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FACULTEIT FARMACEUTISCHE WETENSCHAPPEN

VAKGROEP < ... >
ONDERZOEKSGROEP < ... >

PIC/S GUIDELINES: IMPACT FOR THE RADIOPHARMACY

prof. dr. apr. Filip De Vos

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0. LEARNING OBJECTIVES

- Brief overview of pharmaceutical legislation PIC/S history definition
- Different medicinal radiopharmaceutical products in Belgium
- Content of PIC/S – radiopharmaceutical context

1. BRIEF OVERVIEW OF PHARMACEUTICAL LEGISLATION

- EMA: European Medicines Agency
  Agency of the European Union

- Core business:
  - Facilitating the development of medicines & access to them
  - Evaluating the applications for a marketing authorisation
  - Monitoring the safety of medicines during their lifecycle
  - Providing information to healthcare professionals & patients

- Members: all EU countries - with some countries agreements (USA, Switzerland, Norway, Australia)

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1. BRIEF OVERVIEW OF PHARMACEUTICAL LEGISLATION

- EMA: European Medicines Agency

- Like any other EU agency they have access to different legal acts (described in EUR-Lex)
  - **Regulations**: apply immediately and uniformly in all EU states
  - **Directives**: EU countries individually must adopt measures to insert them in local legislation
  - **Decisions**: binding to whom it is addressed
  - **Recommendations**: suggest a line of action but not binding

1. BRIEF OVERVIEW OF PHARMACEUTICAL LEGISLATION

- EMA: European Medicines Agency

Most important Volumes:

Volume 1 and 5: legislation for human medicine

Volume 2: marketing authorizations

Volume 4: GMP

Volume 10: clinical trials

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1. BRIEF OVERVIEW OF PHARMACEUTICAL LEGISLATION

- European Pharmacopoiea (Ph.Eur): 11th edition (from Jan 2023

  handbook providing quality standards to control the quality of **medicines** and **substances to manufacture those medicines**

  Collection of **monographs**: chapter describing the identity, quality control and methods of analysis

1. BRIEF OVERVIEW OF PHARMACEUTICAL LEGISLATION

– European Pharmacopoiea (Ph.Eur): 11th edition (from Jan 2023

Legal frame work: Council of Europe

Ph.Eur: is legally binding in 39 member states (including all the countries of European Union

Is published by the EDQM: directory general in the Council of Europe that deals with quality of medicines and and healthcare

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COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

edqm

1. BRIEF OVERVIEW OF PHARMACEUTICAL LEGISLATION

-PIC/S: Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

Instrument to improve co-operation between health authorities and the pharmaceutical industry

Mutual recognition of inspection between member countries

Equivalent principles of inspection

GMP guidelines of the PIC/S are since 1989 developed parallel with the GMP requirements of the EMA

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1. BRIEF OVERVIEW OF PHARMACEUTICAL LEGISLATION

-PIC/S GUIDE TO GOOD PRACTIES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS

- Principle
  - Aim: delivery of high quality standard medicines for in-hospital prepared medicinal products
  - Quality system incorporating the principles of Good Preparation Practices
  - Based (but not a complete copy) of PIC/S guide for Pharmaceutical Industry

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1. BRIEF OVERVIEW OF PHARMACEUTICAL LEGISLATION

Table 1 Overview of legally binding and guidance documents for radiopharmaceuticals in Europe (adapted from [7, 8]

	Categories of radiopharmaceuticals		
	Marketing authorization	Clinical trials	In-house preparations
Legally binding documents	Ph. Eur. General and Specific Monographs		
	Directive 2001/83/EC	Directive 2001/20/EC	National governance
	Directive 2003/94/EC	Directive 2003/94/EC	
	Directive 2004/27/EC	Directive 2005/28/EC	
	GMP Annex 3	Regulation 536/2014	
		GMP Annex 13	
Guidance documents	EMA Guideline on Radiopharmaceuticals	EC Guidance IMP/NIMP	Ph. Eur. General Chapter 5.19
		EMA Guideline IMPD	PIC/S GPP 010-4 incl. Annex 3
		EMA Guideline first-in-human clinical trials	EANM guidelines and guidance documents
		EANM guidelines and guidance documents	National documents

European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:1095–1098

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2. WHAT MEDICINAL PRODUCTS DO EXIST?

- **Medicinal Products with a marketing authorization (MA)**
  - Medicines (MA) that only need to be administered to the patient: arranging the patient dose
    - Eg: Fludeoxyglucose 18F IBA/Curium
  - Medicines prepared by combining the radioisotope (MA) with a precursor or cold kit (MA)
    - Eg: ^{99m}Tc generator eluate with ^{99m}Tc MDP-kit for bone scanning

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2. WHAT MEDICINAL PRODUCTS DO EXIST?

- **How to obtain a marketing authorization (MA) for radiopharmaceuticals in Belgium?**
  - Recognition by the EMA and/or FAGG
    - GMP inspected production site
    - GMP authorization for the production of your radiopharmaceutical
    - Provide a complete pharmacological/toxicological dossier with phase I/II/III clinical trials showing the diagnostic/therapeutic potential of your product
  - Recognition by the FANC
  - Finally pricing by the FOD economics (in each member state)

  - Three procedures:
    - Central procedure: at the EMA (Amsterdam)
    - Decentral procedure: recognition in 1 member state (RMS) followed by recognition in the other member states
    - Local procedure: only recognition in 1 member stated (FAGG)

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2. WHAT MEDICINAL PRODUCTS DO EXIST?

- **MAGISTERIAL PREPARATIONS**
  - medicinal product prepared by a pharmacy based on a medicinal prescription for a certain patient or animal
  - Eg: 18F-PSMA-1007
- **OFFICINAL PREPARATIONS**
  - medicinal product prepared in a pharmacy based on the Pharmacopeia or therapeutical magisterial formulation.
  - Eg: 11C-raclopride, 18F-FDG (product with monograph in the Ph.Eur)

  - May only be administered in the own pharmacy/hospital or identity

- **How to obtain a authorization to prepare magisterial and officinal radiopharmaceuticals?**
  - Recognition by the FANC

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2. WHAT MEDICINAL PRODUCTS DO EXIST?

- **MEDICINAL PRODUCTS USED IN CLINICAL TRIALS**
  - **Products already with a MA**
  - **IMP pharmaceuticals**

- **How to obtain a authorization for IMP radiopharmaceutical?**
  - GMP license for medicinal products by the FAGG
  - Approved ethical protocol and study protocol: ethical commission/FAGG
  - Approved IMPD (investigational medicinal product dossier): FAGG
  - Authorisation by the FANC

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3. WHY PIC/S IN BELGIUM?

Implementing: PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments

1. Why?

→ KB 30 September 2020: art.21§2: *“De apotheekbereidingen moeten gebeuren overeenkomstig de PIC/S-normen, zoals opgenomen in Bijlage III./ Les préparations de la pharmacie doivent être effectuées conformément aux normes PIC/S, tels que repris dans l’Annexe III”*

→ PIC’s guideline include Annex 3: Good practices for the preparation of radiopharmaceuticals in healthcare establishments.

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3. WHY PIC/S IN BELGIUM?

Implementing: PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments

1. Why?

Apotheekbereidingen/préparations de pharmacie = PHARMACEUTICAL PREPARATIONS

→ KB 30 September 2020: art.21§2: *"De apotheekbereidingen moeten gebeuren overeenkomstig de PIC/S-normen, zoals opgenomen in Bijlage III./ Les préparations de la pharmacie doivent être effectuées conformément aux normes PIC/S, tels que repris dans l'Annexe III"*

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3. WHY PIC/S IN BELGIUM?

Implementing: PIC/S guide to good practices for the preparation of medicinal products in healthcare establishments

- What are pharmaceutical preparations?

Definition: Every magisterial and or officinal preparation as mentioned in article 6quart, §3 first lid, 1°) and 2°) of the law of 25 march 1964.

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3. WHY PIC/S IN BELGIUM?

What are pharmaceutical preparations?

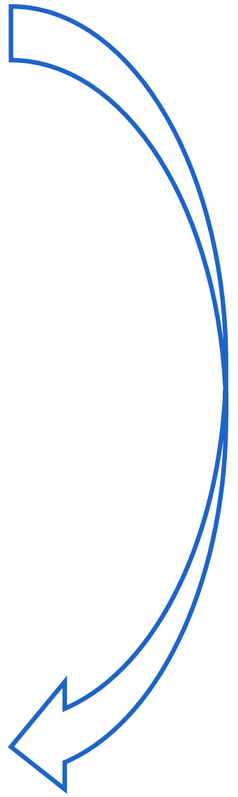
1°) Magisterial preparation: medicinal product prepared by a pharmacy based on a medicinal prescription for a certain patient or animal.
2°) Officinal preparation: medicinal product prepared in a pharmacy based on the Pharmacopeia or therapeutical magisterial formulation.

Out of scope?

- Investigational medicinal products
- Products prepared under Marketing Authorisation
- Arranging patient doses

Big Question

- The radiopharmaceuticals prepared by a person or institution authorized to use such medicinal products on the basis of approved radionuclide generators, kits or radionuclide precursors and this in accordance with the manufacturer's instructions?



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3. WHY PIC/S IN BELGIUM?

– What are pharmaceutical preparations?

1°) Magisterial preparation: medicinal product prepared by a pharmacy based on a medicinal prescription for a certain patient or animal.

2°) Officinal preparation: medicinal product prepared in a pharmacy based on the Pharmacopeia or therapeutical magisterial formulation.

– Out of scope?

- Investigational medicinal products
- Products prepared under MA
- Arranging patient doses
- The radiopharmaceuticals prepared by a person or institution authorized to use such medicinal products on the basis of approved radionuclide generators, kits or radionuclide precursors and this in accordance with the manufacturer's instructions?

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3. WHY PIC/S IN BELGIUM?

- When is compliance needed?

1 January 2026

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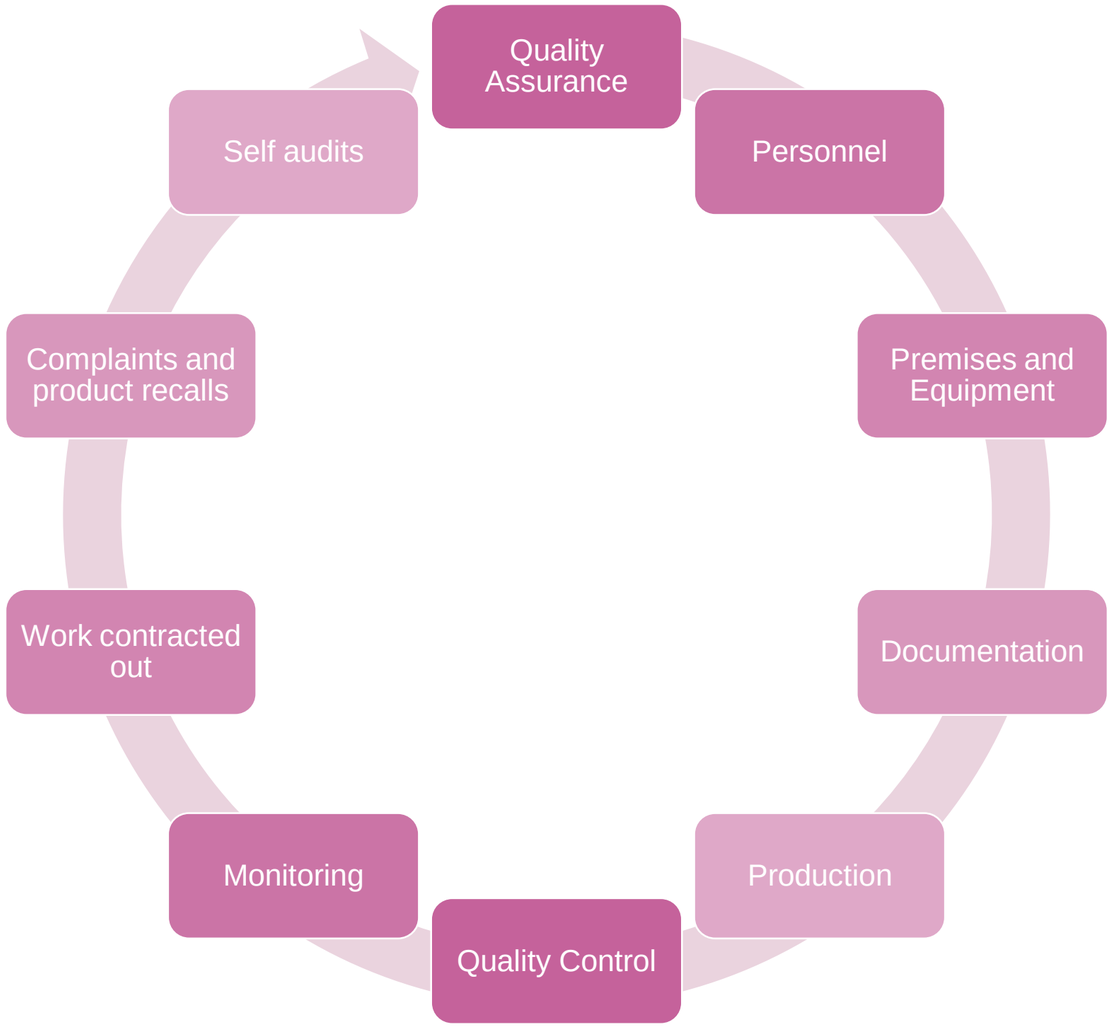
3. HOW? – CONTENT OF PIC/S HOSPITALS



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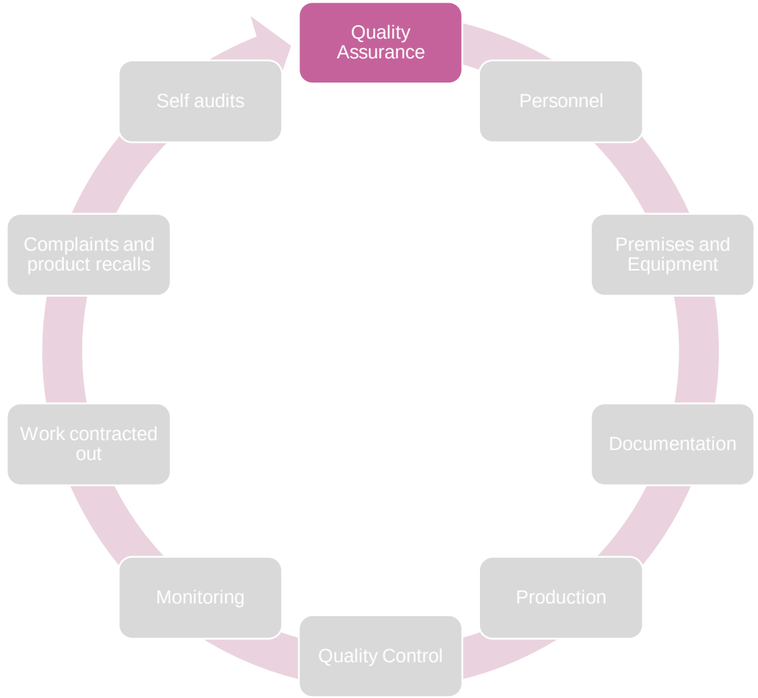
3. HOW? – CONTENT OF PIC/S HOSPITALS

1. Quality Assurance:

Definition: "the sum total of the organized arrangements made with the object of ensuring that medicinal products are of the quality required for their intended purpose."



- Set-up: Organizational structure and procedures
  - Link trainings to function descriptions
- Control of system: Effectiveness and Suitability
- Remain control:
  - Incoming checks on materials based on risk assessment
  - Implementing change control

→ Ensure consistent quality for every product

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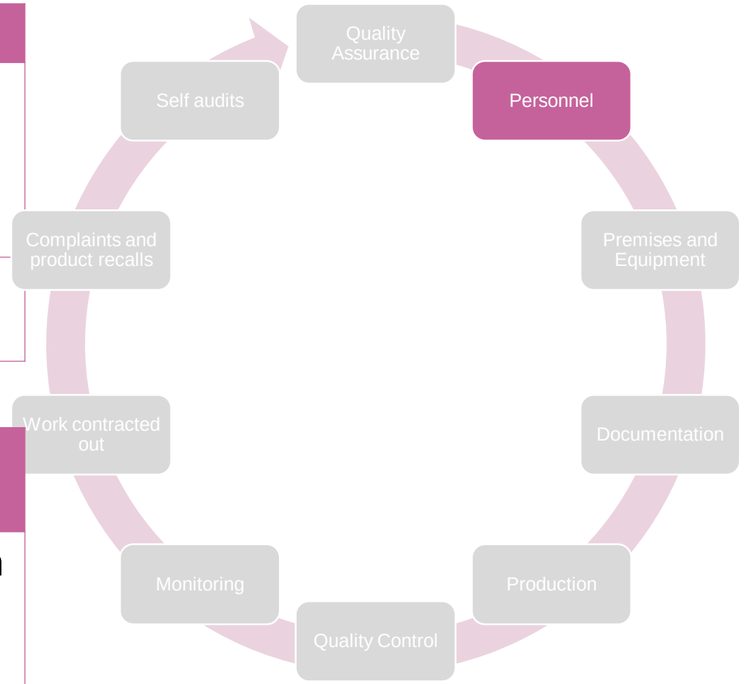
3. HOW? – CONTENT OF PIC/S HOSPITALS

	Magisterial preparations	Comment
General training	Job description and tasks	Example: Production/ QC/ incoming goods, environmental control, hygiene, gowning, aseptic processing, cleaning, GPP and or GMP, etc.
	Working ionising radiation and Radiological protection	

	Magisterial Preparations	Exception: Licensed Radiopharmaceuticals	Comment
Minimum required personnel for production/ preparation	Radio-pharmacist Production ≠ QC/ release	Responsible for quality Preparation ≠ QC Preparation ≠ release	Preferred QC different person then release. Responsible person for quality should have knowledge of GPP, aseptic processing and radiochemistry.



Oral and inhalation products require depending on the preparation a radio-pharmacist or a responsible for quality.

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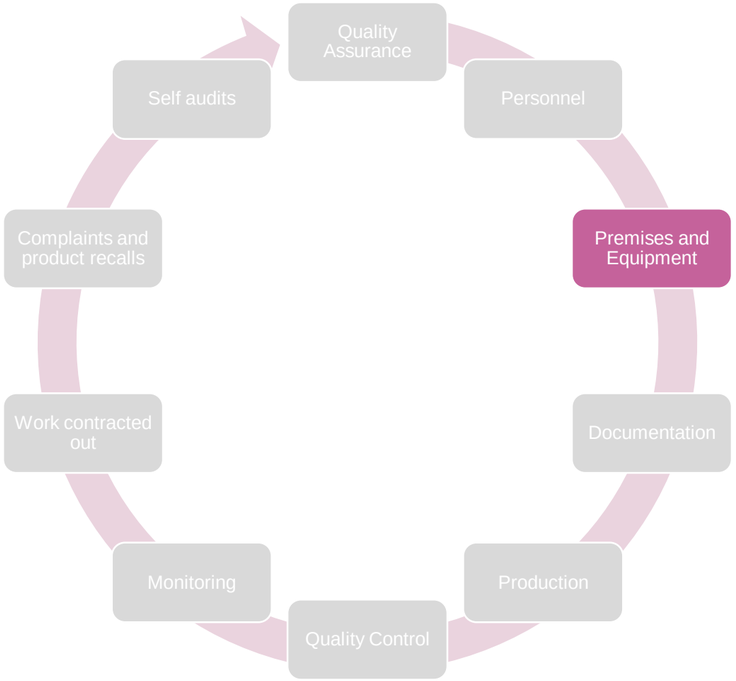
2. HOW? – CONTENT OF PIC/S HOSPITALS

Requirements general in place:

- Access control
- Pest control
- Cleaning of area's
- Temperature control
- Equipment for detection and monitoring for radiation exposure

Additional requirements:

- Temperature and humidity monitoring (storage and preparation area's)
- Dedicated facilities for radiopharmaceuticals
- Storage area: released materials and quarantine zone, rejected, returned and recall area
- Pressure control to protect the product for injection from microbiological contamination as environment from ionising radiation



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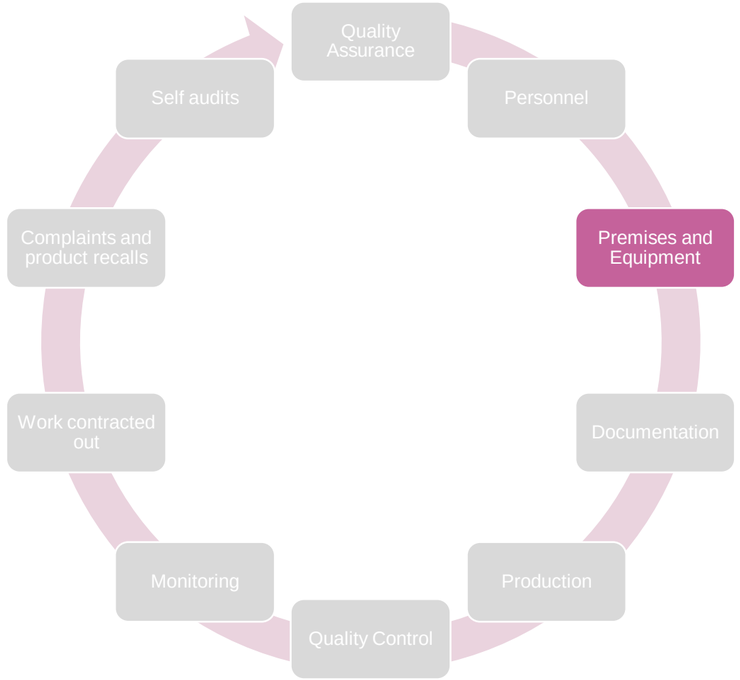
2. HOW? – CONTENT OF PIC/S HOSPITALS

Room requirements for magisterial preparations (excluding reconstitution)

		Open workstation	Closed (isolator)
Working room	Aseptic preparation and filling	A	
	Preparation of solutions to be filtered	C	
	Pre-filling steps as radiochemical synthesis	C[1.]	
Surrounding room	Aseptic preparation and filling	B[1.]	D
	Preparation of solutions to be filtered	D	



1. Different classification based on a risk assessment

Generators: close to preparation workstation – risk assessment

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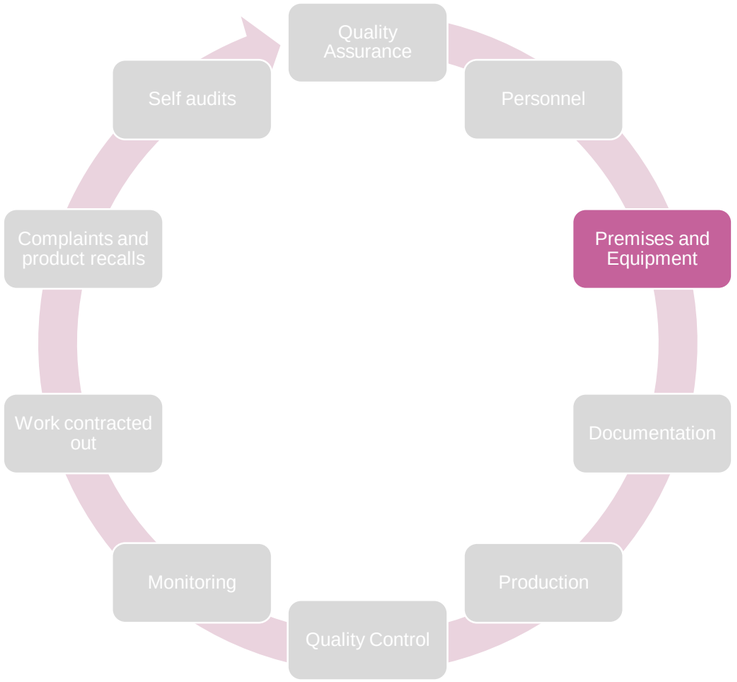
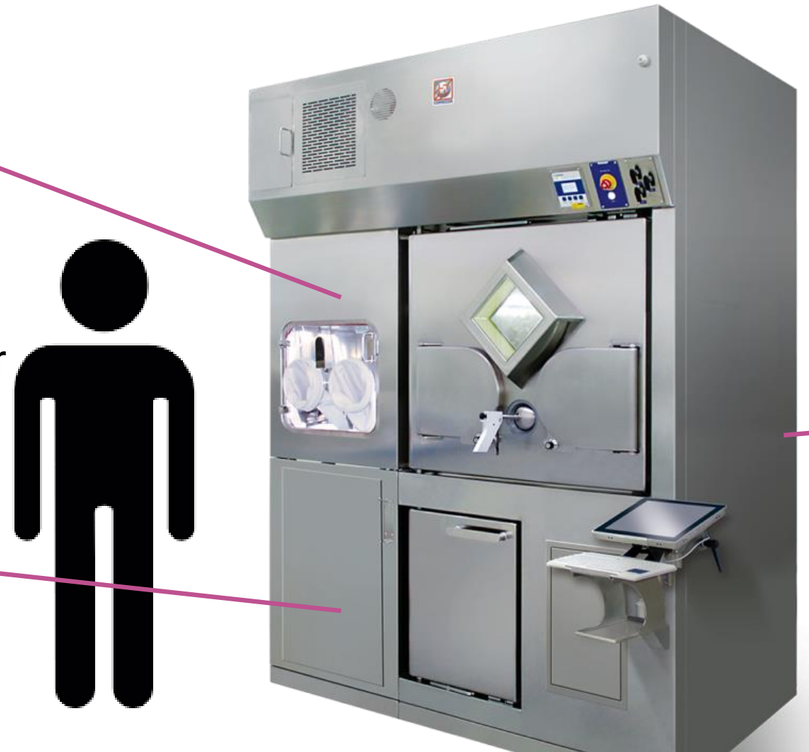
2. HOW? – CONTENT OF PIC/S HOSPITALS

		Open workstation	Closed (isolator)
Working room	Aseptic preparation and filling	A	
	Preparation of solutions to be filtered	C	
	Pre-filling steps as radiochemical synthesis	C[1.]	
Surrounding room	Aseptic preparation and filling	B[1.]	D
	Preparation of solutions to be filtered	D	



- Surrounding clas B[1]
- Laminair flow
- To insert material

- Class C for personnel

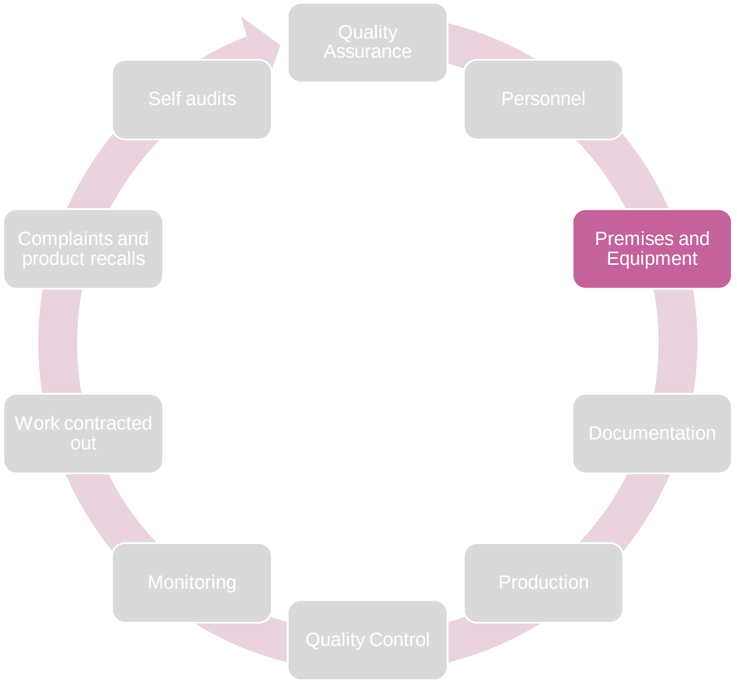


- Radiochemical synthesis
- Class C

- Open workstation for aseptic filling: no gas sterilisation
- Class A inside
- Vertical laminar flow

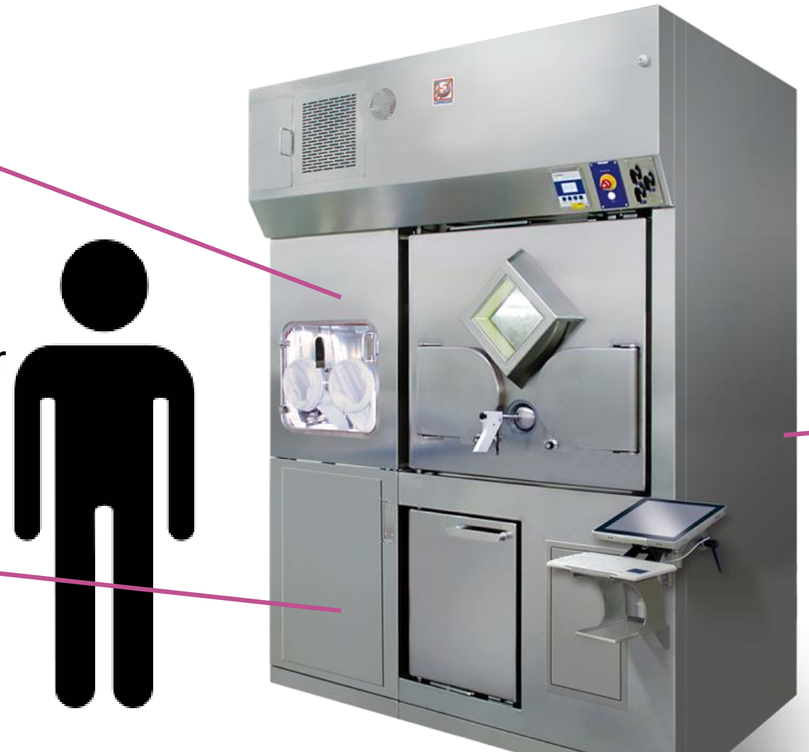
2. HOW? – CONTENT OF PIC/S HOSPITALS

		Open workstation	Closed (isolator)
Working room	Aseptic preparation and filling	A	
	Preparation of solutions to be filtered	C	
	Pre-filling steps as radiochemical synthesis	C[1.]	
Surrounding room	Aseptic preparation and filling	B[1.]	D
	Preparation of solutions to be filtered	D	



- Closed workstation for prefilling steps
- Gas sterlisation
- Class A inside

- Class D for personnel



- Radiochemical synthesis
- Class C

- Closed workstation for aseptic filling: gas sterilisation
- Class A inside

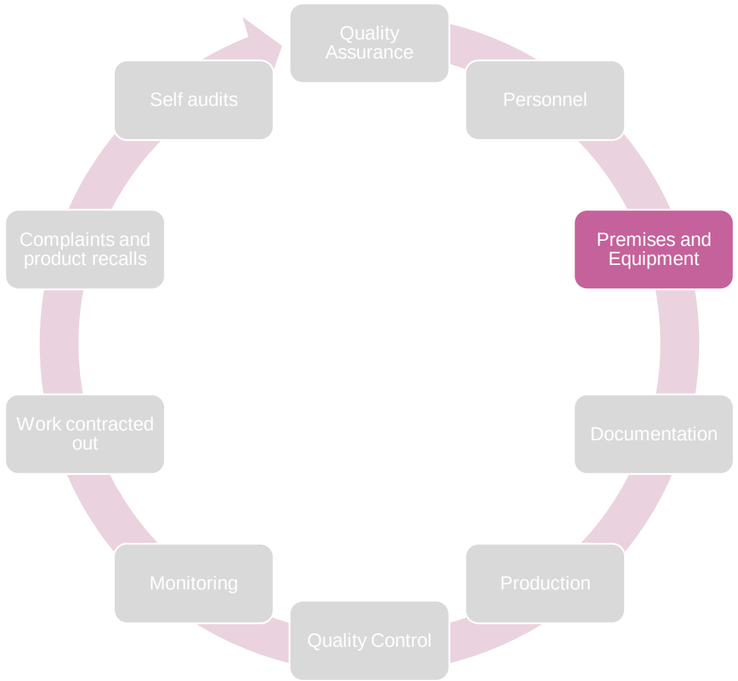
2. HOW? – CONTENT OF PIC/S HOSPITALS

Room requirements for magisterial preparations reconstitution

			Open workstation	Closed (isolator)
Working room	Aseptic preperation	Closed Aseptic	A or C[1.]	
Surrounding room			C	D

1. Based on a risk assessment

Closed aseptic: filling of the final product into a single container for immediate use “the elution from a generator into a sealed vial and then drawing the contents into a syringe through the septum would be classified as a closed method of preparation.”



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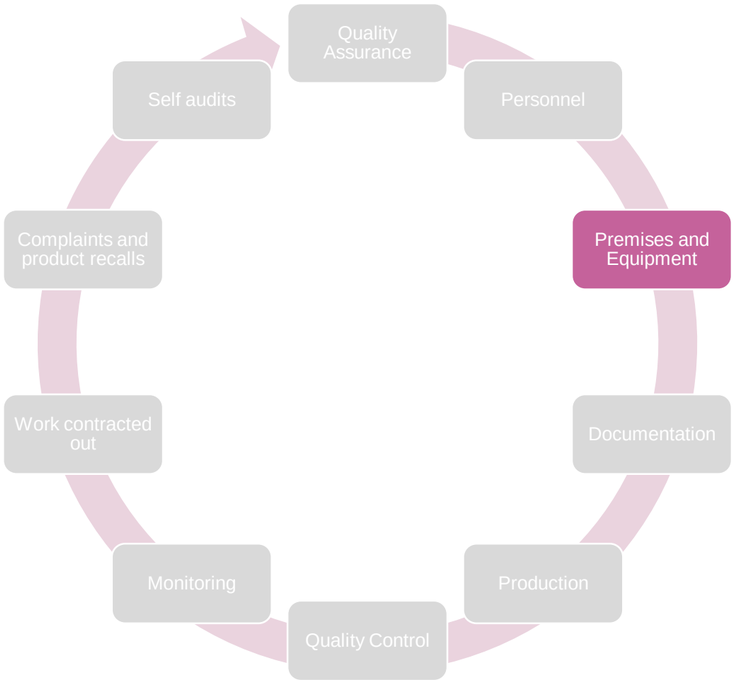
2. HOW? – CONTENT OF PIC/S HOSPITALS

			Open workstation	Closed (isolator)
Working room	Aseptic preperation	Closed Aseptic	A or C[1.]	
Surrounding room			C	D



– Class C for personnel

– Class A for LAF cabinet

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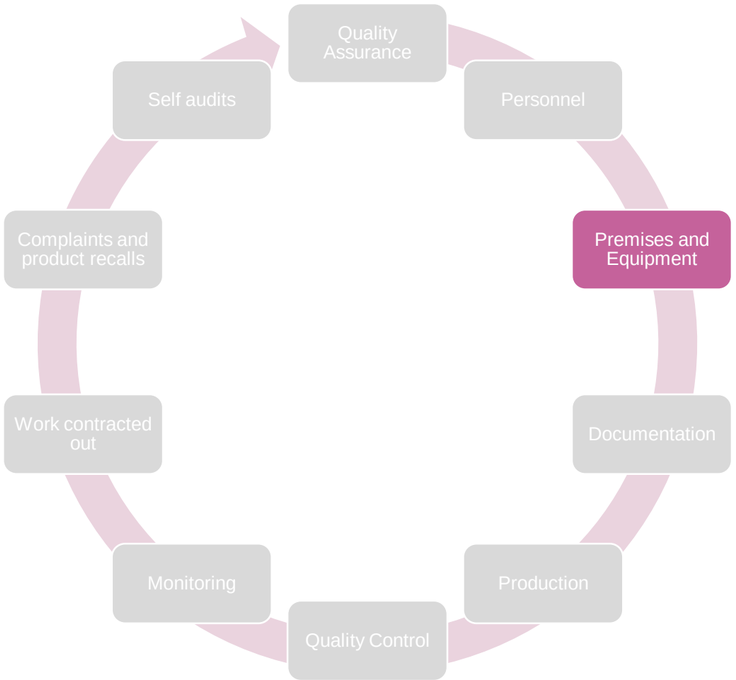
2. HOW? – CONTENT OF PIC/S HOSPITALS

			Open workstation	Closed (isolator)
Working room	Aseptic preperation	Closed Aseptic	A or C[1.]	
Surrounding room			C	D



– Class C for personnel

– Workbench in class C
– Based on risk analysis

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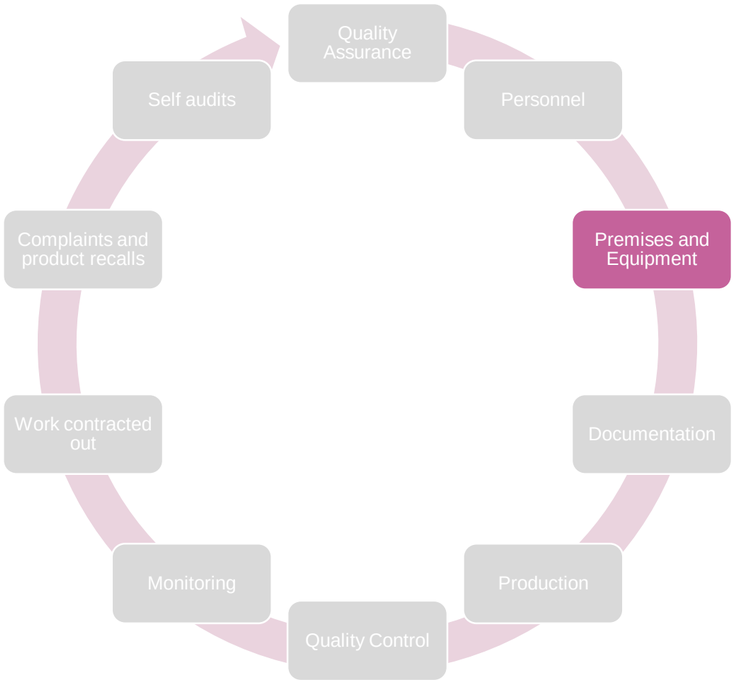
2. HOW? – CONTENT OF PIC/S HOSPITALS

			Open workstation	Closed (isolator)
Working room	Aseptic preperation	Closed Aseptic	A or C[1.]	
Surrounding room			C	D



– Class D for personnel

– Isolator class A
– With interlocks for transfer of material

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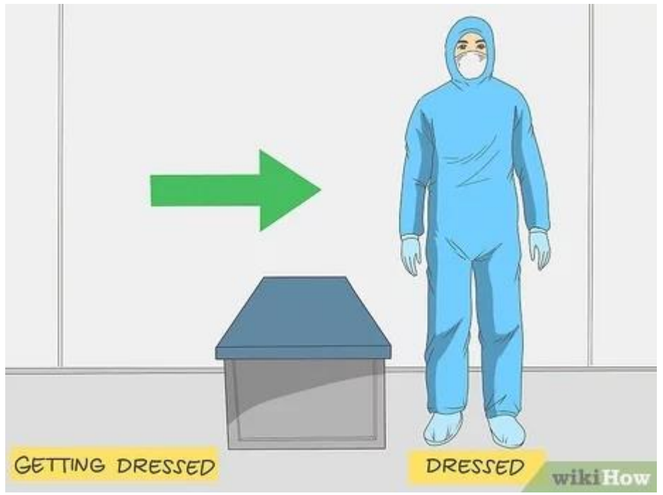
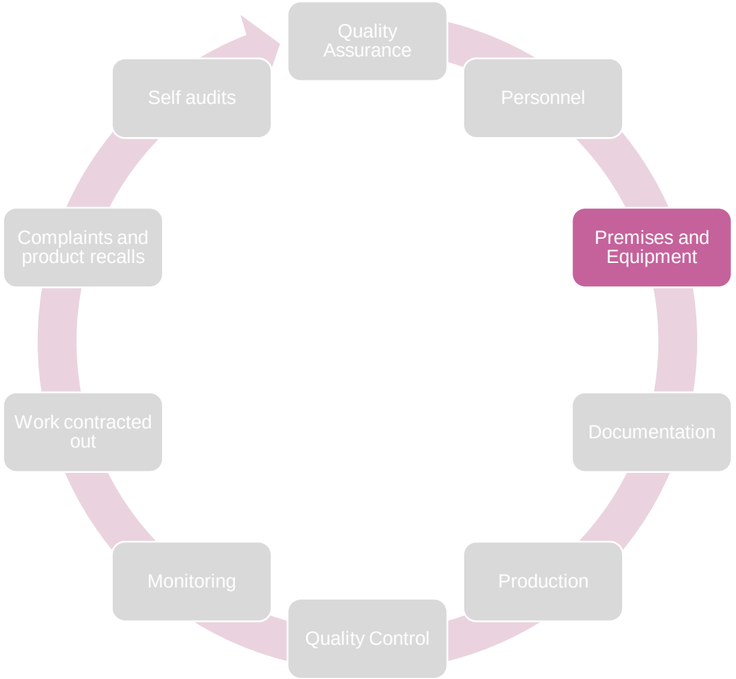
2. HOW? – CONTENT OF PIC/S HOSPITALS

- Class C
- Dressing protocol





- Protectice coverall
- Gloves
- Shoe covers
- Face mask
- Hair mask

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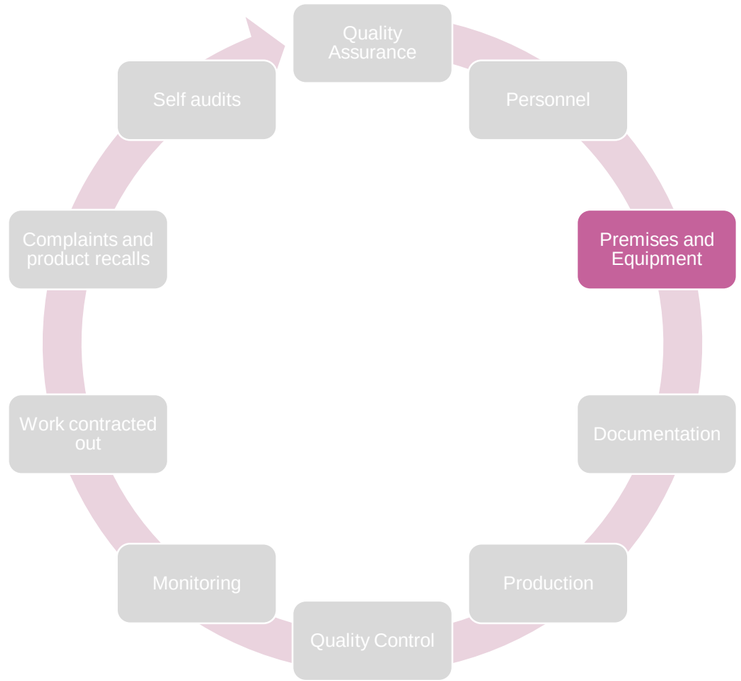
2. HOW? – CONTENT OF PIC/S HOSPITALS

Room requirements for Oral and inhalation products:

- No specific classifications are given but:
  - Separate dedicated room from aseptic preparations
  - Appropriate clothing
  - Safety cabinets
  - Working room and surrounding rooms: different pressure.



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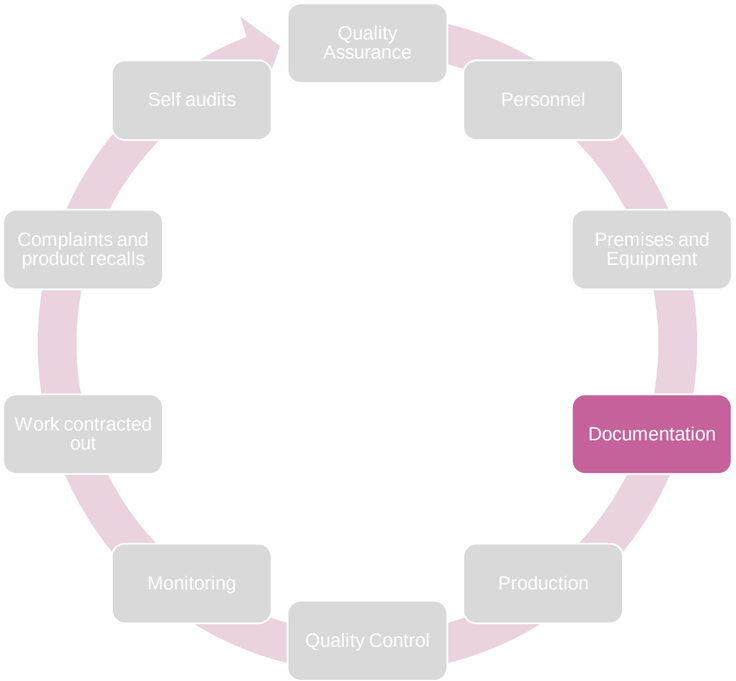
2. HOW? – CONTENT OF PIC/S HOSPITALS

1. Documentation should demonstrate the complete history of a product (batch record documentation, etc)
2. General procedures (release, training, validation, etc)



Retain:

- Records: one year after expiry
- Procedures and instructions: 5 years after their use

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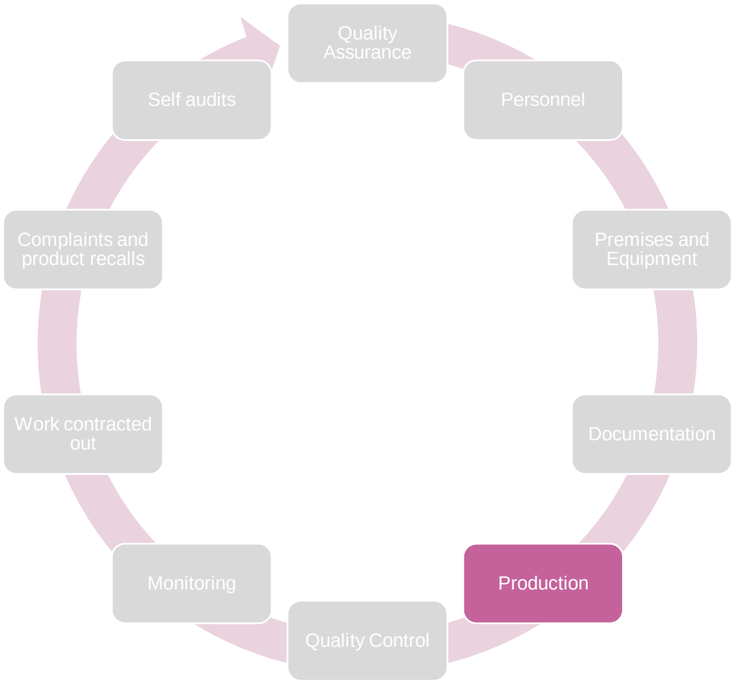
2. HOW? – CONTENT OF PIC/S HOSPITALS

1. Perform a control on starting materials
2. Synthesis unit:
   - Dedicated components and equipment
   - Cleaning effectiveness
   - Validation on computer systems or detailed written instructions
3. Workstation:
   - ≠ Different products at the same time



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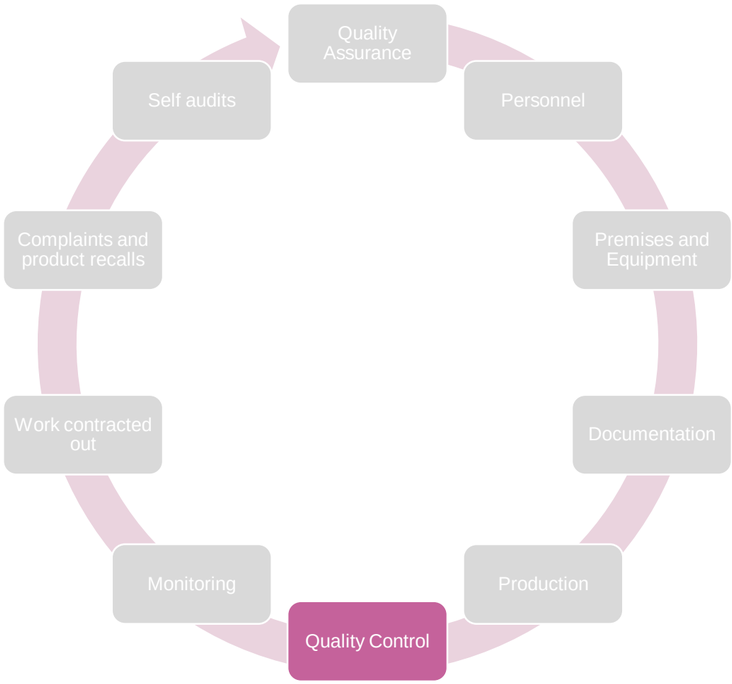
2. HOW? – CONTENT OF PIC/S HOSPITALS

	Magisterial preparations	Exception: Licensed Radiopharmaceuticals	Comment
QC testing	Pharmacopeia or related monographs	As described in SmPC	Activity is measured for each dose
Release	Radio-pharmacist release	Responsible for quality release	Different person then production person
	Multiple step: 1. Pre-release: release before dispatch and release before administration 2. Final release	Single step	



Oral and inhalation products require depending on the preparation a radio-pharmacist or a responsible for quality.

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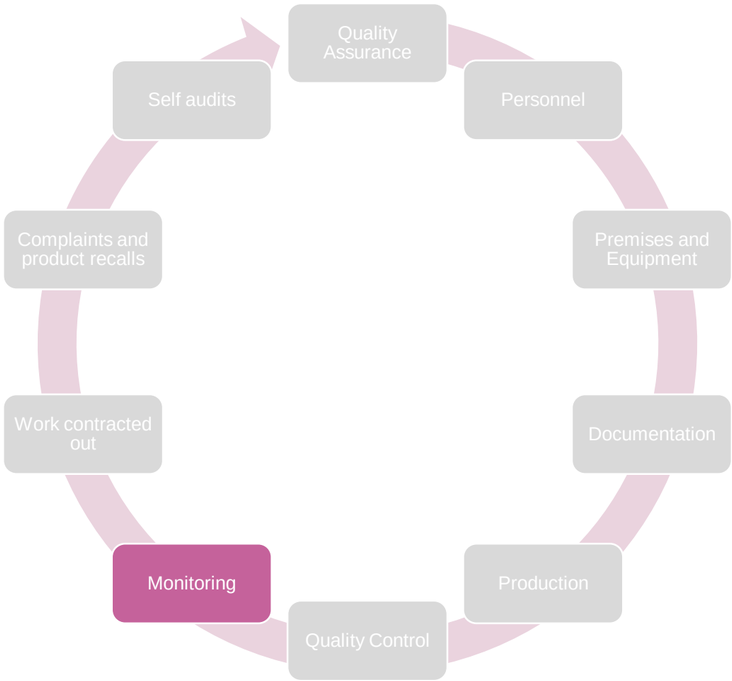
2. HOW? – CONTENT OF PIC/S HOSPITALS

Aseptic process validation – Media Fill :

- Initially and regularly
- Routine aseptic procedures and handlings including equipment and materials used
- Qualification of production personnel
- Media fill = worst case situation



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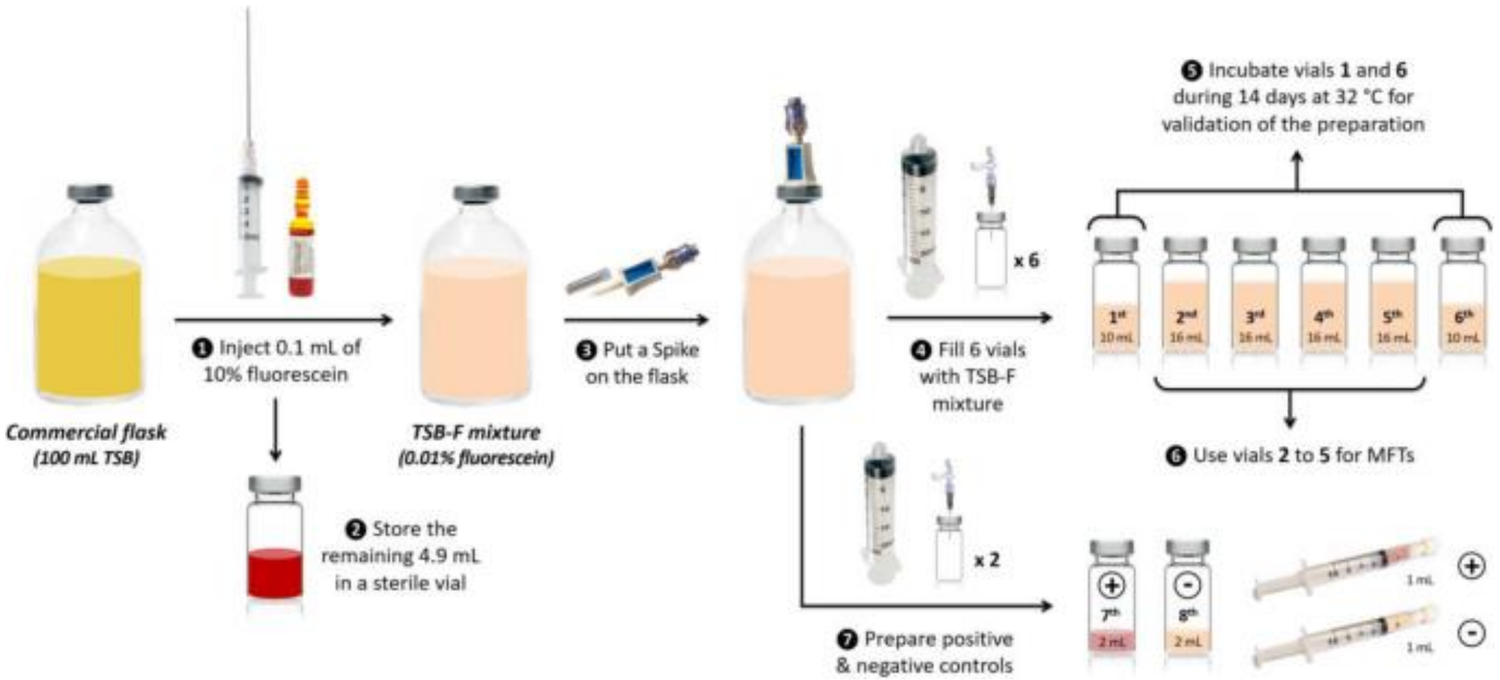
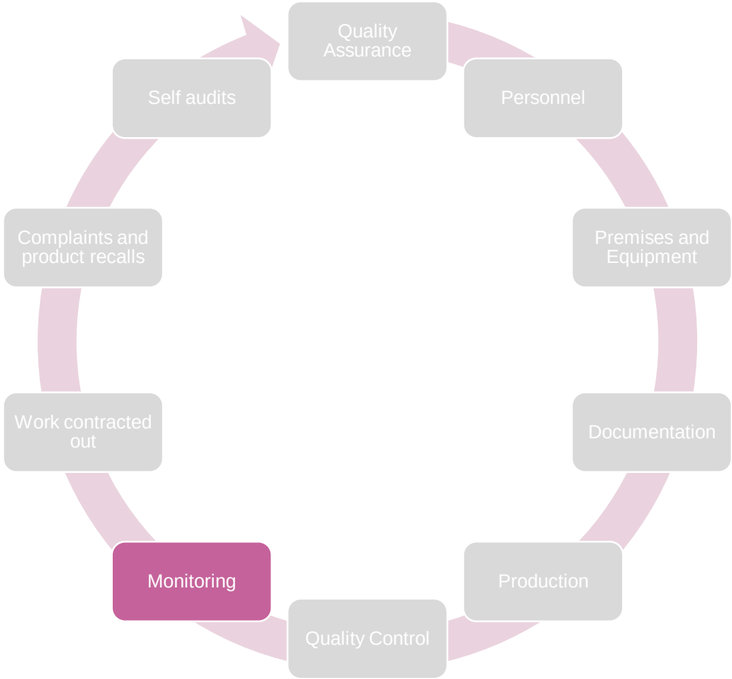
2. HOW? – CONTENT OF PIC/S HOSPITALS

Aseptic process validation – Media Fill :





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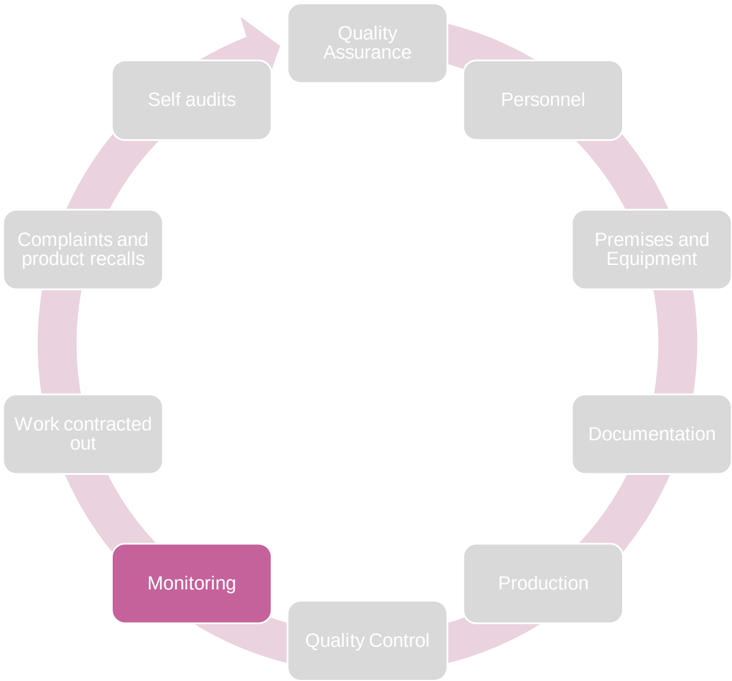
2. HOW? – CONTENT OF PIC/S HOSPITALS

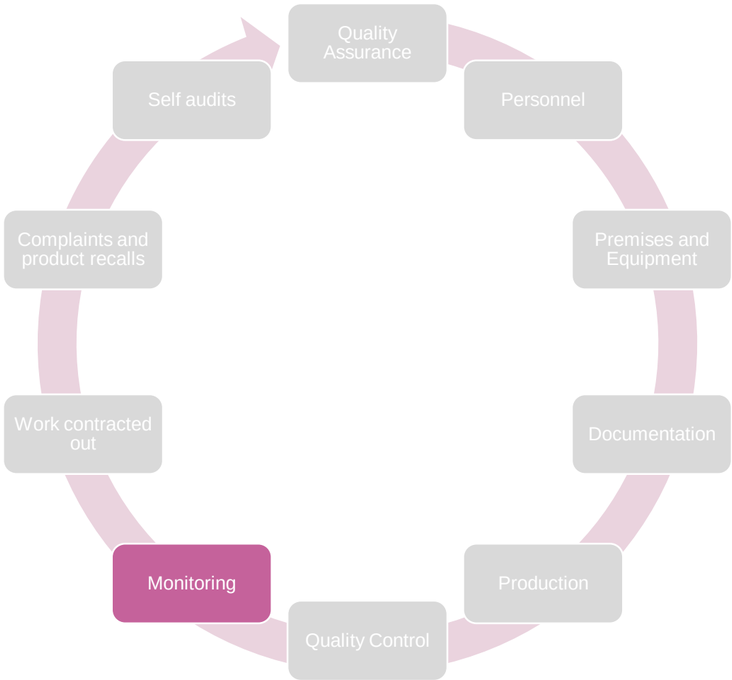
	At rest		In operation	
Physical monitoring	**Open workstation**	**Isolator**	**Open workstation**	**Isolator**
Particle counts	Yearly	/	Quarterly	/
	/	/	During filling	
Room air changes per hour	Yearly	/	/	/
Air velocities on workstations	Yearly	/	/	/
Hepa filter integrity checks	Yearly	Yearly	/	/
Isolator alarm test	/	Yearly	/	/
Isolator leak test	/	Yearly	/	/
Pressure differences rooms	/	/	Daily or before start	/
Pressure differences HEPA - workstations	/	/	Daily or before start	Daily or before start
Glove integrity	/	/	/	Visual check before start
Isolator hold test	/	/	/	Weekly



2. HOW? – CONTENT OF PIC/S HOSPITALS

Grade	At Rest		In Operation	
	Maximum permitted number of particles/m^3 equal to or above			
	0.5µm	5µm	0.5µm	5µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	not defined	not defined

Table 1: Particle Count Limits per Cubic Meter [EU GMP Annex1]



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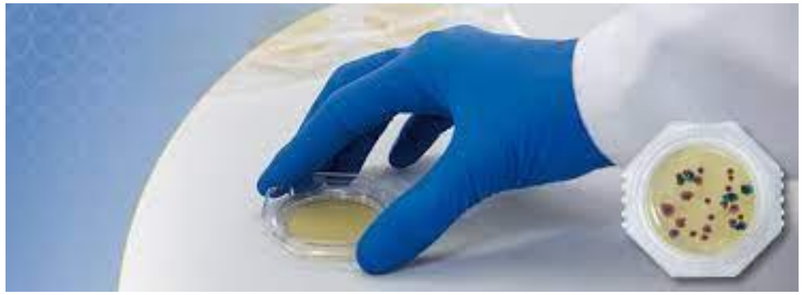
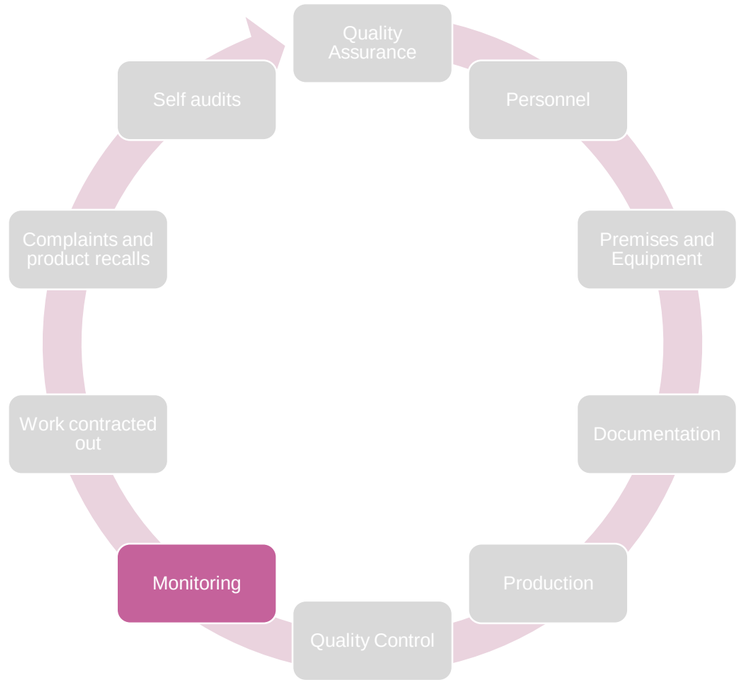
2. HOW? – CONTENT OF PIC/S HOSPITALS

	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m³	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-





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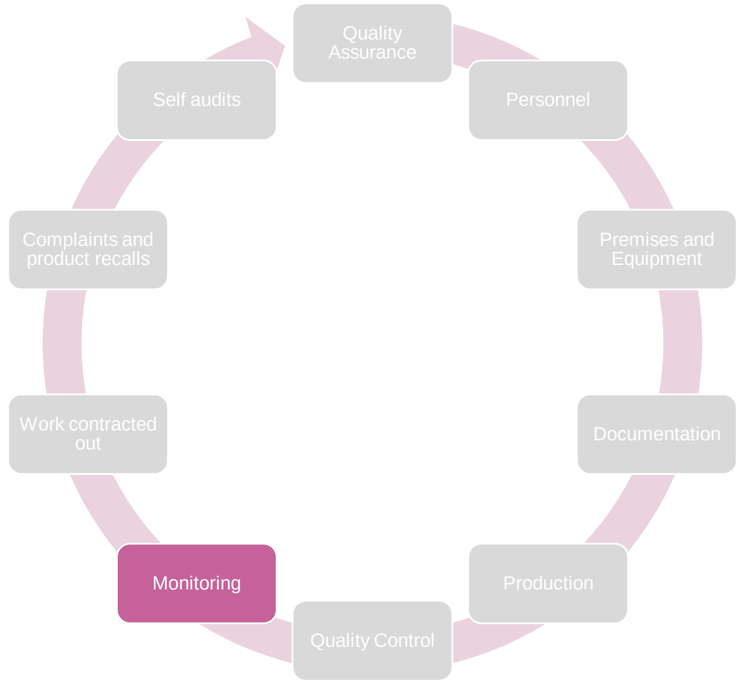
2. HOW? – CONTENT OF PIC/S HOSPITALS

	In operation	
microbiological monitoring	**Working room**	**Surrounding rooms**
Settle plates	Every working session	Weekly
Glove fingers	End of every working session	End of every working session
Surface samples (swabs or Contact plates)	Weekly	Monthly
Active air samples	Quarterly	Quarterly



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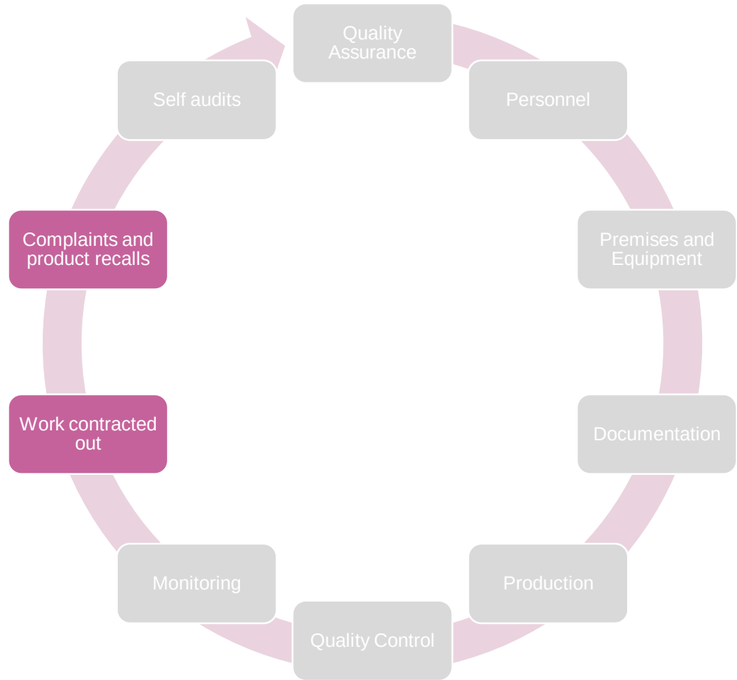
2. HOW? – CONTENT OF PIC/S HOSPITALS

Work contracted out:

- Technical agreement
- External audit

Complaints and product recalls:

- CAPA



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3. SUMMARY

- Implementation before 1ste january 2026
- PIC’s ≠ GMP
- Work together

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4. ACKNOWLEDGEMENTS

- Caroline Vermeiren: QA responsible and QP – Radio-pharmacy UZA
- Nick Van Laeken: Radiopharmacist and QP - Radio-pharmacy UZ Gen

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