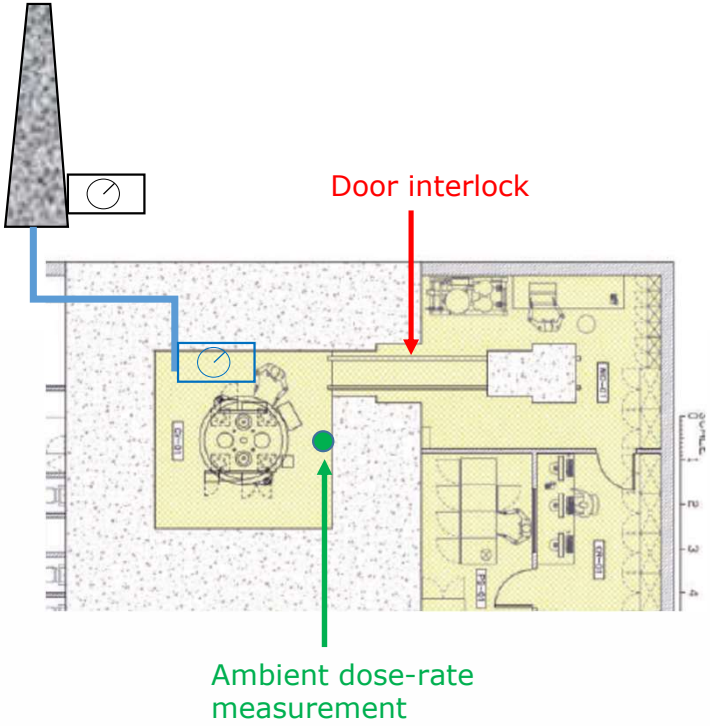
- Irradiation of targets with protons inside cyclotron vault
- Negative pressure
  - Lowest of facility
  - Interlock on cyclotron start-up
- During irradiation
  - Very high dose-rates (> Sv/h)
  - Target activities at end of irradiation: 100-1000 GBq
  - Activation of air (very short lived radionuclides)
  - Activation of cyclotron components

Radionuclide production (2)



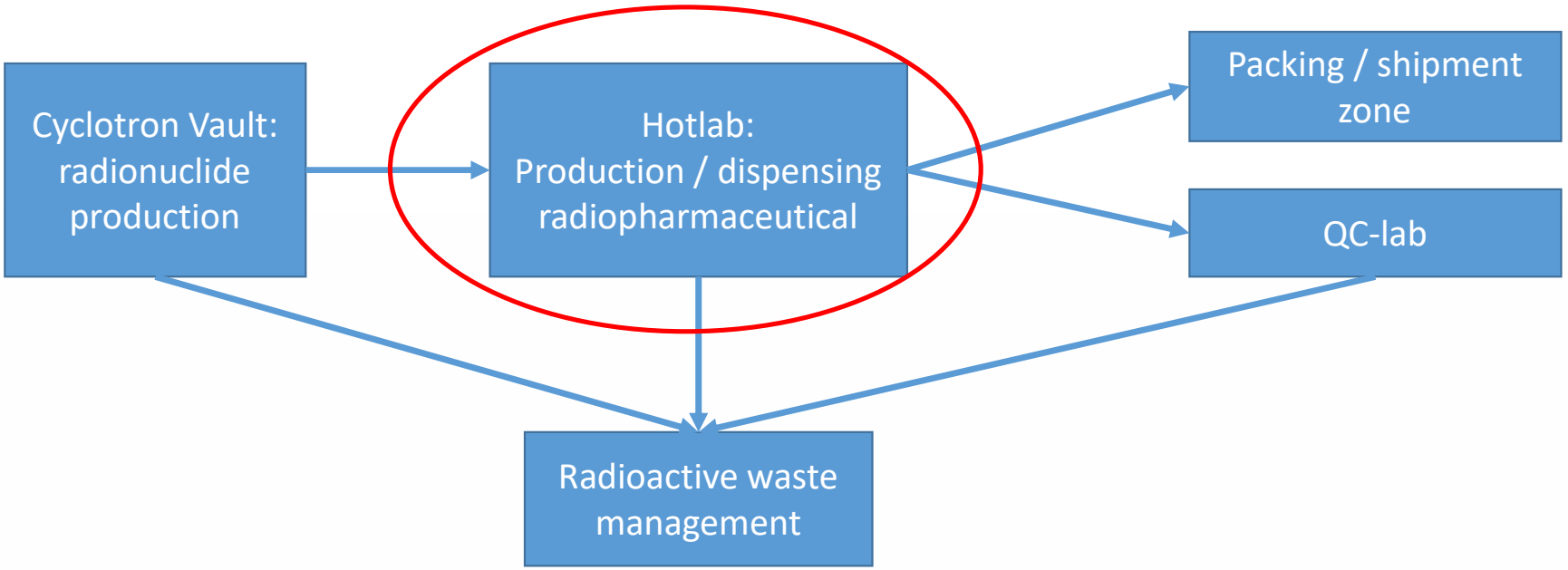
- Door interlock
  - Cyclotron operation
  - Ambient dose-rate measurement
- After irradiation
  - Transfer of target content → Hotlab
  - Activated air quickly removed by standard multiple air changes inside the vault
  - Ambient dose-rate > 1 mSv/h for several hours (door interlock prevents vault entrance)

Radionuclide production (3)

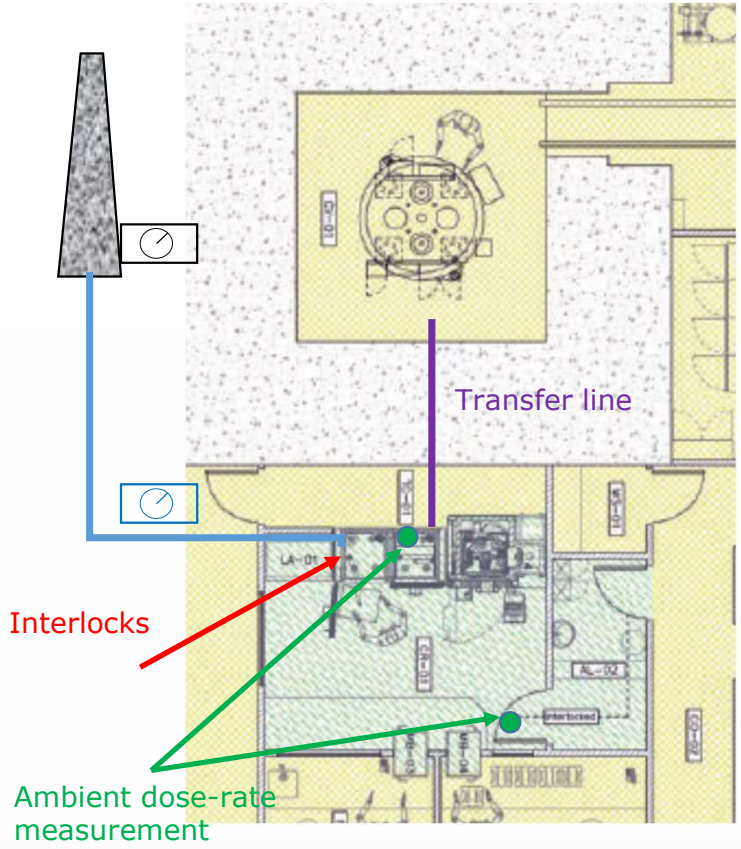


- Worker exposure outside the vault
  - Optimised by vault design (concrete shielding)
  - Very limited during routine irradiations
- Worker exposure during cyclotron maintenance
  - Relatively high dose rates in close contact with cyclotron parts (> 1 mSv/h)
  - Periodic maintenance can lead to 0.5-1 mSv per month (~ 5 mSv/y)
- Dosimetry of workers
  - Passive chest dosimeter, extremity dosimeter
  - Active alarm dosimeter

The daily road of radiation sources

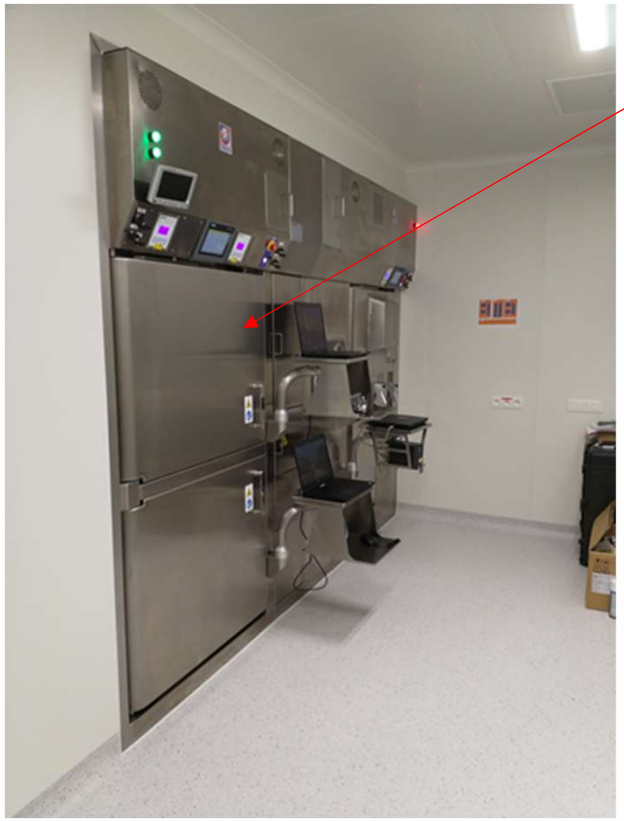


Radiopharmaceutical preparation (1)



- Transfer of irradiated target through shielded transfer lines from cyclotron to hotcell in production room (hotlab)
  - Small volumes (2 – 4ml)
  - Dose rates up to 20 µSv/h in e.g. corridors during few minutes
  - Visual / auditive signal of ongoing transfer
  - Interlock between target transfer ↔ open hotcell (2 directions)
  - Interlock between transfer ↔ hotcell negative pressure
- Production room
  - Positive pressure (GMP-requirement)
  - Ambient dose rate monitoring
  - Contains production hotcell(s), dispensing hotcell(s)

Radiopharmaceutical preparation (2)



Production hotcell

- Negative pressure (RP-requirement), leak tight
- Designed to receive high activities of PET-radionuclides
- Ambient dose rate measurement inside
- Interlock: ambient dose-rate measurement ↔ hotcell door
- Full automatic synthesis module (e.g. $^{18}F \rightarrow {}^{18}FDG$)
- Release of volatile ^{18}F-compounds during synthesis
  → ventilation system

Radiopharmaceutical preparation (3)

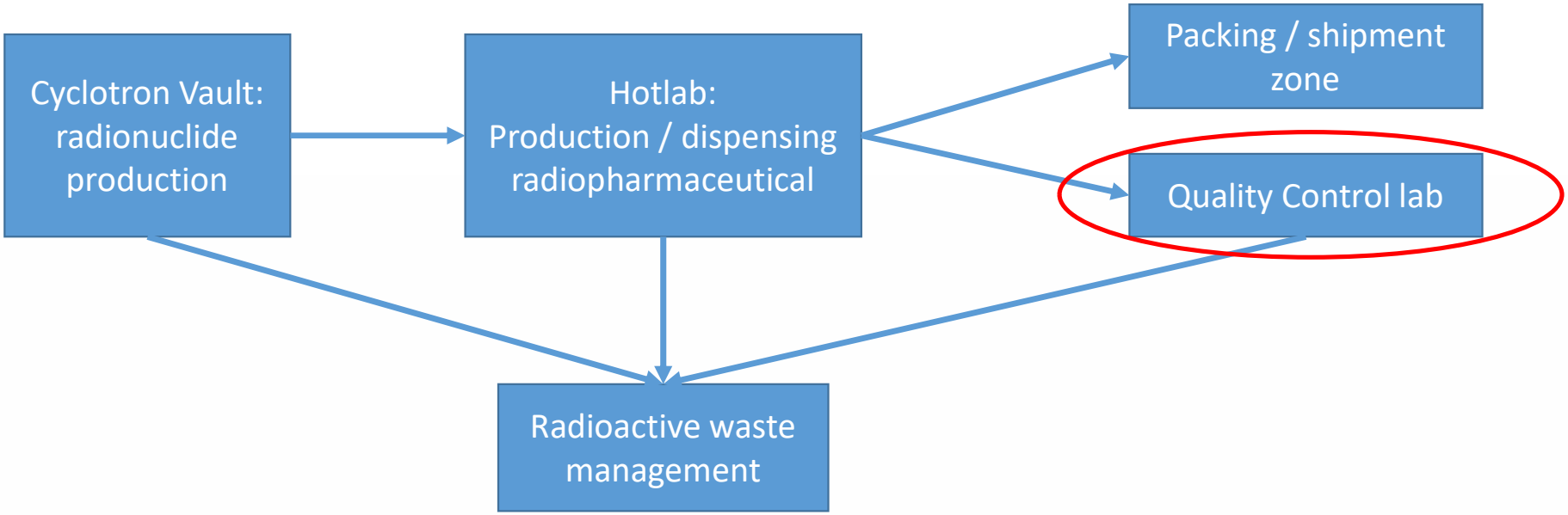
Dispensing hotcell

- Positive pressure (GMP-requirement), leak tight
- Pre-chamber to enter consumables (GMP-requirement)
- Designed to receive high activities of PET-radiopharmaceuticals
- Ambient dose rate measurement inside
- Interlock: ambient dose-rate measurement ↔ hotcell door
- Fully automatic dispensing module
- Drawer system delivers vials in shielded containers

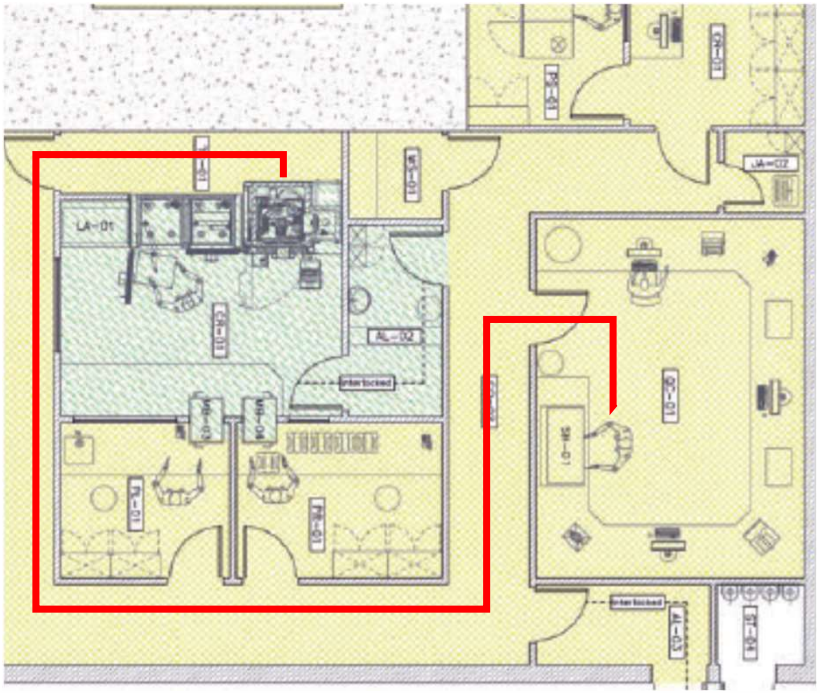
Radiopharmaceutical preparation (4)

- Worker exposure
  - Very limited during routine productions
  - Contamination risk during preparation synthesis (residual long-lived radionuclides)
- Dosimetry of workers
  - Passive chest dosimeter, extremity dosimeter
  - Active alarm dosimeter

The daily road of radiation sources

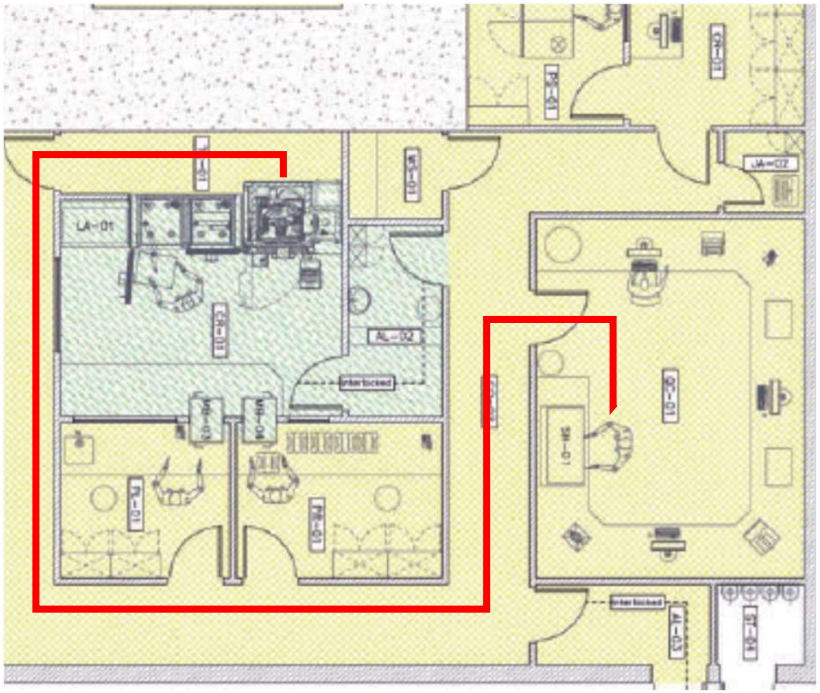


Quality Control (1)



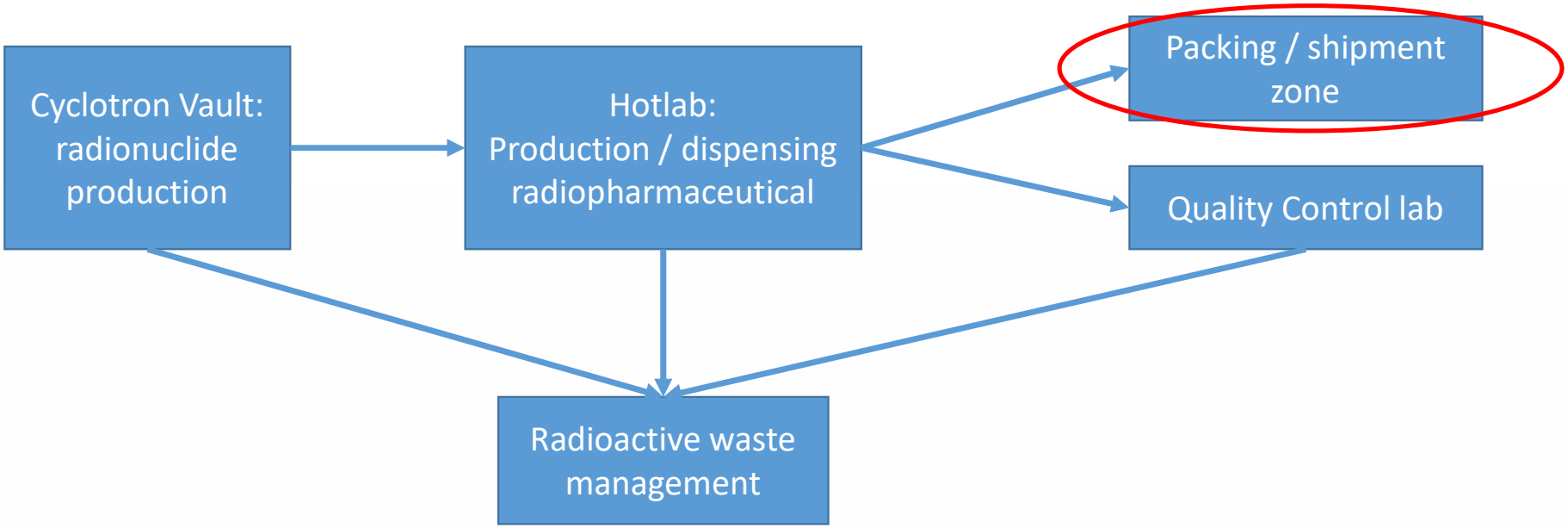
- Transport of quality control sample in shielded container from hotcell drawer system to QC-lab
- QC-lab
  - Organised as "ordinary" radionuclide laboratory
  - Negative pressure (RP-requirement)
  - Workbenches with table top lead-shielding
  - QC-apparatus

Quality Control (2)

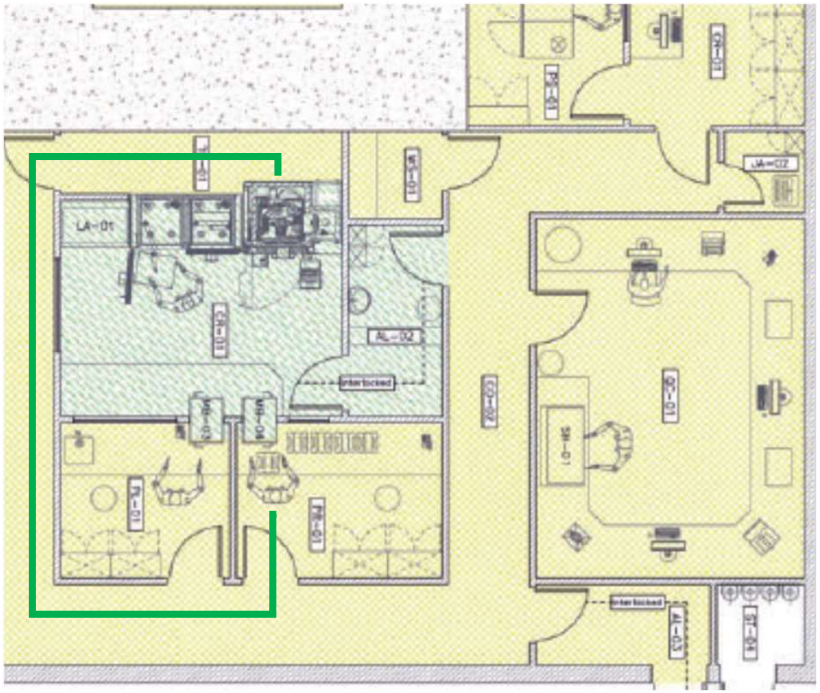


- Worker exposure
  - Relatively low activities (2 GBq/day) → limited external exposure
  - Manual handling of sources
  - Contamination risk during preparation of samples / dilutions / manipulating QC-apparatus
- Dosimetry of workers
  - Passive chest dosimeter, extremity dosimeter

The daily road of radiation sources

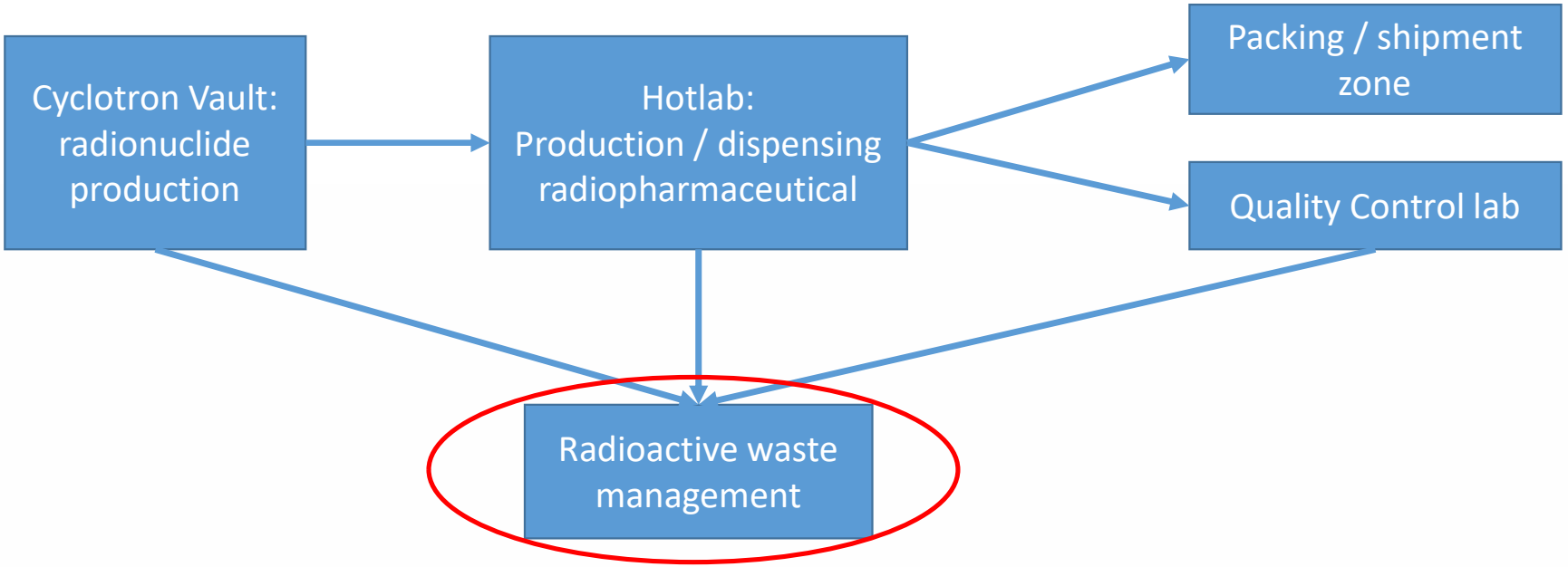


Packing multidose vial(s) for transport



- Transport of multidose vial(s) in shielded containers from hotcell drawer system to shipment zone
- Shipment zone
  - No specific negative/positive pressure required
  - Zone for administrative tasks, designed to handle sealed packages, preparation of transport documents
  - Performing package dose rate measurements, labelling, sealing transport packages
- Dose rates up to 100 µSv/h
- Dosimetry of workers
  - Passive chest dosimeter

The daily road of radiation sources

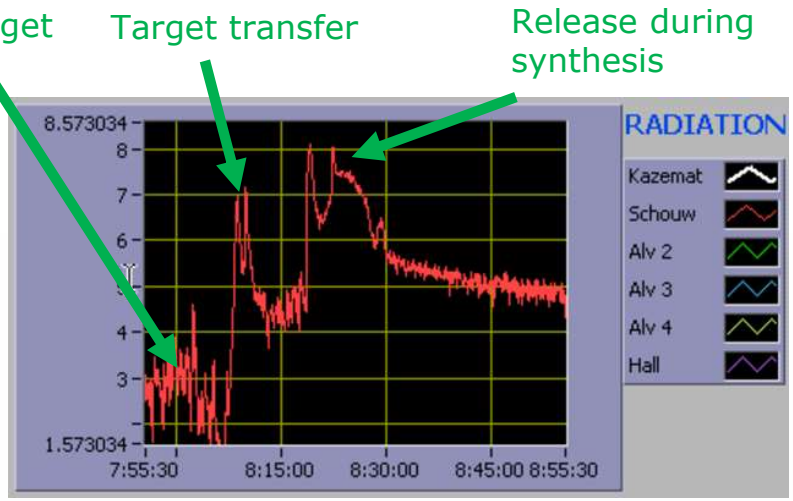


Radioactive waste management

- Radioactive waste generated during all steps of the production process
- Relatively small volume, mass
- Cyclotron maintenance
  - Activated cyclotron parts
  - Medium high activities containing long-lived radionuclides
- Radiopharmaceutical synthesis
  - Short-lived high activity waste decays in hotcell for a few days
  - After decay short-lived waste: relatively low activities of long-lived radionuclides!
- QC: relatively low activities of short-lived waste
- If properly managed very little contribution to worker exposure!

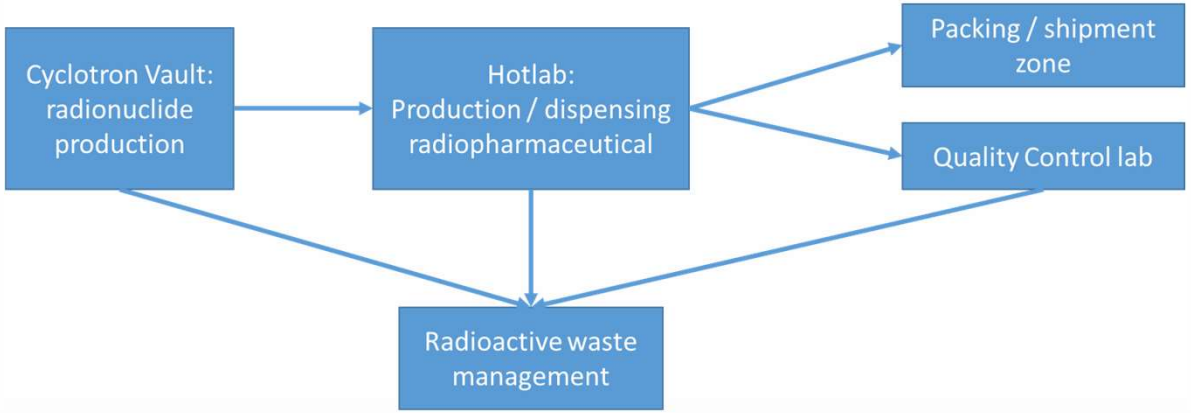
Radioactive emissions

- Production of PET-radiopharmaceuticals involves the emission of radioactivity
- Emission optimised
  - Filtration system
  - Collection bags inside hotcells
- Maximum emission values specified in the licence
- Continuous chimney monitoring
- Monthly reporting to FANC



Training, education and working procedures

- Entire production process cannot run smoothly without:
  - Sustainable working and safety procedures for each step
  - Well educated and trained staff
  - Well educated and trained Radiation Protection Officers participating in daily production process



That’s not all!

When something does not run smoothly…

Risk analysis for abnormal conditions

- "What if?" analysis and radiological impact studies needed (worst case scenarios)
  - Failure of one or more safety systems
  - Accidental release of radioactivity
  - Radioactive contamination of staff members
  - …
- Provide redundant solutions where possible
- (Emergency) procedures needed
  - Some may result in a very temporary production delay
  - Other may result in a facility shutdown for a specific period

Responsibility / task of facility management

- Sustainable maintenance program for technical installations
  - HVAC
  - Fire safety
  - Safety systems
  - …

  } Could require temporarily facility shutdown

- Control program
  - Periodic testing of interlocks (HVAC, target transfer, opening doors,…)
  - Periodic testing of integrity of transfer lines
  - Hotcell leakage tests
  - QC ambient dose-rate monitors, alarm dosimeters, contamination monitors, chimney monitor
  - All other specific technical infrastructure that can have impact on radiation protection and nuclear safety

To conclude…

- Radiation protection and nuclear safety in a PET-radiopharmaceutical production site starts with a proper risk analysis and facility design!
- High exposure rates → Class IIA → special regulatory requirements
- Daily radiation protection of workers is (should be) supported by numerous safety systems / working procedures
- Under normal conditions following dedicated procedures:
  - Highest risk for external exposure of workers: during cyclotron maintenance
  - Highest contamination risk for worker exposure: during QC
- Procedures for abnormal situations!
- QA/QC in RP and nuclear safety by maintenance and control program

Thanks for the attention