M. Marengo

Basic concepts in the design of radiopharmaceutical laboratories

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Definitions

From the EU Directive 2001/83/EC

Medicinal product:

Any substance or combination of substances presented for treating or preventing disease in human beings.

Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product.

Radiopharmaceutical:

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

The peculiarity of radiopharmaceuticals is that in their preparation it is necessary at the same time to:

- protect the operator from the radiations emitted by the product
- protect the product from possible contamination by the external environment and by the operator

This requires a very specific approach. It has frequently been said that there are divergent demands in this field between the needs of radiation protection and pharmaceuticals.

Instead, I believe that the requirements deriving from the pharmaceutical aspects also favor the safety and protection of the operators and can be well inserted in the logic of radiation protection, by adopting appropriate solutions.

Reference documents

- IAEA. Operational Guidance on Hospital Radiopharmacy. STI/PUB/1342 , 2008
- IAEA. Radiation Protection and Safety in Medical Uses of Ionizing Radiation. IAEA Safety Standards Series No. SSG-46 , 2018
- EudraLex. The Rules Governing Medicinal Products in the European Union Volume 4. EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Chapter 3: Premises and Equipment / Annex 1 - Manufacture of Sterile Medicinal Products. / Annex 3 Manufacture of Radiopharmaceuticals. 2020.
- IAEA. Nuclear Medicine Resources Manual. IAEA Human Health Series No 37, 2020

Credits for several materials in this presentation are to Andrea Taddei

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

Part I - Basic Requirements for Medicinal Products

- Chapter 1 - Pharmaceutical Quality System EN (into operation since 31 January 2013)
- Chapter 2 - Personnel EN (into operation since 16 February 2014)
- Chapter 3 - Premise and Equipment EN (into operation since 1 March 2015)
  - See transitional arrangement for toxicological evaluation on page 1 of Chapter 3
  - Previous version EN
- Chapter 4 - Documentation EN (January 2011)
- Chapter 5 - Production EN (into operation since 1 March 2015)
  - See transitional arrangement for toxicological evaluation on pages 1-2 of Chapter 5
  - Previous version EN
- Chapter 6 - Quality Control EN (into operation since 1 October 2014)
- Chapter 7 - Outsourced activities EN (into operation since 31 January 2013)
- Chapter 8 - Complaints and Product Recall EN (into operation since 1 March 2015)
- Chapter 9 - Self Inspection EN

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

Annexes

Annex 1	**New** - Manufacture of Sterile Medicinal Products EN ••• - The deadline for coming into operation of Annex 1 is 25 August 2023, except for point 8.123 which is postponed until 25 August 2024 Manufacture of Sterile Medicinal Products EN ••• (previous version)
...	
Annex 3	Manufacture of Radiopharmaceuticals EN •••

General principles of the GMP regulation

- Minimize the risk of product contamination from the surrounding environment → Production environment qualification
- Minimize the risk of contamination of the product by the personnel in charge → Operating procedures; staff training; proper dressing; training validation
- Quality assurance and validation → Need for a control structure (personnel, equipment and procedures). Validation of operating procedures.
- Performing only final tests on the finished product is not acceptable → The checks must be carried out throughout the production cycle

Production environment

Controlled contamination environment

Particle contamination:
Limit to the number of particles ≥ 0.5 µm per unit volume

Microbiolgoic contamination:
Limit to the number of colony forming units (CFU)

Contamination limits from EuDralex Regulations, Part 4 – Annex 1

Maximum permitted number of particles/m3 equal to or greater to the tabulated size				
Grade	**At rest**		**In Operation**	
	0.5 μm	**5 μm**	**0.5 μm**	**5 μm**
A	**3520**	**20**	**3520**	**20**
B	**3520**	**29**	**352 000**	**2 900**
C	**352 000**	**2 900**	**3 520 000**	**29 000**
D	**3 520 000**	**29 000**	**n.d.**	**n.d.**

The guidance given for the maximum permitted number of particles “at rest” condition corresponds approximately to the US Federal Standard 209 and the ISO 14644 Part 1 classification as follows:

- grades A and B corresponds with class 100 , M 3.5, ISO 5
- grade C with class 10 000, M 5.5, ISO 7
- grade D with class 100 000, M6.5, ISO 8

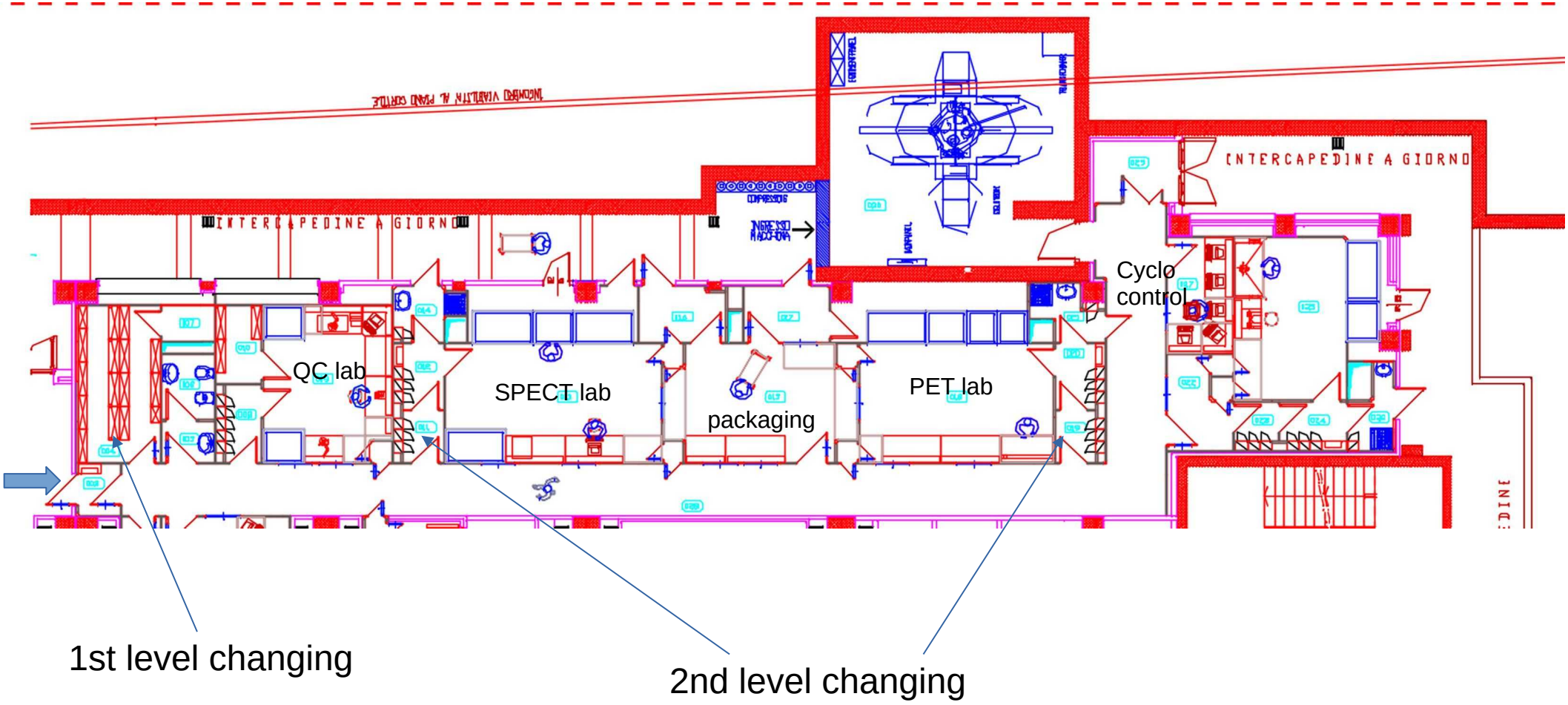
Contamination limits from EuDralex Regulations, Part 4 – Annex 1

Recommended limits for miocrobial contamination				
Grade	air sample CFU/m^3	Settle plates (diameter 90 mm) CFU/4 hours	Contact plates (diameter 55 mm) CFU/plate	Glove print 5 fingers CFU/glove
A	<1	< 1	< 1	< 1
B	10	5	5	5 mm
C	100	50	25	n.d.
D	200	100	50	n.d.

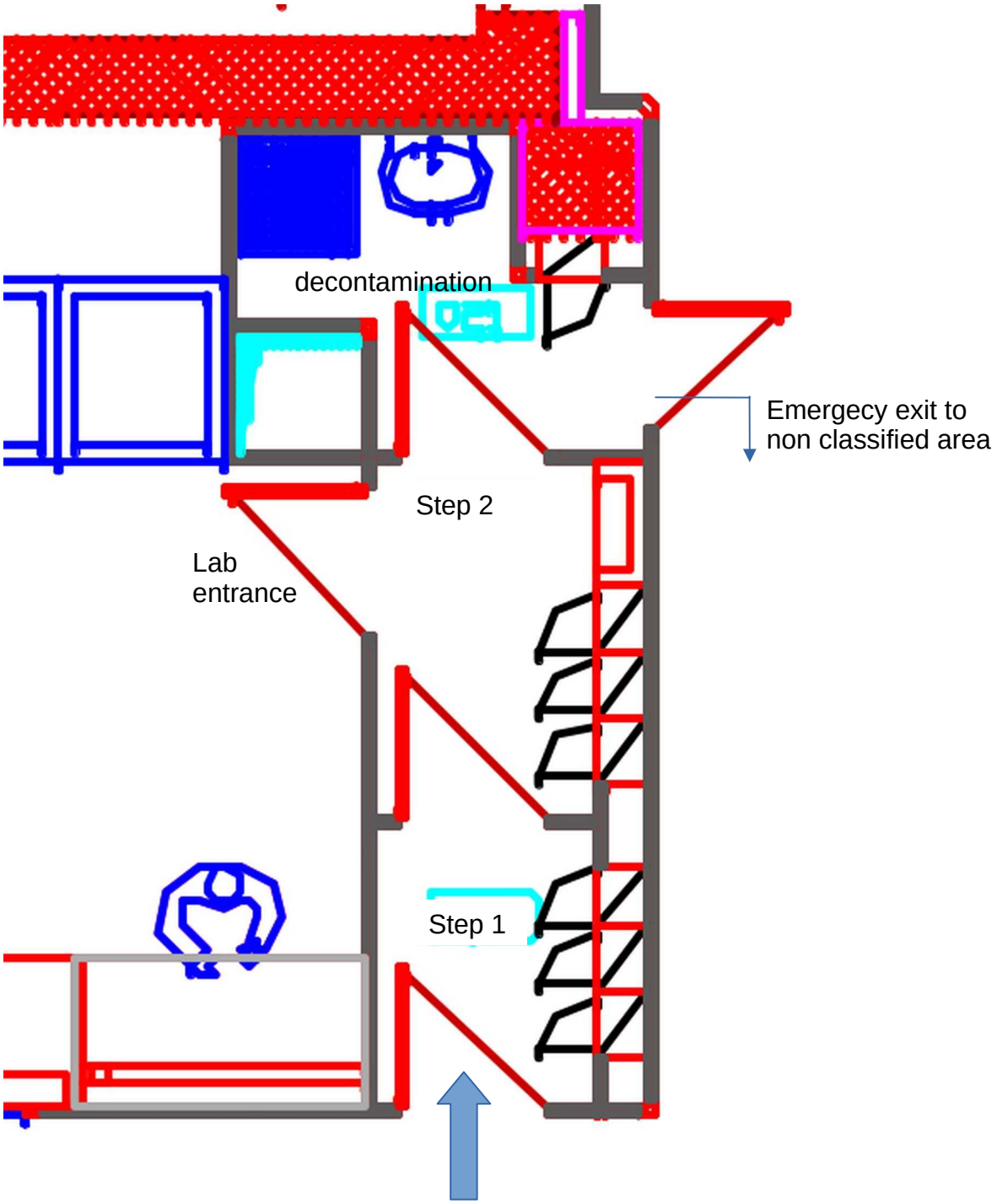
How a controlled contamination environment is created

- Layout
  - Staff access (changing rooms)
  - Access of materials (SAS or pass through boxes)
  - Products exit (SAS)
- Finishes
  - Walls
  - Floor
  - Doors
  - Electrical system and lighting
  - Details
- Ventilation system
  - Control of temperature
  - Control of humidity
  - Control of pressure
  - Control of air purity (filtration)

Example of layout



Two step changing rooms



Changing rooms

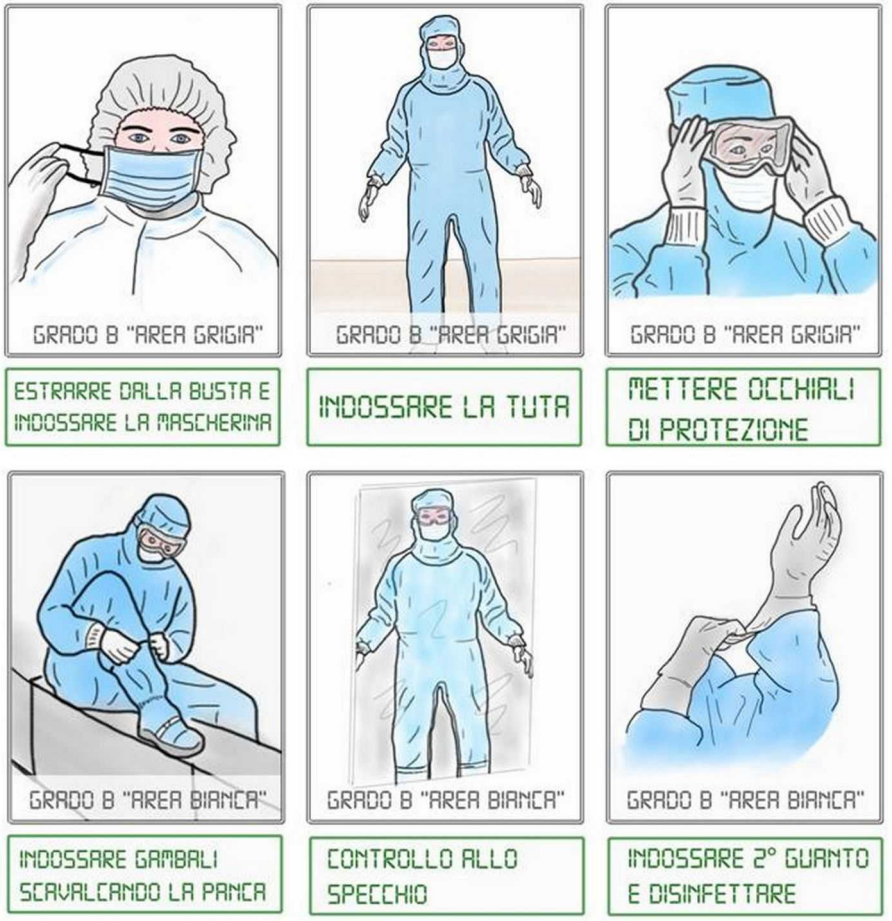
In the changing rooms there are usually ventilated wardrobes for placing clothes and footwear; a bench divides the changing area, so that the operator changes one shoe at a time, bypassing the "grey area" to the clean area. Also, there must be a hand wash or hand sanitizing system, and a mirror, to check proper clothing.

Clothing

Proper clothing with:

- Hat
- Hands washing
- Face mask
- Suit
- Shoe cover
- Gloves

- Check at the mirror
- Disinfect gloves

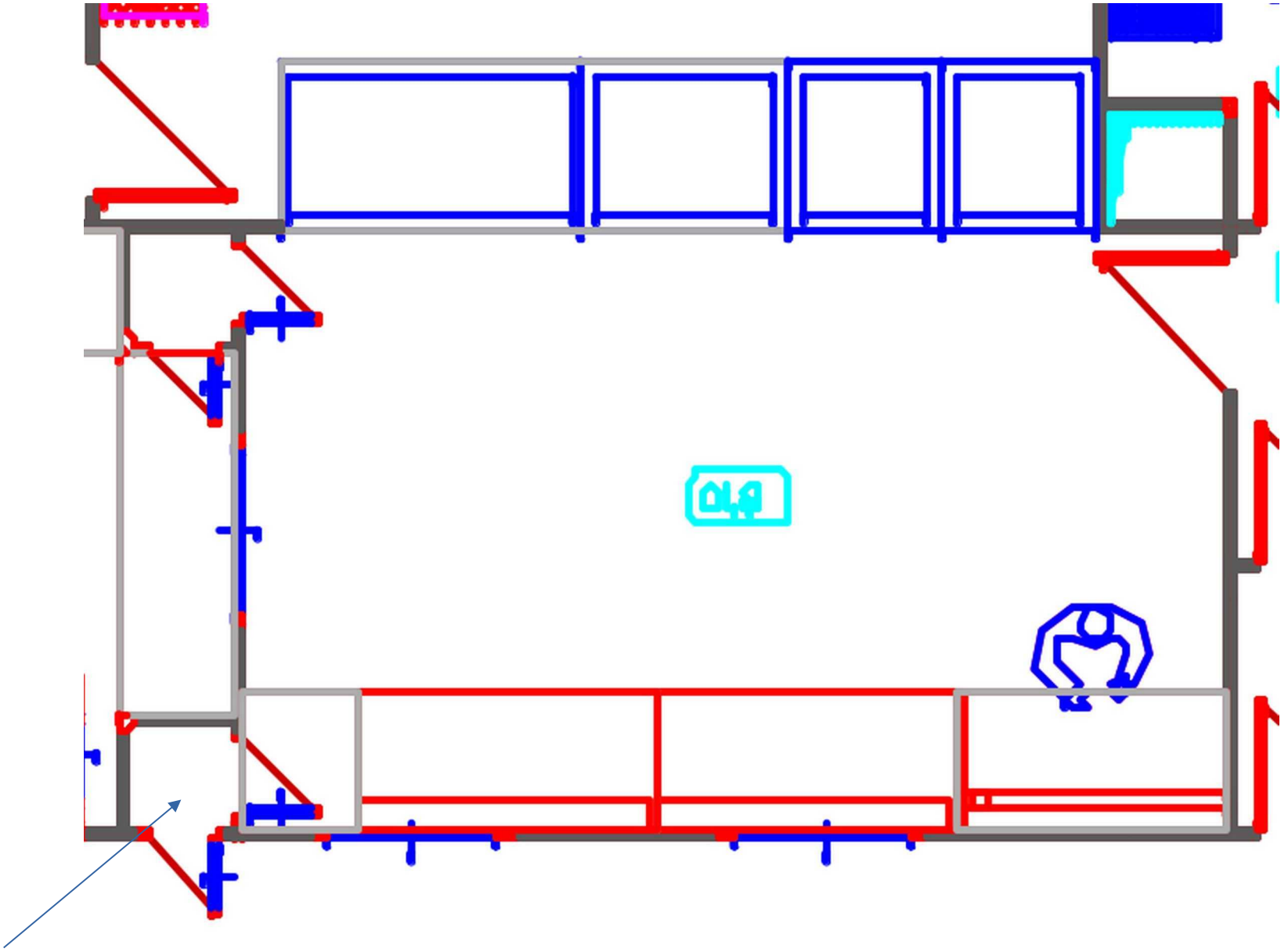


Pass through boxes

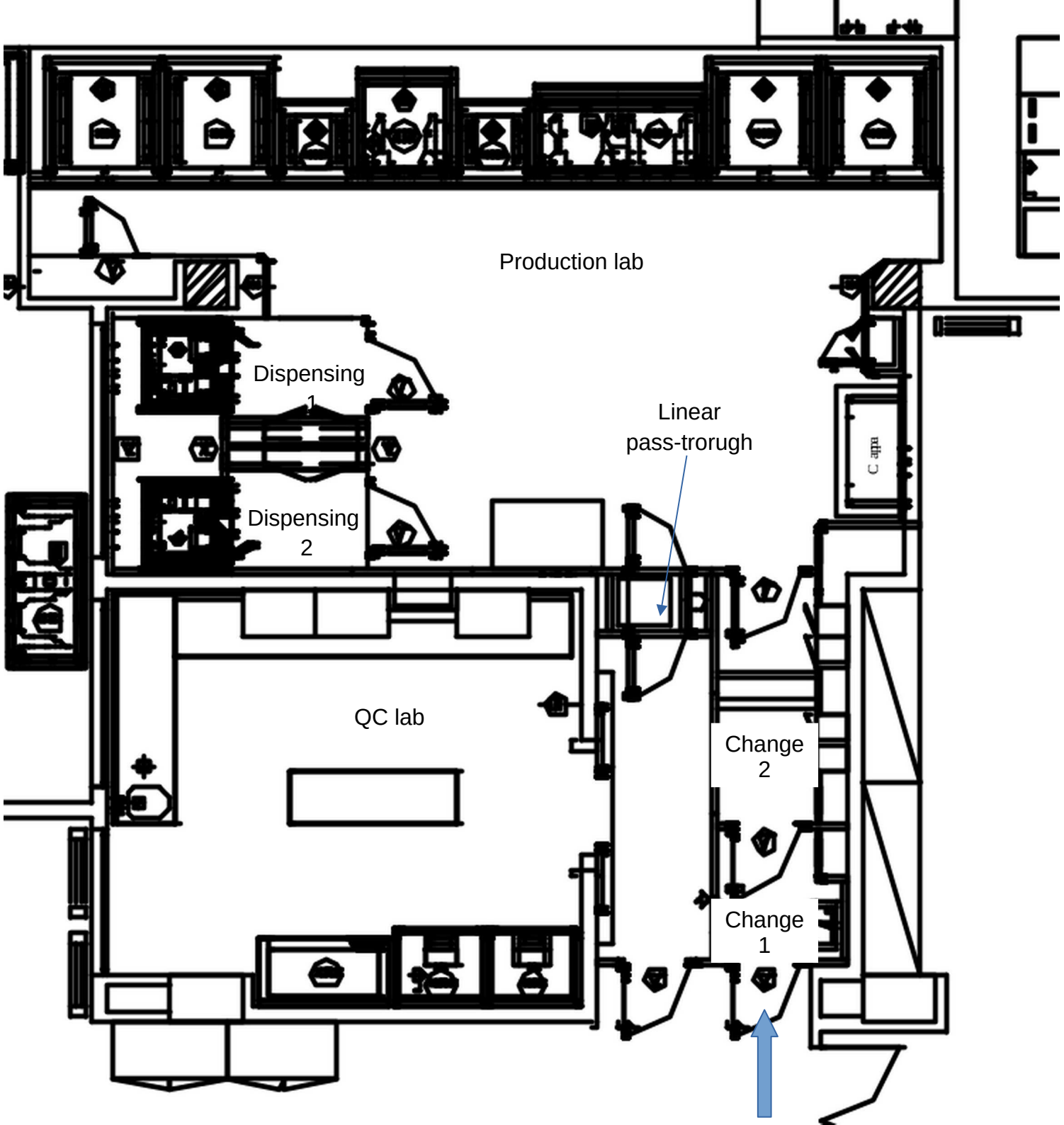
termed also SAS or hatch

These equipment are specifically designed for the transfer of materials between classified areas or between a classified area and a non-classified area, with decontamination using HEPA filtered air. The ventilation system provides filtered air to ensure a clean environment inside the chamber, before the opening of the door.

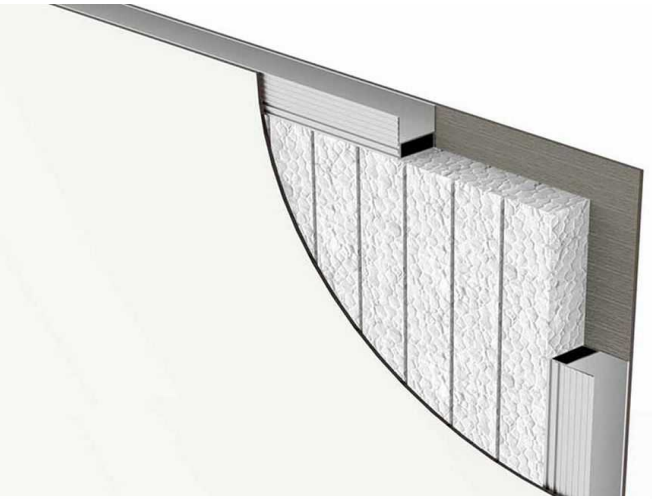
The doors are interlocked. A delay time can be set for the opening, to allow sufficient time of cleaning thanks to the flow of clean air.

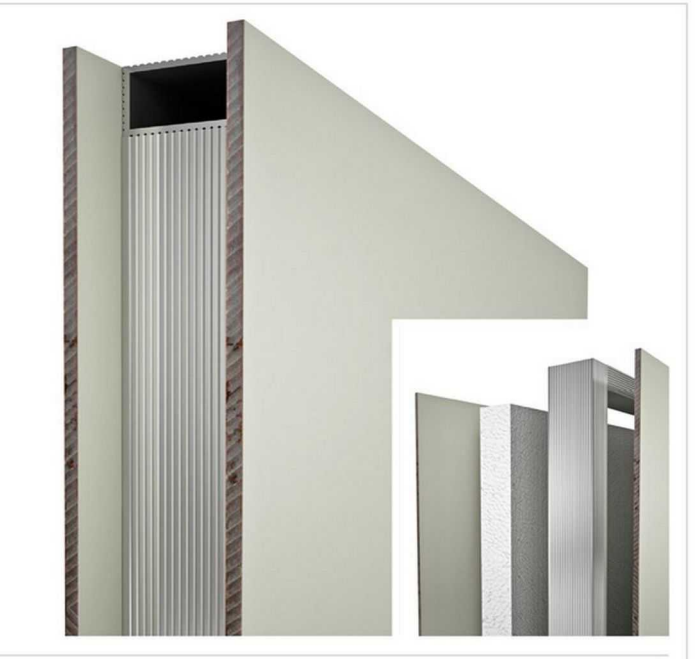


Angluar pass through


Production lab
Dispensing 1
Dispensing 2
Linear pass-trorugh
QC lab
Change 2
Change 1

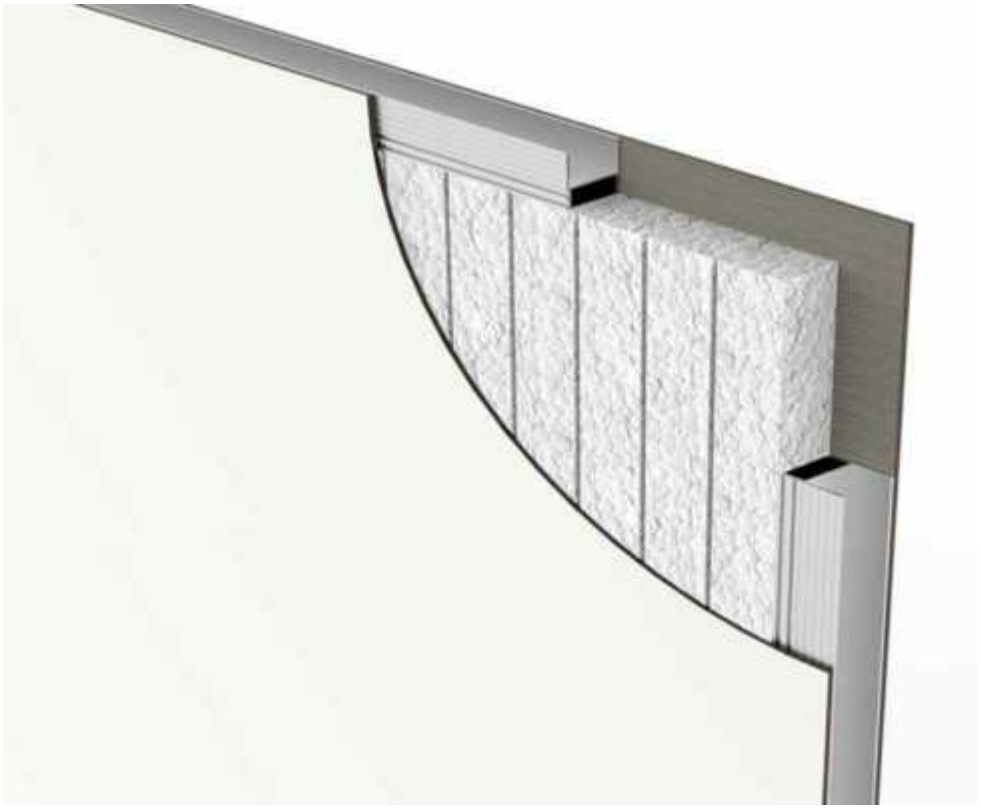
Pharma walls





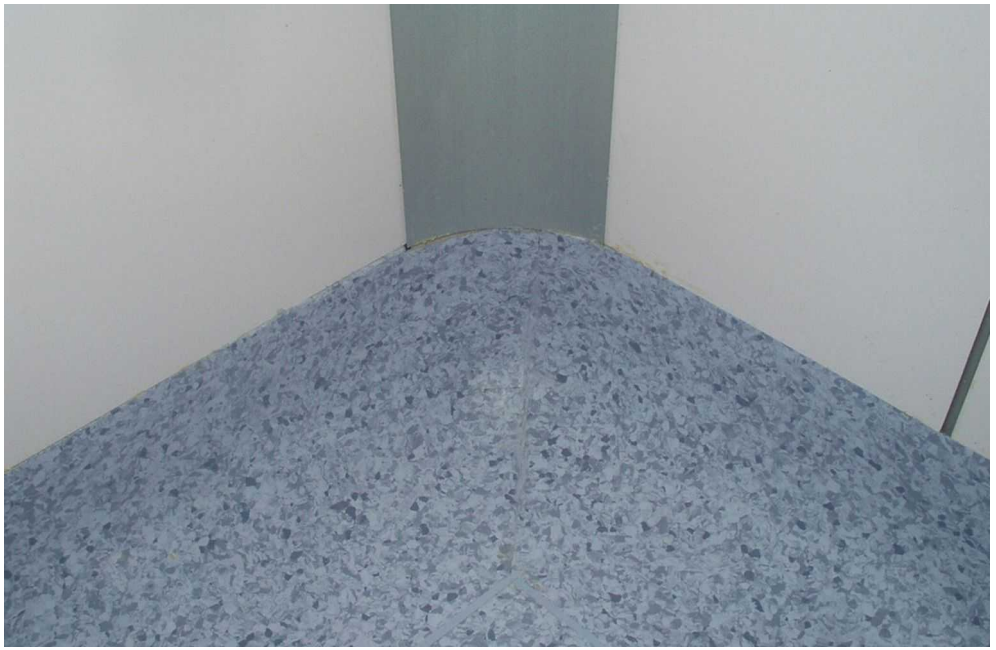
Pharmaceutical grade walls are a covenient and effective solution. They are externally coated on both sides with a melamine laminate sheet, 4 mm thick. Internally, an insulating layer of polystyrene, or a honeycomb structure, between a laminated aluminum frame. Total thickness 45mm.

The joint between the panels is made by an aluminum profile, with gaskets.



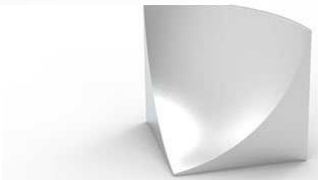
Example of walls in HPL with polistyrene (Delta2000)

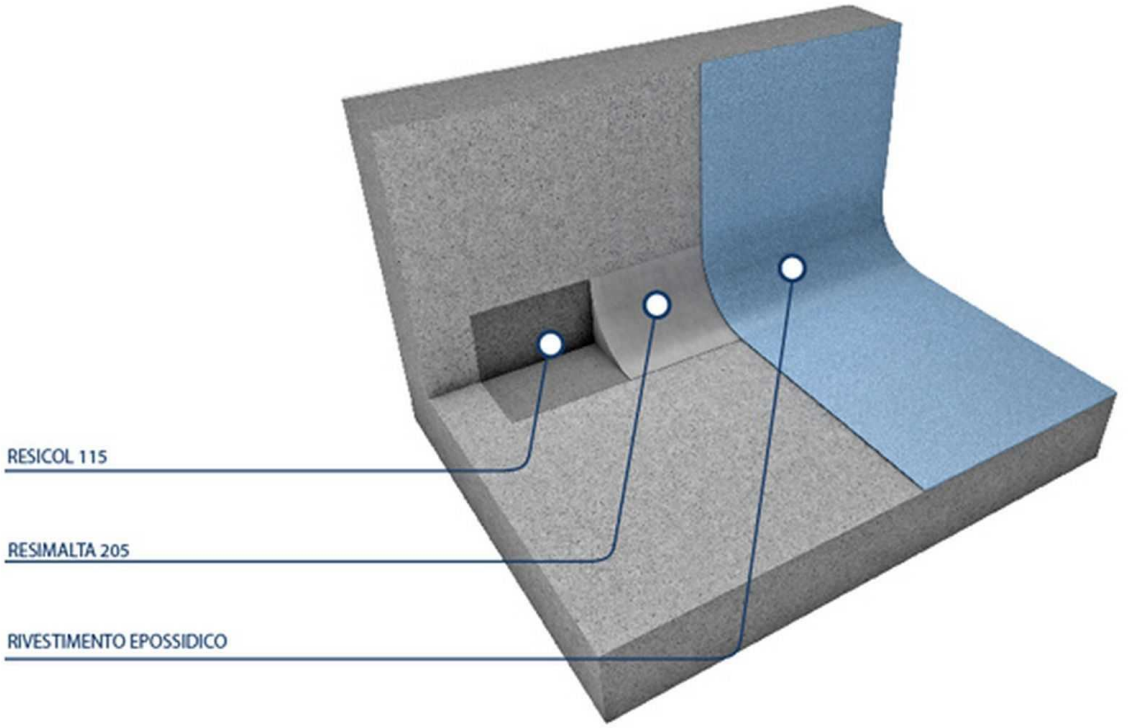
Walls and corners



In Radiopharmacy Laboratories, depending on the classification, the walls should be made with pharmaceutical grade walls, or at least painted with suitable washable and decontaminable resins.

All corners must be rounded; there is a wide range of specific materials developed for the pharmaceutical industry which represent the ideal solution.





Coving, to round corners. Coving cover the seam or transition between two surfaces, such as the edge between two walls or between a wall and the ceiling or floor. Typically, curved coving allows a 45° angle instead of the traditional 90° of a room’s corner.

Floor

The floor must also be suitable for a controlled contamination environment. Homogeneous vinyl floors are usually made, with PVC finishes on the surface of the floor itself.

The profiles of the doors and the rounded profiles of the corners and walls allow for curved floor finishes and facilitate cleaning. The joints between the floor and the panels are made with a permanent sealant (e.g. polyurethane elastomer)

Ceiling

The pharmaceutical grade ceiling is made of plastic laminate or aluminum, welded and disinfectable.

The light fixtures should be integrated, coplanar and welded to the rest of the false ceiling.

Doors

The pharmaceutical door panels are assembled with the same panels as the wall system.The outer frames are made with rounded profiles in anodized or epoxy coated aluminum with double airtight gaskets. All fasteners for hinges and catches can be recessed into the door frame.

Doors

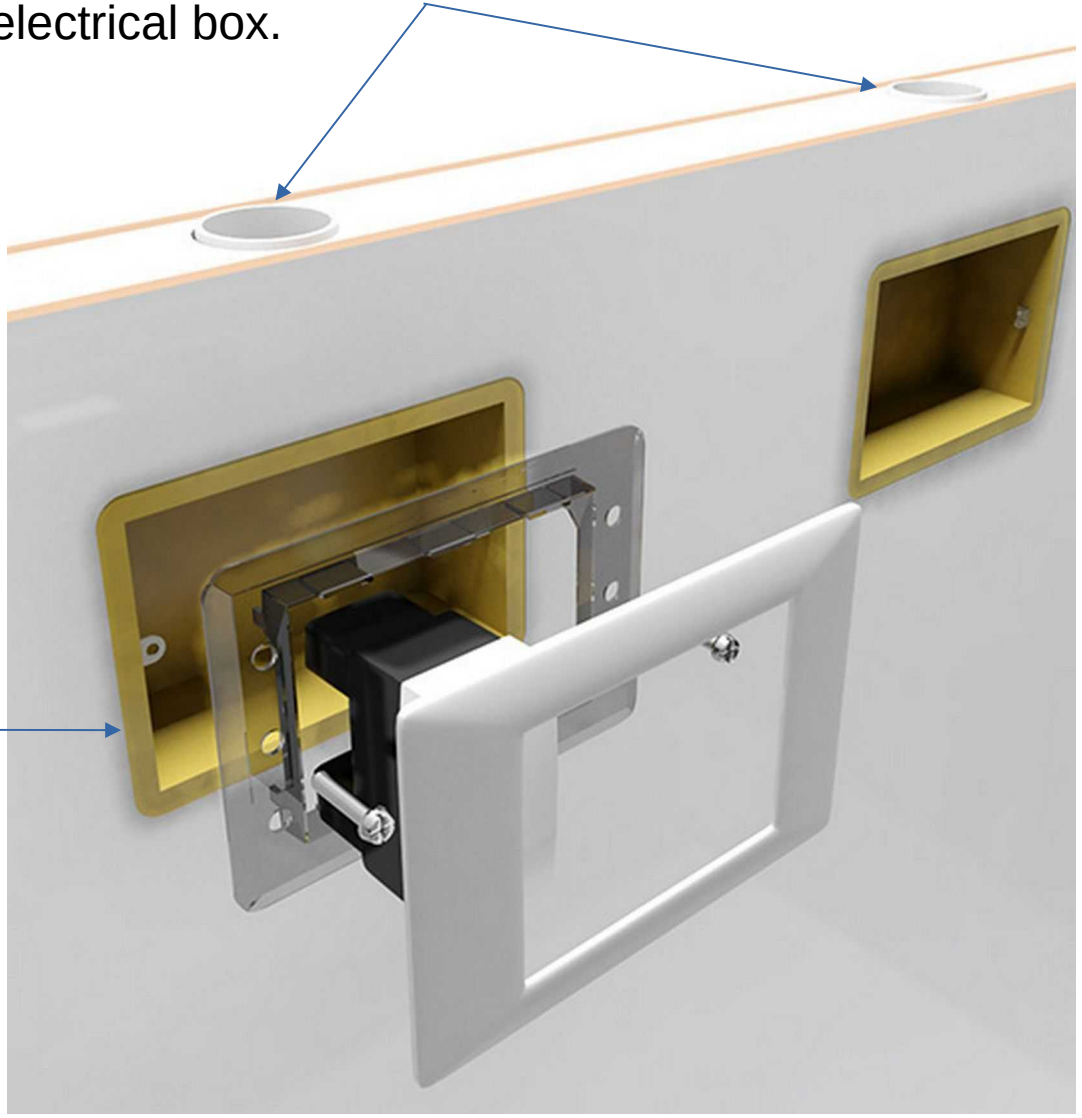
There is a variety of coplanar and sanitizable controls for doors, with light signaling, numeric keypad or badge reading

Windows

In order to maintain air quality, windows in controlled contamination environments must not be openable. To guarantee the view towards the outside or between rooms, windows made of a double layer of glass are used, fixed on an aluminum frame and sealed

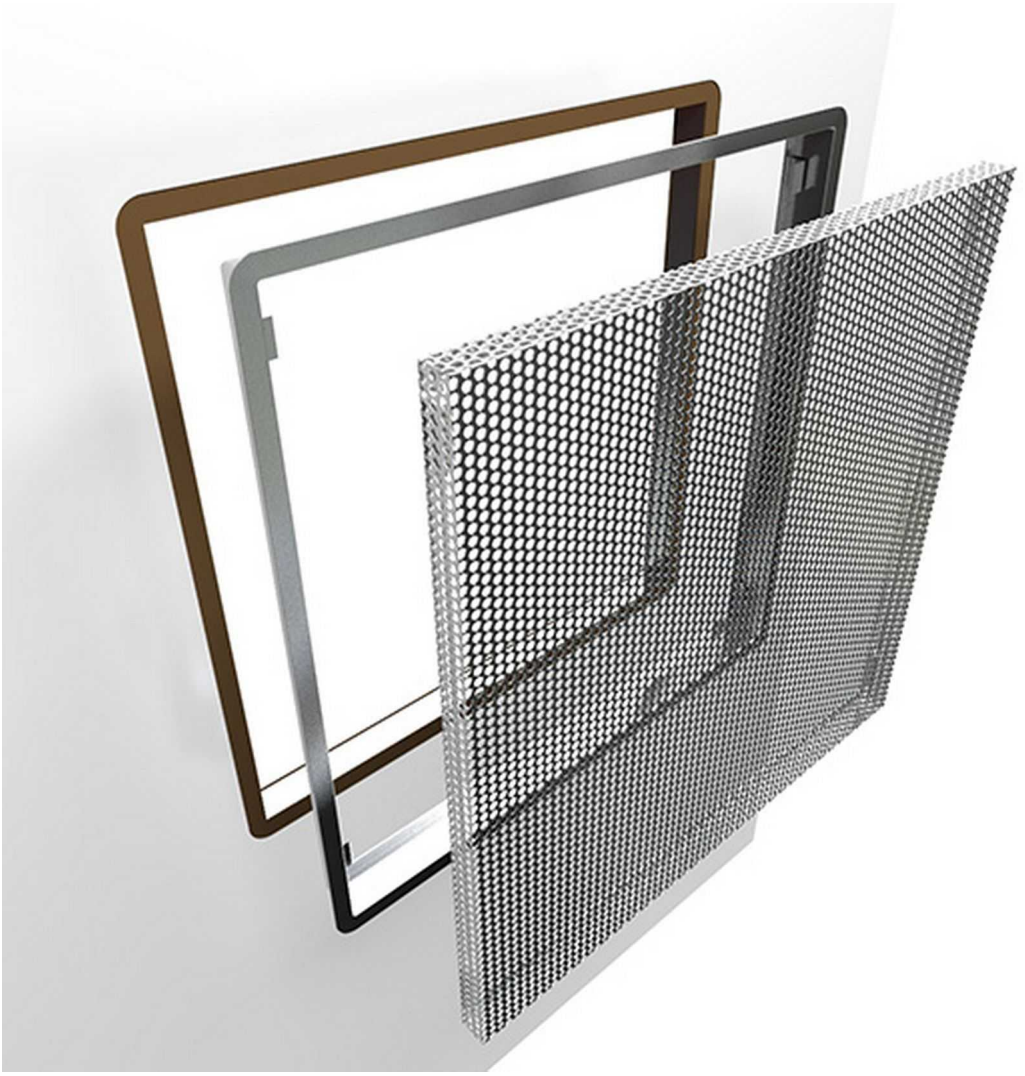
Details

Electric drops can be provided inside the sandwich panels, made using a 30mm diameter PVC pipe inserted inside the wall module and positioned near each required electrical box.



Electrical boxes should be sealed

Details



Wall-mounted return air filtration system. Prepared for housing the pre-filter and any regulation damper

Details

Differential pressure gauges and other display for visualizing the parameters of the clean room are typically wall mounted and allow for continuous monitoring of correct set point and operation of the ventilation system.

HVAC

Heating, Ventilation and Air Conditioning

The HVAC system plays a central role in the design of a Nuclear Medicine department and in particular of a Radiopharmacy, given the need to control both the possibility of radioactive contamination of personnel and the environment, due to the products (considered as unsealed radioactive sources) used, and the possibility of microbiological contamination of the products (considered as medicines) by the personnel and the external environment.

For these reasons, HVAC system design requires a more rigorous approach than even shielding calculations and should be addressed at an early stage of the department's design.

HVAC

Heating, Ventilation and Air Conditioning

In general, airflow should be directed from areas with the least risk of contamination to those with the highest risk. Normally this is achieved by keeping the latter at a lower pressure than the former. Radiopharmacy Laboratories are an exception to this principle, and should be managed with specific solutions.

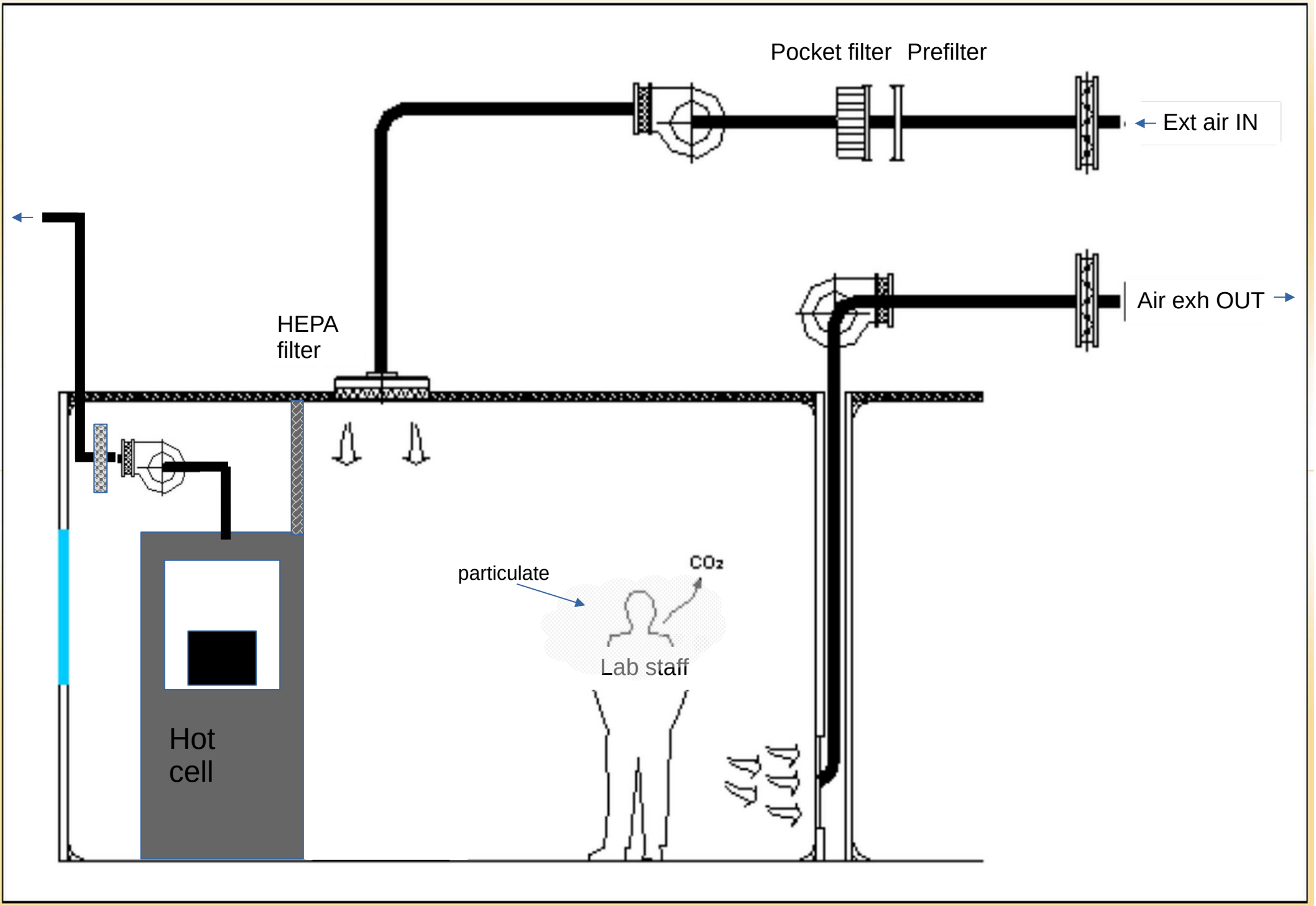
The air coming from outside must be filtered to reduce the entry of dust and particles.

The external air intakes must be located in such a way as to avoid the possibility of recirculation of the discharged air.

The emitted air must be expelled outside through suitable filters, according to the area of origin.

In rooms where hot cells or fume hoods are installed, there should be a dedicated exhaust duct for each device. Incoming air diffusers should be located as far away as possible from cell opening doors and vents.

When the ducts of the HVAC system have to penetrate a screen, coordination is required between the designer and the Radiation Protection Expert, to verify the feasibility and conditions.


Pocket filter
Prefilter
Ext air IN
Air exh OUT
HEPA
filter
particulate
CO2
Lab staff
Hot
cell

Notes on ventilation: is there really a conflict ?

ICRP 57

par.6.1.2 General principles

(251) A fumehood, operating under negative pressure, is necessary for certain procedures in the production of radiopharmaceuticals. If sterile procedures are employed, a fully exhausted vertical laminar flow system ***under positive pressure*** is recommended.

par.6.1.3 Design of specific areas - Radiopharmacy

(258) The planning of this area with respect to radiation protection of the worker is most complex. It is in this area that the greatest amount and variety of radionuclides are present. Each administered aliquot is handled in this area. Adequate storage space, appropriately shielded, is necessary for the radionuclides and radionuclide generators in use. Working surfaces should be non-porous and easily cleanable. An aseptic preparation area should be available with laminar airflow, and ***positive or negative airflow should be controllable***. A fumehood may be required. Proper ventilation is essential.

(IAEA SSG-46 par. 4.28)

For reasons of asepsis, some radiopharmacies may require a positive rather than a negative pressure. In this case, the pressure gradient can be obtained by placing other workstations requiring negative pressure next to the radiopharmacy workstation.

Eudralex annex 3

3. In order to contain the radioactive particles, ***it may be necessary for the air pressure to be lower where products are exposed than in surrounding areas***. However, it is still necessary to protect the product from environmental contamination.

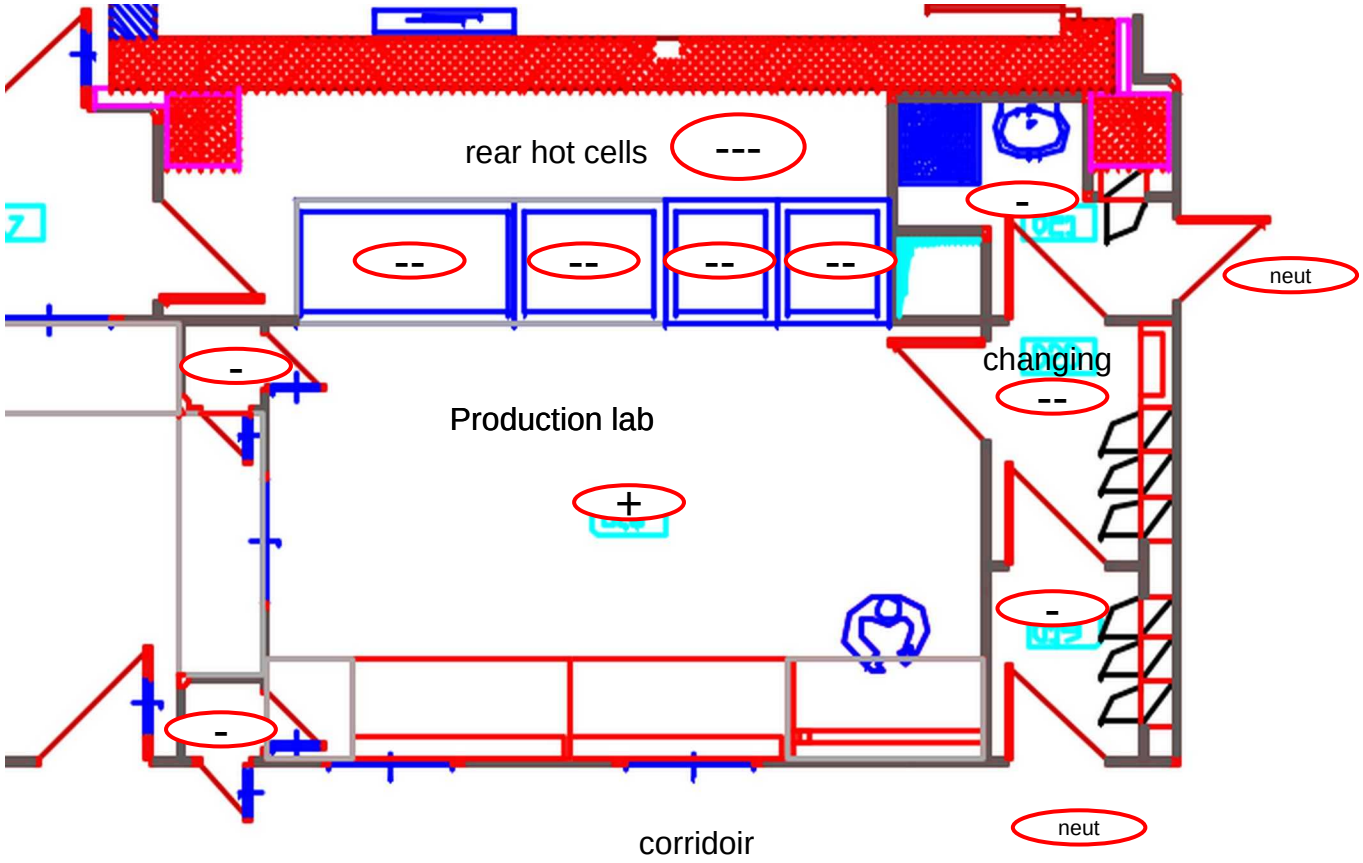
General indications on ventilation in NM

	Pressure Relationship to Adjacent Areas	Differential pressure (Pa)	Minimum Air Changes (vol/hour)	Maximum Air Changes (vol/hour)	All Air Exhausted Directly to Outside	Air Recirculated Within Room Units	Filters (typical)
"Hot" waiting room	Negative	15	2	10	YES	NO	EU9
Administration room	Negative	15	5	10	YES	NO	EU9
Diagnostic imaging room	Negative	15	5	10	YES	NO	EU9
Control room	Neutral or Negative	0 – 15	5	10	YES	NO	EU9
Corridoirs	Neutral or Negative	0 – 15	2	5	YES	NO	EU9
Radiopharmacy laboratory	Neutral or positive	0 – 15	10	> 10	YES	NO	EU14 + charcoal
Radiopharmacy changing room	Negative	> 30	10	> 10	YES	NO	EU14 + charcoal
Radiation therapy ward	Negative	15	5	10	YES	NO	EU9 + charcoal

From IAEA NM Resource Manual ed. 2020

***Note**: the above reported are general indications, to be cross checked against national regulations*

Example of pressure cascade



All the front of the hot cells and the walls and ceiling of the production lab should be sealed.
Is selaing is correctly made, the flow of infiltration Q_{inf} is transcurable.
In this case, if P_{in} is the pressure inside and P_{out} the pressure outside an area, and Q_{in} and Q_{out} are the flow of air input and output:

$$\Delta P = P_{in} - P_{out}$$

$$\Delta P \approx Q_{in} - Q_{out}$$

Example of (approximate) calculation

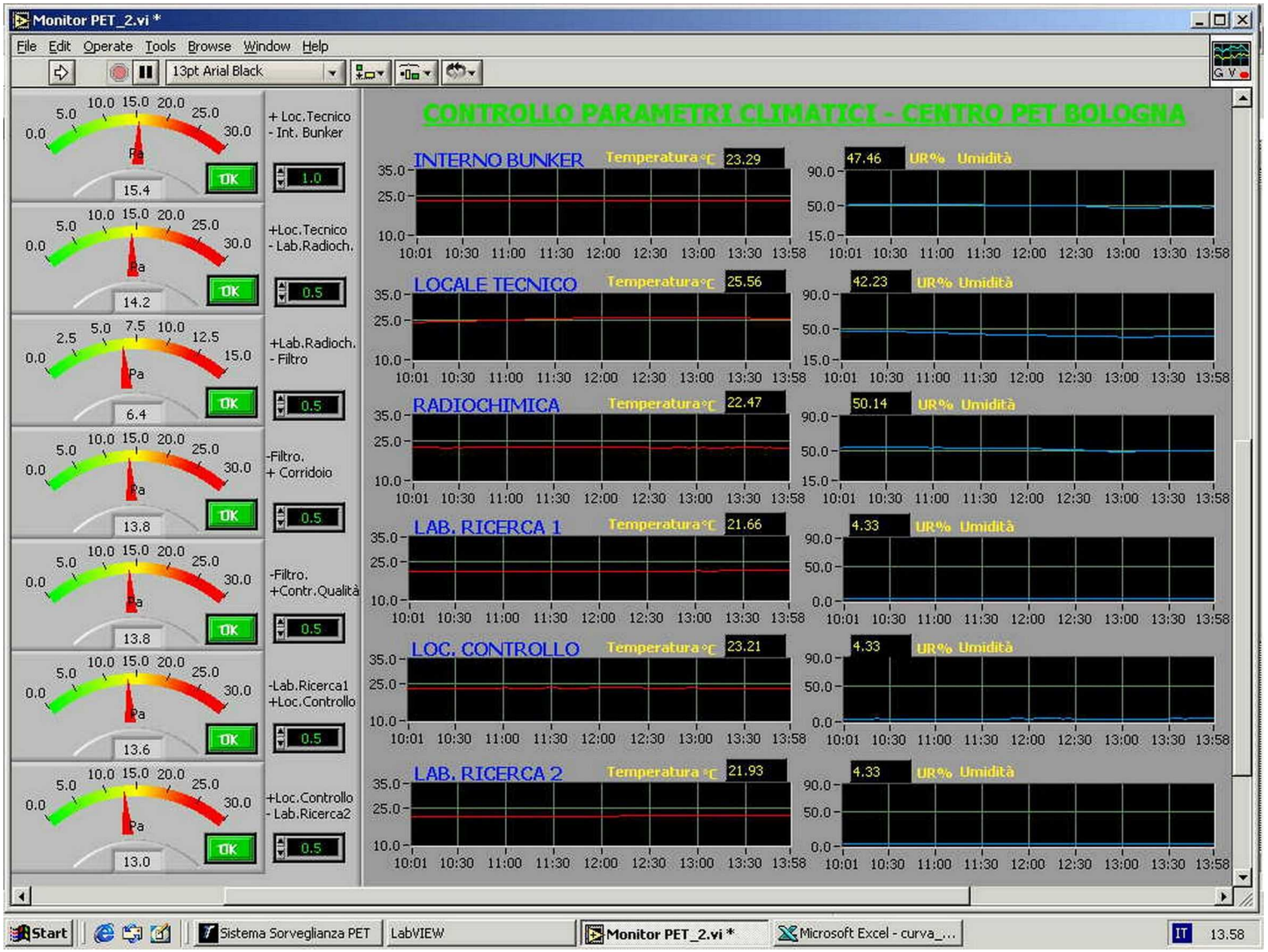
Assume infiltration Q_{inf} is transcurable.
In this case, if P_{in} is the pressure inside and P_{out} the pressure outside an area, and Q_{in} and Q_{out} are the flow of air input and output:

$$\Delta P = P_{in} - P_{out}$$

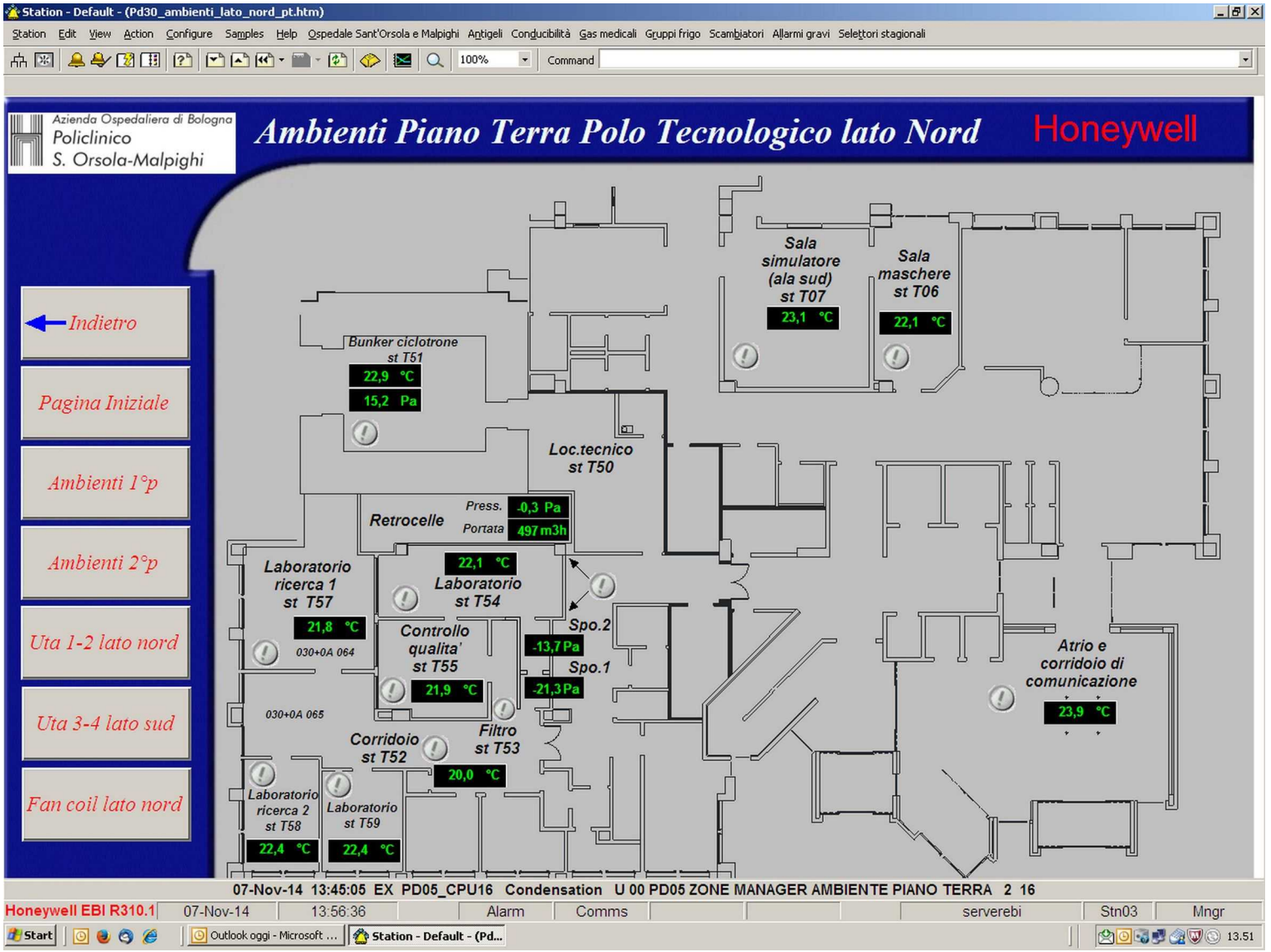
$$\Delta P \approx Q_{in} - Q_{out}$$

Consider that infiltration is never really negligible ! But it can be reduced to a very limited extent.

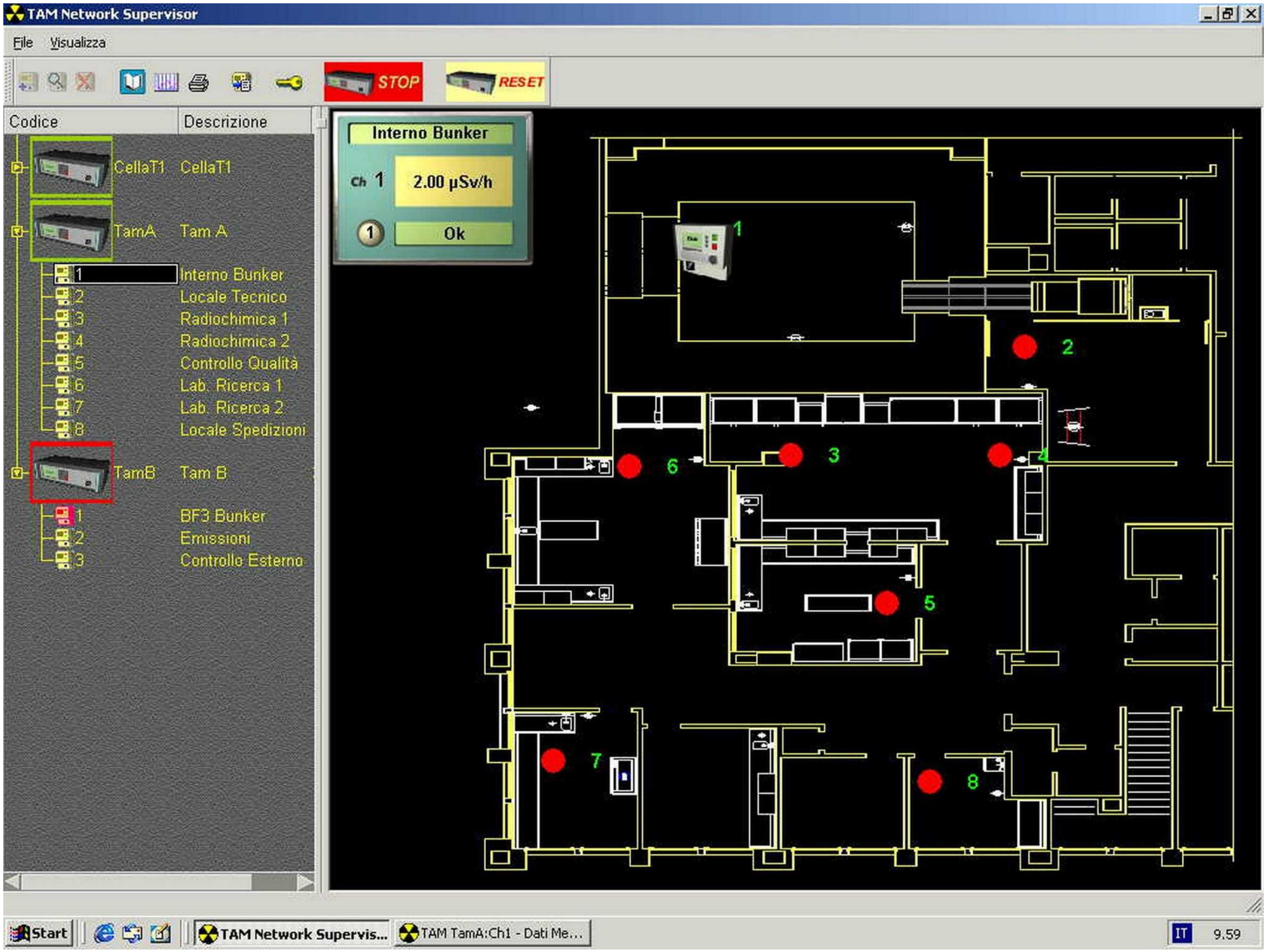
Display of the environmental monitoring system



Display of HVAC control system



Display of the radiation monitoring system



Example of results of a test of environmental validation

(Class C laboratory at rest)

RISULTATI PROVE

[1]Dimensione Particellare: 0,5 µm					
Punto di Campionamento	Unità di misura	Risultato	Valori di riferimento	Metodo di prova	Conforme/Non Conforme
1	Conteggi/m^3	68.421	352.000	UNI EN ISO 14644-1:206	Conforme
2	Conteggi/m^3	67.628	352.000	UNI EN ISO 14644-1:206	Conforme
3	Conteggi/m^3	67.006	352.000	UNI EN ISO 14644-1:206	Conforme
4	Conteggi/m^3	68.982	352.000	UNI EN ISO 14644-1:206	Conforme

Example of results of a test of environmental validation

(Class C laboratory at rest)

RISULTATI PROVE

[1]Dimensione Particellare: 0,5 µm					
Punto di Campionamento	Unità di misura	Risultato	Valori di riferimento	Metodo di prova	Conforme/Non Conforme
1	Conteggi/m³	#1.103.360	352.000	UNI EN ISO 14644-1:2016	Non Conforme
2	Conteggi/m³	#1.241.180	352.000	UNI EN ISO 14644-1:2016	Non Conforme
3	Conteggi/m³	#1.810.620	352.000	UNI EN ISO 14644-1:2016	Non Conforme
4	Conteggi/m³	#1.581.710	352.000	UNI EN ISO 14644-1:2016	Non Conforme

Ouch !

- Check / change filters
- Check / correct flow of the ventilation system
- Check / repeat cleaning

Radiopharmacy laboratories

IAEA. *Operational Guidance on Hospital Radiopharmacy. 2008*

Operational Level	Description
1 a	Operational level 1a is the dispensing of radiopharmaceuticals purchased or supplied in their final form from recognized and/or authorized manufacturers or centralized radiopharmacies. This includes unit doses or multiple doses of prepared radiopharmaceuticals for which no compounding is required.
1 b	Operational level 1b is the dispensing of radioiodine and other ready to use radiopharmaceuticals for radionuclide therapy or palliation. This includes ready to use injections of strontium and samarium for pain palliation.
2 a	Operational level 2a is the preparation of radiopharmaceuticals from prepared and approved reagent kits, generators and radionuclides (closed procedure). This is the most common activity in nuclear medicine departments, with routine use of a technetium generator and reconstitution of pre-sterilized radiopharmaceutical cold kits.
2 b	Operational level 2b is the radiolabelling of autologous blood cells. This includes radiolabelling of red bloods cells, platelets and white cells commonly used for infection or inflammation imaging.
3 a	Operational level 3a is the compounding of radiopharmaceuticals from ingredients and radionuclides for diagnostic application (including open procedure); modification to existing commercial kits; in-house production of reagent kits from ingredients, including freeze dried operation; related research and development.
3 b	Operational level 3b is the compounding of radiopharmaceuticals from ingredients and radionuclides for therapeutic application (including open procedure) together with related research and development. Examples include radio-iodination of meta-iodobenzyl guanidine (MIBG-iobenguane) and rhenium labelled lipiodol.
3 c	Operational level 3c is the synthesis of positron emission tomography (PET) radiopharmaceuticals. This includes the increasingly popular fludeoxy-glucose (18F) injections (FDG). The compounding of radiopharmaceuticals produced from unauthorized or long lived generators such as gallium (68Ga) or rhenium (188Re) — mostly related research and development — also falls under operational level 3c.

Indications for classification of areas in IAEA SSG-46

4.65. Various areas and rooms in a nuclear medicine facility should be classified as controlled or supervised areas, in line with the requirements given in BSS.

Once designated, these areas should meet the requirements detailed in the BSS for controlled areas and for supervised areas, ***including requirements for area delineation, signage, protection and safety measures, control of access,*** provision of personal protective equipment, provision of individual and area monitoring, provision of equipment for monitoring for contamination, and provision of personal decontamination facilities.

All other rooms and areas, not so-designated, are considered as "public domain" and levels of radiation in these areas should be low enough to ensure compliance with the dose limits for public exposure. … it would be expected that final decisions by the licensee for a given medical radiation facility would be based on the expert advice of the medical physicist, qualified expert in radiation protection, or RPO …

Indications for classification of areas in IAEA SSG-46

From Para. 4.66.

In a Nuclear Medicine facility, rooms for:

- ***radiopharmaceutical preparation (i.e. radiopharmacies or hot labs)***
- ***injection of the radiopharmaceuticals***
- ***storage and decay of radiopharmaceuticals***
- ***Imaging, particularly those housing radiopharmaceutical dispensing equipment (i.e. PET radiopharmaceutical and radioactive gas and aerosol dispenser devices***)
- waiting rooms dedicated to patients who have been injected with radiopharmaceuticals (e.g. uptake rooms in a PET facility)
- hybrid machines that have an X ray component (SPECT-CT, PET-CT)
- rooms for patients undergoing radiopharmaceutical therapy

meet the criteria for controlled areas and should be so designated.

From Para. 4.67.

Supervised areas may include examination rooms with probes, corridors and other areas where there are patients who have been administered with radiopharmaceuticals.

Radiopharmacy laboratories

IAEA SSG-46 (2018) par. 4.21

Radiopharmacies or laboratories where unsealed radioactive materials are handled, such as the source preparation area, should have:

(a) **Means to prevent access** by unauthorized persons;
(b) Adequate storage space for equipment used in the given room or area to be available at all times, to minimize the potential for spreading contamination to other areas;
(c) A contained workstation for easy decontamination; ***separated !***
(d) **Shielded storage for radioactive sources**;
(e) **Shielded temporary storage for both solid and liquid radioactive waste**, and places designated for the authorized discharge of liquid radioactive effluent;
(f) **Shielding to protect workers** where significant external exposure may occur;
(g) A wash-up area for contaminated articles, such as glassware **(*)**;
(h) **An entry area where protective clothing** can be stored, put on and taken off, and which is provided with a hand wash-up sink and a contamination monitor;
(i) Taps and soap dispenser that are operable without direct hand contact and disposable towels or a hot air dryer **(*)**;
(j) An emergency eyewash, installed near the hand washing sink **(*)**;
(k) An emergency shower for decontamination of persons **(*)**.

(*) due to the concurrent requirement for pharmaceutical processing, these areas **should not be within the same area** dedicated to pharmaceutical operations.

Radiopharmacy laboratories

IAEA SSG-46 (2018) par. 4.22

Radiopharmacies, laboratories and other work areas for manipulation of unsealed radioactive materials should be provided with equipment kept specifically for this purpose, which should include:

(a) **Tools for maximizing the distance** from the source, for example tongs and forceps;
(b) **Syringe shields**;
(c) **Containers for radioactive materials**, with shielding as close as possible to the source;
(d) Double walled containers (the outer being unbreakable) for liquid samples;
(e) Drip trays for minimizing the spread of contamination in the case of spillage;
(f) *Disposable tip automatic pipettes* (alternatively, hypodermic syringes to replace pipettes);
(g) Lead walls or bricks for shielding;
(h) **Lead barriers with lead glass windows**;
(i) **Barriers** incorporating a low atomic number material (i.e. acrylic) **for work with beta emitters**;
(j) **Radiation and contamination monitoring equipment** (surface and air);
(k) **Shielded carrying containers**, wheeled if necessary, for moving radioactive materials from place to place;
(l) Equipment to deal with spills (**decontamination kits**).

Radiopharmacy laboratories

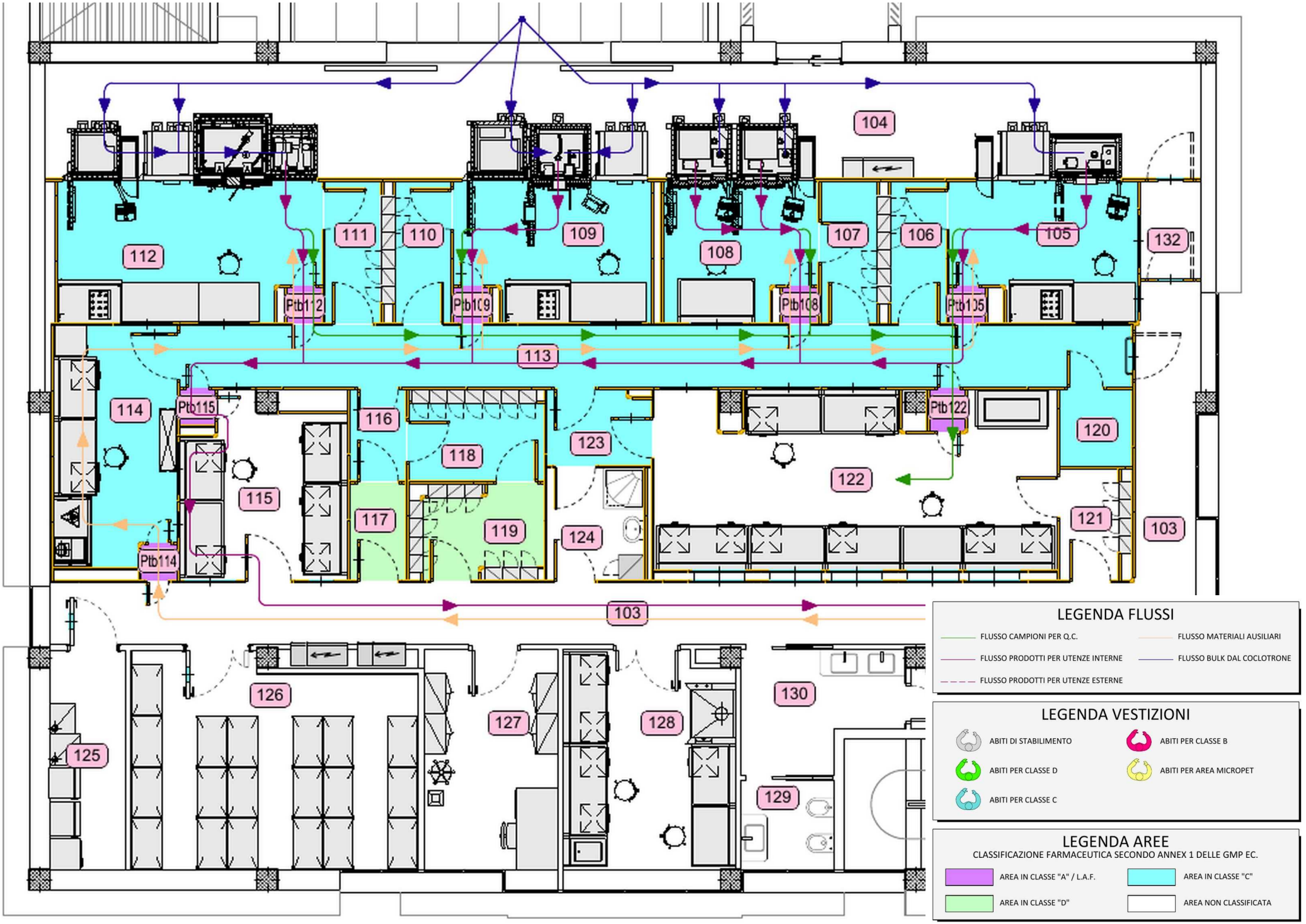
IAEA SSG-46 (2018) par. 4.23 & 4.24

Drainpipes from sinks in the radiopharmacy or laboratory should go as directly as possible to the main building sewer and should not connect with other drains within the building, unless those other drains also carry radioactive material.

This is to minimize the possibility of a ‘backup’ contaminating other non-controlled, areas.

The final plans of the drainage system, which are supplied to maintenance personnel, should clearly identify the drains from radiopharmacies and laboratories. Pipelines through which radioactive materials flow should be marked to ensure that monitoring precedes any maintenance.

Some countries require that drainpipes from a nuclear medicine facility and especially from radionuclide therapy wards terminate in a delay tank. Requirements on this issue differ very much among countries but each nuclear medicine facility should comply with their country’s regulations.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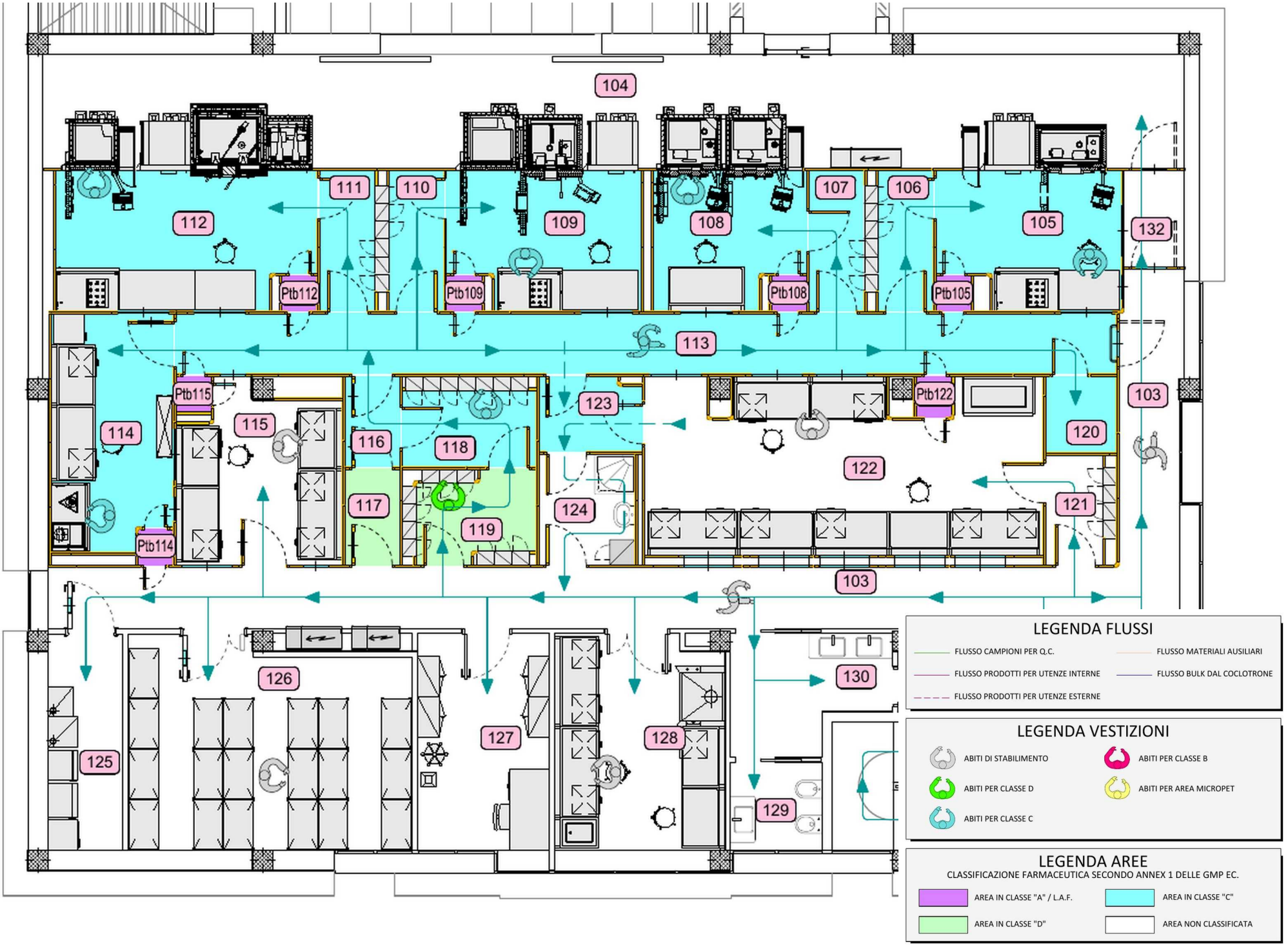
FLUSSO MATERIALI AUSILIARI
FLUSSO PRODOTTI PER UTENZE INTERNE
FLUSSO BULK DAL COCLOTRONE
FLUSSO PRODOTTI PER UTENZE ESTERNE
LEGENDA VESTIZIONI
ABITI DI STABILIMENTO
ABITI PER CLASSE B
ABITI PER CLASSE D
ABITI PER AREA MICROPET
ABITI PER CLASSE C
LEGENDA AREE
CLASSIFICAZIONE FARMACEUTICA SECONDO ANNEX 1 DELLE GMP EC.
AREA IN CLASSE "A" / L.A.F.
AREA IN CLASSE "C"
AREA IN CLASSE "D"
AREA NON CLASSIFICATA

PIANO PRIMO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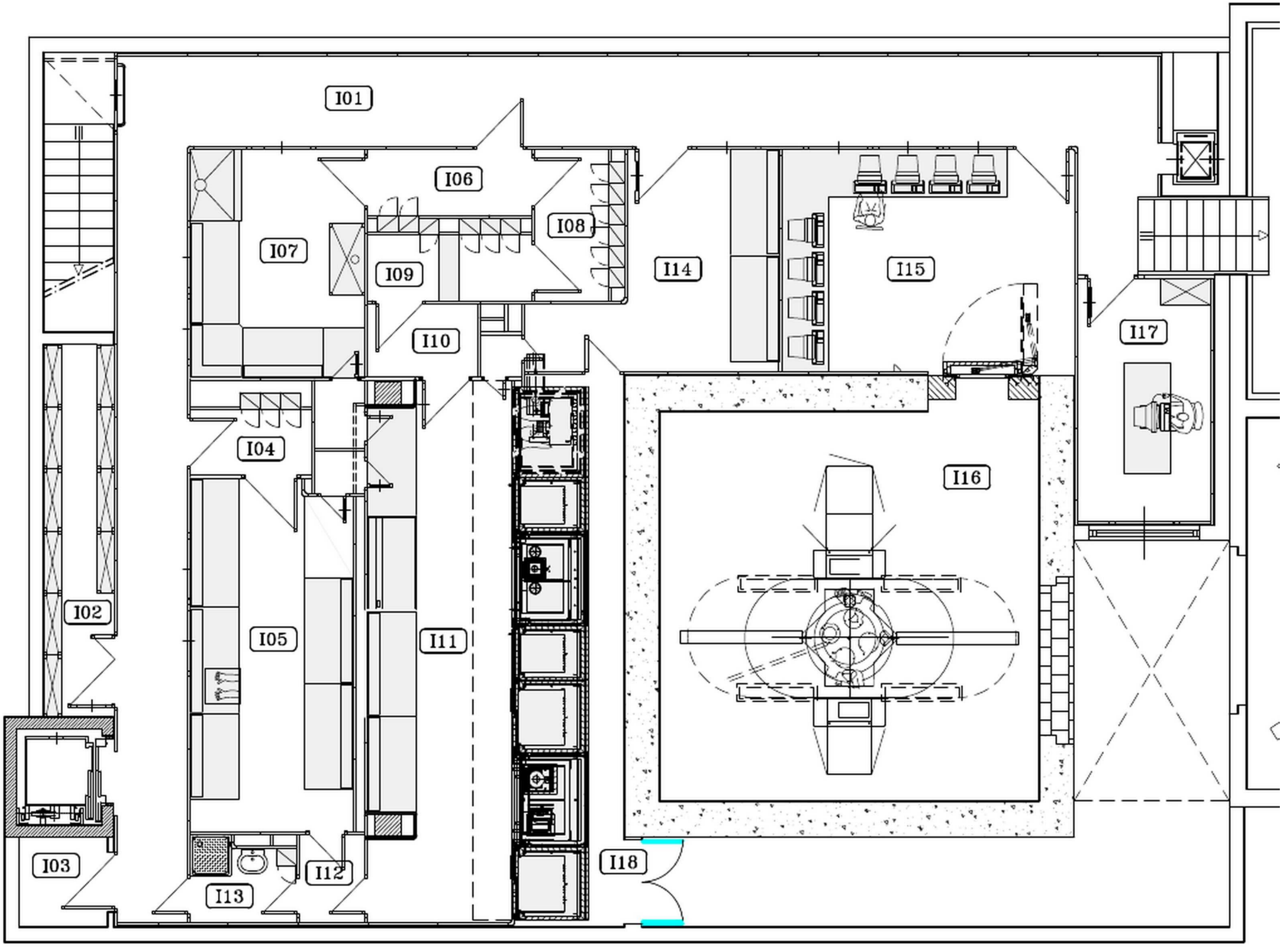
CLASSIFICAZIONE FARMACEUTICA SECONDO ANNEX 1 DELLE GMP EC.
AREA IN CLASSE "A" / L.A.F.
AREA IN CLASSE "C"
AREA IN CLASSE "D"
AREA NON CLASSIFICATA

200
260
QC lab
Production lab
changing
Cyclotron control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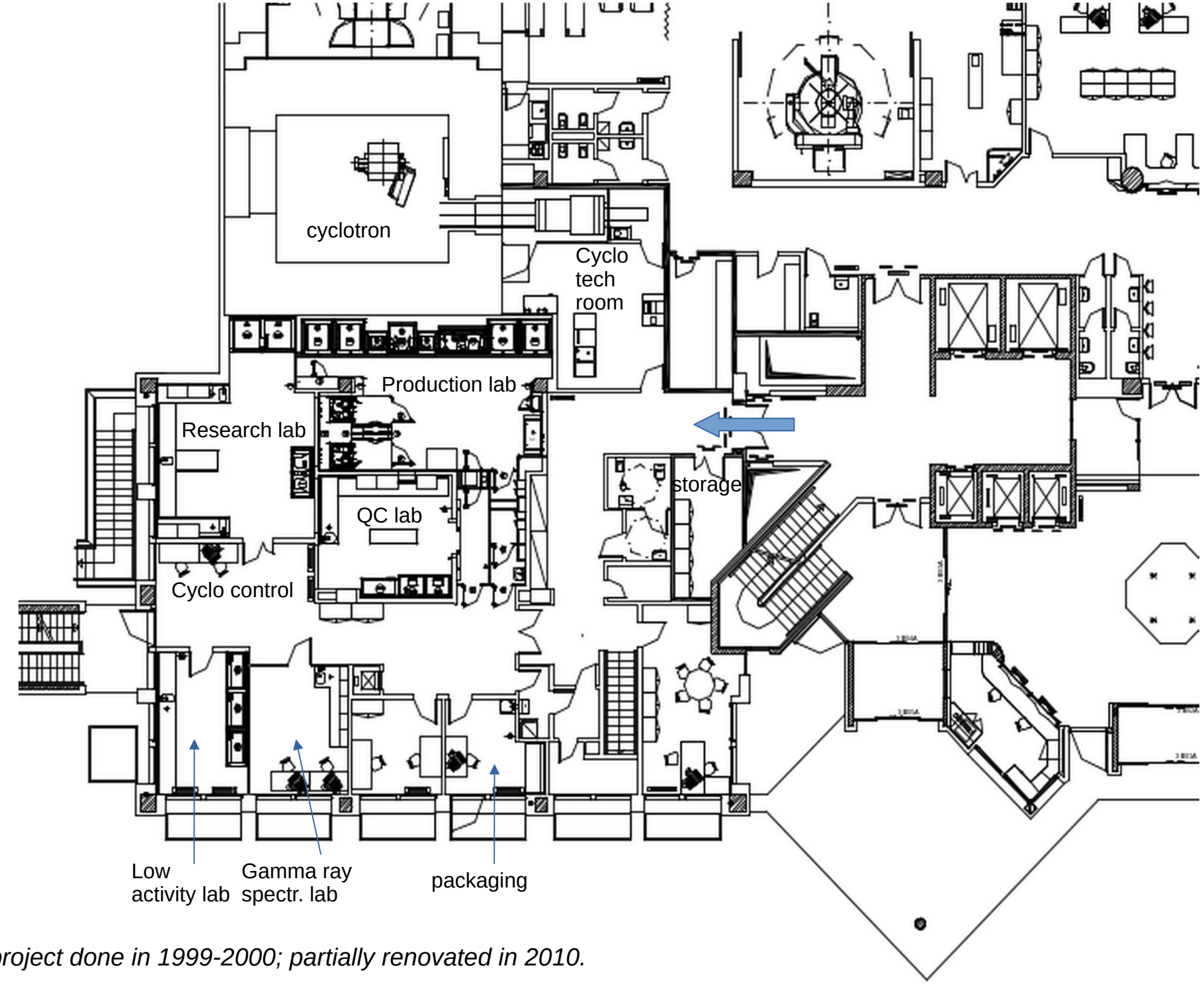
Cyclotron PET Radiopharmacy in Bologna



Original project done in 1999-2000; partially renovated in 2010.

Cyclotron PET Radiopharmacy in Bologna