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ARTICLE

Review of operational indications on the design of facilities for radiopharmaceutical manufacturing in italy☆

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Abstract – Purpose. In this article, the authors propose useful operational indications to approach in the best possible way the issues concerning the design of a facility for manufacturing radiopharmaceuticals, with focus on organizational and safety aspects. **Methods.** Several documents produced by authoritative bodies, national and international scientific institutions and associations were examined and referenced, to the purpose of reviewing all available information in the field. **Results.** Indications are gathered for the design stage, including the organization of accesses and routes and characteristics and requirements of premises and systems. **Conclusions.** Main goal is to guide the reader in evaluating and choosing the most suitable features and equipment to limit the risks due to ionizing radiation and to prevent contamination of the workers and the environment.

Keywords: radiation protection / radiopharmaceutical / nuclear medicine / occupational safety

1 Introduction

The use of radionuclides in the healthcare sector is now increasingly widespread in nuclear medicine (NM) applications, *i.e.* in activities concerning the production and use of sealed and/or unsealed sources for medical purposes, both diagnostic and therapeutic. The diagnostic applications, characterized by the administration of radiopharmaceuticals to patients and subsequent external detection of gamma emissions, have the ability to provide specific clinical information and often represent the elective method. Likewise, therapy with radioisotopes, which exploits the metabolic characteristics of radiopharmaceuticals prepared *ad hoc* to deliver an appropriate absorbed dose of radiation, is having a great development thanks to the specificity of new carriers and radionuclides in targeting the tumor to be irradiated.

Manufacturing of radiopharmaceuticals takes place in installations dedicated for this purpose, sometimes located within hospitals, called radiopharmacies or radiopharmacy laboratories.

Handling, storage and disposal of unsealed radioactive substances can expose workers to a risk of both external exposure, which is the main source of risk, and internal contamination. It is therefore clear that the design requires specific features and equipment to limit radiation risks and prevent contamination of staff, working environment and equipment, and dispersion of radioactive substances outside the facility, thus also ensuring the protection of the population.

For this purpose, the design must meet various technical and organizational requirements, including:

- correct spatial arrangement and organization of premises;
- adequate choice of coating surfaces;
- appropriate ventilation system;
- installation of special equipment, including fume hoods, laminar airflow cabinets, glove boxes, shielding and monitoring systems;
- adequate solutions for the management and storage of solid and liquid waste and gaseous effluents;
- working procedures aimed to the safe management of activities involving risks with ionizing radiation.

2 Materials and methods

In the following discussion, reference is made to various documents produced by authoritative bodies, and national and

☆ Dedicated to the memory of our friend and colleague Giulio Cocomello

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international scientific institutions and associations, such as ICRP publication 57 (ICRP, 1989), UNI standard 10491 (UNI, 1995a), IAEA TRS No. 471 (IAEA, 2009), Italian standards of good manufacturing of radiopharmaceuticals in nuclear medicine (Ministry of Health, 2005), and Good Manufacturing Practices (GMP) of the European Commission (2008) and the WHO (2011).

In particular, UNI standard 10491 (UNI, 1995a) indicates the minimum criteria to be adopted in the design and construction of the facilities covered in this document; IAEA TRS 471 (IAEA, 2009), HHS 11 (IAEA, 2010), SSG 46 (IAEA, 2018) can be considered as the most updated and specific references and can also be used.

3 Results and discussion

3.1 General indications and classification of areas

For the correct management of activities in a radiopharmacy laboratory, it is necessary to identify areas with different classification according to the potential presence of radioactive substances: "cold area", "hot area" and "filtering area" (personnel airlock).

To prevent potential radioactive contamination of workers or general public, it is necessary to organize the premises in such a way that the cold areas are distinct and separate from the hot areas, which must be delimited by fixed physical barriers, adequately marked and with access regulations, providing for specific areas of contamination control inside the filtering areas.

The cold area, not susceptible to contamination, contain all the premises dedicated to administrative work and waiting rooms for patients before the radiopharmaceutical administration.

The hot area includes the premises where there is a risk of external exposure and contamination, *i.e.* those areas where activities involving the use of radioactive substances are carried out:

- room for the preparation and storage of radiopharmaceuticals;
- room for quality assurance/quality control;
- temporary storage area for solid radioactive waste; depending on the workload, the type of radioactive substances used and the volume of the solid waste produced, the temporary storage can also be in an area adjacent to the radiopharmacy laboratory or the facility;
- storage room for cleaning equipment or other tools that must not be used outside the hot area;
- room for the administration of the radiopharmaceutical to the patient, in case of a hospital.

It is indeed essential to distinguish two different scenarios:

- a radiopharmacy laboratory installed within a nuclear medicine department;
- a radiopharmacy laboratory within a production facility.

Before accessing (or leaving) the areas with risk of contamination, it is necessary to go through a filtering area (personnel airlock). This zone must be equipped with a hand–foot–clothing monitor and a sink for immediate decontamination of the hands when leaving the areas with risk of radioactive contamination. The washbasins must be equipped with a pedal/elbow/photocell-operated control. A shower (with collected discharges or drainpipes terminating in a delay tank), to be used for a possible decontamination following an event of contamination of the whole body or the head (events which however have a low probability of occurrence), should be provided inside the filtering area leaving the facility and/or the radiopharmacy laboratory (if it is located in an independent building).

The staff changing rooms must be located in the cold area, separated from the hot area but preferably adjacent to the access filtering area. This design solution would allow personnel leaving the hot area to recover their personal items after control of contamination and, if needed, decontamination inside the filtering area.

The "cold" changing rooms should have an appropriate size, meeting any healthcare accreditation requirements, designed according to criteria that ensure privacy and equipped with lockers for clothes and personal items; in the filtering area, there must be lockers for work clothes and containers for contaminated clothes.

Access to the premises, their intended use and the routes reserved for workers and patients must also comply with certain rules for the containment of the risk of contamination.

At the planning stage, therefore, three basic requirements must be considered:

- structural requirements: design of the shielding and arrangement of the premises pertaining to the activities;
- technological requirements: specific requirements for systems and finishing;
- organizational requirements: organization of activities and personnel by means of work procedures and instructions.

Finally, when planning the premises and the related systems, it is useful to optimize the choices also according to the future management procedures, both in the ordinary phase and during the maintenance operations, according to the following criteria:

- pipes and channels positioned in easily accessible areas (corridor ceilings or shafts) and marked to be easily distinguishable from those not dedicated to the transport of radioactive material;
- easily removable concealment systems;
- provision of structures for accessibility to single parts of complex and large machines, such as walkways or illuminated systems;
- provision of appropriate areas around certain equipment for maintenance operations.

3.2 Design of a radiopharmacy laboratory

The laboratory must be divided into two areas: one dedicated to preparation operations and a second one where other activities take place (Ministry of Health, 2005). The estimate of activity to be handled is necessary to dimension the facility.

The area for radiopharmaceutical preparation must be separated from the rest of the premises and the entrance to the laboratory must be through specific filtering areas (personnel

airlock), where the staff wears work clothes and, if necessary, personal protective equipment, checks any contamination before leaving (with the hand-foot-clothing monitor) and perform operations of personal decontamination, if needed (using a sink with eye bath and a shower with controlled drain).

Depending on the pharmaceutical classification of the laboratory, two interlocked doors could be provided both for access from the outside to the filtering room and from the latter to the radiopharmacy laboratory, providing the doors with gaskets to eliminate infiltration of air from non-classified (in terms of air quality) areas towards classified ones. In particular, access to premises such as the radiopharmacy laboratory and those in which radioactive sources are kept should be limited to authorized personnel only, by means of a badge or numerical code. Each door that overlooks the laboratory should have a viewing panel to prevent accidents when opening the door, and also to allow visual inspection in the laboratory in case of an accident or emergency.

The space available must put the personnel in a condition to work safely: the requirements should be assessed according to the type of work, hopefully trying to guarantee at least 3 m^2 of free surface per person (IAEA, 2009). Therefore, depending on the workload and the number of workers, the laboratory should be organized as a complex of rooms; in any case, space for storage of radionuclides (radioactive waste and sources) with adequate shielding should be available. At the planning stage, the weights of all the equipment must be estimated in order to avoid floor overload problems, with particular attention to the cells for manipulation and the hoods which are particularly heavy, due to the shielding they are equipped with.

Laboratory areas equipped with autoclaves should have sufficient space to allow their access and maintenance. The drainage of the autoclave must be designed to prevent or minimize flooding and damage to the floor. The drainpipes of the sinks in the laboratory should go as directly as possible (or, when appropriate according to the amount of activity to be handled, through temporary delay tanks) to the main sewer system without connecting to other building drain pipes, unless the latter also carry radioactive material; this precaution is aimed at minimizing the possibility of the drainage system 'backing up' with potential contamination of other areas (IAEA, 2018).

The environmental conditions inside the laboratory must be controlled to allow a safe preparation of radiopharmaceuticals and the correct operation of equipment. All extemporaneous injectable preparations must be sterile. Sterility must be guaranteed through a series of suitable measures, such as: strict observance of the standards for good manufacturing practice of pharmaceutical products, the implementation of dedicated and controlled environments, the use of appropriate equipment, the presence of qualified personnel, the preparation of stringent cleaning and disinfection procedures, the use of aseptic techniques and environmental microbiological monitoring.

The standards for good manufacturing practice of pharmaceutical products classify the environments dedicated to the preparation of medicines according to the degree of risk of the process used, in accordance with Annex 1 of the GMP (European Commission, 2008), which classifies the environments or work areas, "at rest" and in "operation", in four grades (A, B, C and D) depending on the maximum permitted concentration of particles in the air with a diameter of 0.5 μm and 5 μm (in accordance with UNI EN ISO 14644 in terms of ISO classes) (UNI, 2016).

Preparations that have higher microbiological risk (aseptic subdivisions, handling of sterile products, preparations that cannot be subjected to terminal sterilization) must take place with aseptic procedures inside a class A laminar flow hood placed in a class B room, or an isolator that guarantees a sterile environment, placed in a grade D zone (Ministry of Health, 2005); the choice must be made during the planning stage of the facility and depends on the solutions implemented and described later in the paragraph dedicated to ventilation.

The lower risk preparations (those for which terminal sterilization is possible) can be carried out in class A laminar flow hoods in a grade D room (Ministry of Health, 2005).

The laminar flow hoods consist in a handling area, shielded towards the outside and covered in decontaminable stainless steel, placed on a support frame. The incoming and extracted air must pass through HEPA filters; in addition, if necessary, the outgoing air could pass through an additional activated carbon filter. The level of radioactivity of the effluents must be monitored downstream of the filtration system, so that, in the event of an accidental release, the control system activates the closure of the incoming and outgoing air and activates an acoustic and luminous alarm. The hoods are mainly aimed at protecting the radiopharmaceutical from any external contamination and guarantee only partial protection of the operator and of the work environment.

The isolator represents the highest level of protection from the risk of product and operator contamination, thanks to its main characteristic of physically "isolating" the critical area and requiring transfer systems based on high containment technologies. The thickness of the shielding must be calculated or chosen based on the type, energy and activity of the radioactive material being handled.

From a structural point of view, the internal walls must be smooth, waterproof and with rounded edges for complete decontamination and cleaning; permanent installation of components that cannot be effectively cleaned should also be avoided. The incoming and outgoing air must pass through HEPA filters; the outgoing air must, when necessary, also pass through an additional activated carbon filter.

The main advantage of an isolator is that it can be installed in a class D laboratory, thus avoiding the creation of a cleanroom.

Depending on the type of handling, the radionuclide and the activities being handled, the most suitable type of isolator (glove boxes or hot cells) must be chosen to ensure adequate radiation protection conditions.

In glove boxes, all operations are performed inside the isolator by means of a pair of gloves positioned on the front wall and the material is transferred through the pre-chamber (in class B), as the main chamber must never be in direct communication with the external environment.

Hot cells are used, for example, for the preparation of PET radiopharmaceuticals, so that adequate shielding must also be considered between adjacent cells when evaluating shielding.

The internal surface of each compartment must be smooth, made of stainless steel with rounded edges for decontamination and sanitation.

The cells are generally equipped with a double interlock system:

- the first enables the transfer of the isotopes produced by the cyclotron, if present, to the synthesis modules, which can only take place when the module doors are closed, the internal pressure gradient is negative and the radioactivity detection systems are active and reveal values lower than the preset thresholds;
- the second is linked to two detection systems, one located inside the cell and the other in the channel expelling the air from the cell. If dose rate presets inside the cell are exceeded, the system automatically locks the door; on the other hand, if presets are exceeded within the canalization, the system blocks the emission of gases and conveys them into the compression and storage device, until their decay.

The final phase of the process takes place in the fractionation system, where, under sterile conditions, the automated preparation of the individual doses to be administered to the patient inside shielded syringes or bottles and the automated measurement of the final activity through a dose calibrator are carried out.

If the laboratory is located inside a hospital, the preparations must be delivered to the staff operating in the injection room, which should be positioned near the laboratory in order to allow the shielded syringes to pass quickly and safely through special material airlocks. In the event that, for design reasons, this is not possible, it is advisable to provide another laboratory, adjacent to the injection room, dedicated to the fractionation and equipped with a material airlock, or to provide a procedure that regulates the transport of the shielded syringes by operators ensuring short routes. In case of PET radiopharmaceuticals, whenever possible an automatic dose administration system could be used to replace manual syringing, in order to optimize radiation protection. If this unit is mobile and equipped with an automatic injection system, it can be transported to the administration room where the selected dose is administered to the patient. If the dispensing system and the injection system are separate, the portable injectors must be carried according to appropriate procedures.

Otherwise, if the laboratory prepares doses intended for shipment, like for example an industrial laboratory, the finished product must be properly packaged in an adjacent room.

3.3 Accesses and routes

The design of a radiopharmacy, from a radiation protection point of view, requires a careful organization of the routes and evaluation of the requirements of the premises and the areas necessary for a correct and efficient performance of the activities.

Access to the laboratory must be regulated and controlled in order to guarantee the interdiction of risk areas to all unauthorized subjects, in other words to reserve access to authorized personnel only. Access must therefore take place through normally closed doors, equipped with opening consent devices such as intercoms/video intercoms; authorized personnel will have free access using badges or numerical code.

The radiopharmacy laboratory must be designed so as to guarantee accesses and routes specifically dedicated to the transit of operators and radioactive material, following the direction of the radioactivity gradient.

Moreover, if the laboratory is located inside a hospital, the accesses and routes dedicated to operators and radioactive material must be differentiated from those identified for patients, with the aim of minimizing the risk of exposure.

It is advisable to provide a dedicated entrance/exit with a bell, located near the radiopharmacy, which allows the staff to accept incoming and outgoing radioactive material (verifying delivery note, etc., and integrity of the package) and transfer it to the storage room with a minimal route.

It is preferable to move radioactive materials, including waste, according to procedures, defining routes and times, codified in collaboration with the radiation protection expert, to warrant minimal presence of both staff and population (short routes in low attendance area and times), with the ultimate aim of reducing the risk of possible undue exposure (Fig. 1).

3.4 Premises and systems

In order to guarantee the radiation protection requirements related to NM activities, it is essential to apply strict criteria in the choice of design solutions and materials to be used for the realization of the facilities covered in this work.

3.4.1 Walls and surfaces

The type of surfaces and their coating are elements of considerable importance when designing and setting up work areas where radioactive substances are handled and, in general, all hot areas.

The floor and the surfaces of the walls must be easily decontaminated and, as far as possible, without interruption, with finishes that must be adequate to the requirements for radiation protection. The joint between the floor and the walls must be rounded, with a rise on the walls of about 20 cm, so as to avoid corners and roughness. The entire floor covering must be waterproof and function effectively as a basin, so that the building structure and the floors under the laboratory are protected from potentially contaminated water. The floor of the work spaces must therefore be made of smooth material, without interstices, roughness or imperfections that can trap the contaminant, for example with plastic sheets welded together and glued to the floor. Tiles are not recommended due to the large number of connections.

The materials must also be chosen taking into account their resistance to corrosion by any chemical agents used. The sheets of non-pigmented or plasticized PVC are more resistant to contamination and can be decontaminated more easily than those of other materials. However, it is good practice to renew these coatings periodically.

As an alternative to the PVC sheets, walls could also be covered by washable paints (epoxy paints, enamel or chlorinated rubber) non-porous, resistant to chemical reagents and mechanical actions. Work surfaces, where radionuclides are used or stored (benches, tables and chairs), must be finished with a material which is hard, non-porous, waterproof, washable and resistant to heat, stains and chemicals. This

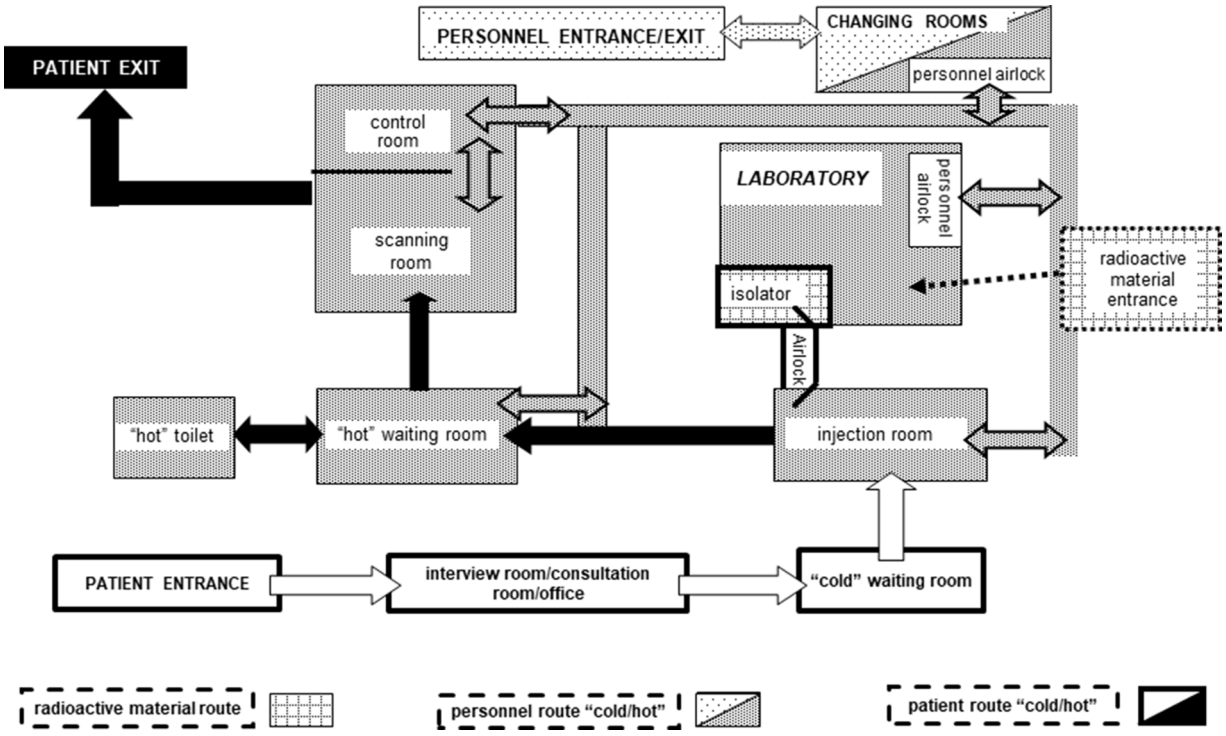

Fig. 1. Block diagram of a radiopharmacy laboratory inside a nuclear medicine department, with accesses and routes.

should be applied in large sheets with a minimum number of connections. It is also appropriate that the edges are raised to avoid dripping. Stainless steel is often used for laboratory sinks, drains and racks.

Cleaning must be carried out regularly according to appropriate procedures, which guarantee sanitation and, if required, sanitization of the environment.

Pipes and wires must be coated in order to facilitate cleaning and possible decontamination.

3.4.2 General characteristics of a ventilation system

The ventilation of the rooms where unsealed sources are handled must be controlled by a system that allows an adequate number of air changes, according to the activity carried out and such as to guarantee adequate microclimatic conditions of temperature and relative humidity.

The ventilation system must therefore be separated from other similar systems of the hospital in which this facility is possibly located. In hot areas, air intake and filtering systems must also be installed, with pressure levels differentiated according to the classification and level of risk of the rooms.

The ventilation system has a fundamental role in the management and minimization of risks, both radioactive contamination (of personnel and environment), and microbiological contamination of radiopharmaceutical products by personnel and external environment; the system must therefore prevent the spread of potentially contaminated air from one room to another inside the building (recirculation must be avoided) and reduce the concentration of radioactivity in the air of a potentially contaminated environment through an adequate number of air changes and suitable pressure gradients. The characteristics of the pressure gradients of the rooms must be adequate to protect the preparation from contamination and comply with the radiation protection requirements, at the same time.

The air introduced into the premises must be properly filtered to reduce the dust load and thus limit the re-suspension of contaminated particulates and, if possible, the flow should preferably be directed downwards.

The air must be expelled through high efficiency filters appropriate to the nature and quantity of the effluent (UNI, 1975, 2010). The exhaust air duct must be separate from the building's normal exhaust duct, and the external intake must be located so as to avoid the recirculation of the exhaust air. The fan motor must be positioned outside the duct, in order to avoid any possible contamination and facilitate maintenance.

The reference standard UNI 10491 (UNI, 1995a) provides for the classification of laboratory areas where unsealed radioactive sources are handled into four different categories: A_U, B_U, C_U and D_U in relation to the levels of irradiation and/or contamination, increasing from A_U to D_U, and to working conditions.

Zone "A_U" (low risk) must be designed and constructed in such a way that, in normal working conditions, the doses received by staff who usually work in that area cannot exceed 3/10 of the maximum allowable dose.

Zone "B_U" (low risk) must be designed to ensure an appropriate containment of the contamination towards zone A_U and/or outwards, and so that, under normal working conditions, the absorbed doses to staff who usually work in the area cannot be higher than the maximum allowable dose, although it can exceed 3/10 of this limit.

Zone "C_U" (medium risk) must be designed and constructed to ensure an appropriate containment of the contamination towards the lower order areas (zones A_U and B_U) and outwards.

Table 1. Number of air changes in laboratory areas according to UNI 10491 (UNI, 1995a).

Zone	No. of air changes (h^{-1})
Zone A_U e B_U	2–5
Zone C_U	5–10
Zone D_U	>10

In zone C_U, the levels of irradiation and contamination can cause the maximum absorbed dose to be exceeded in the case of continuous work. To prevent exceeding of the maximum absorbed dose, the work in this area is subject to time limits and/or the obligation to wear appropriate protective clothing.

Zone "D_U" (high risk), given the high levels of irradiation and/or contamination involved, must be designed and constructed to prevent access during normal working conditions and to ensure appropriate containment of contamination and suitable radiation shielding to all other areas and/or to the outside.

The above-mentioned UNI standard provides for the following air change values (Tab. 1).

In the event of a handling activity taking place inside hot cells, they must be considered zone D_U (UNI, 1995a), while the surrounding room can be classified as a lower risk area.

However, when assessing the number of air changes per hour to be guaranteed inside each room, it is also necessary to take into account the applicable good technical standards, such as UNI 10339 (UNI, 1995b), and regional laws in force regarding the minimum authorization requirements for accreditation.

In conclusion, as a general indication, in almost all cases it is advisable to guarantee a minimum number of air changes between 5 and 10 per hour.

The air flow must be directed from the areas with lower potential contamination to the areas with higher potential contamination, keeping the latter with negative pressure compared to the former.

The pressure gradients between different areas are chosen by the radiation protection expert according to the radiation protection needs and in compliance with the GMP, referring to the applicable good technical standards and international safety standards (IAEA, 2009, 2010).

The ventilation system, according to the radiation protection appropriate criteria, must therefore guarantee a slight depression in the hot area, *i.e.* the one with the higher risk of contamination, compared to the adjacent rooms, and a growing depression from the areas where the risk of contamination is lower towards those in which it is higher, to avoid the spread of potentially contaminated air towards the areas with lower risk.

Radiation protection criteria sometimes conflict with the standards of good manufacturing of radiopharmaceuticals which require an overpressure in the preparation room.

3.4.3 Ventilation in the radiopharmacy laboratory

The characteristics of the pressure gradients of the laboratories in which radiopharmaceuticals are handled must protect the preparation from contamination and at the same time, however, comply with radiation protection requirements.

In these cases, it is necessary to identify a design solution satisfying both needs. A good compromise could be the construction of a filtering area (personnel airlock) to access the radiopharmaceutical preparation area. This filtering area is set in depression with respect to both the hot area and the corridor (IAEA, 2009, 2010), and equipped with an interlock system that prevents the simultaneous opening of the two access doors (otherwise, the pressure gradients would be lost). In this case, the airlock must be provided with a mushroom switch for emergency opening, and procedures must be codified for manual opening of the doors in the event of malfunction of the mushroom button.

This solution creates a pressure gradient, directed from the laboratory to the filtering area, able to prevent the inlet of unfiltered air into the critical area and at the same time to allow expulsion toward a duct under control.

Therefore, when designing the ventilation system serving a radiopharmacy laboratory, reference should also be made to Annex 1 of the GMP (European Commission, 2008). The maximum permitted airborne concentration of particles (dust, etc.) and microbiological contamination in air (based on the classification of the areas) can be guaranteed through the pursuit of different design choices, including:

- access through a filtering area (personnel airlock) set in depression with respect to both the hot area and the corridor, characterized by the same degree of classification established for the preparation laboratory;
- number of air changes greater than 10 per hour (UNI, 1995a): the exact value must be assessed according to the type of work equipment available, the number of workers and the type of systems present, also in collaboration with the radiation protection expert;
- fresh air conditioning system, without recirculation: the system must prevent the air expelled outside from being reintroduced through the supply system;
- filtration of the incoming air through multiple filtering systems, upstream and inside the ventilation ducts, suitable for the required level of protection, according to Annex 5 of the WHO (2011). Filters must be easily replaceable and periodic replacement must be scheduled;
- suitable position of air supply and return vents inside the laboratory;
- the number of staff operating in the work area must be minimized (generally, maximum two people);
- the entry/exit of materials, radiopharmaceuticals and samples for quality control must be carried out by means of airlocks equipped with a ventilation system suitable to guarantee a classification of the environment of the same degree of the area dedicated to the preparation of radiopharmaceuticals. Inside the material airlocks the pressure gradient must be such as to prevent air flowing from the surrounding areas towards the preparation laboratory. Access to the material airlocks must be regulated by special interlocks to prevent the simultaneous opening of the two doors.

When designing the air return system, it is necessary to identify two distinct areas, in order to control the risk of contamination:

- for rooms where activities with manipulation of radionuclides are not carried out, the air extraction system is equipped with absolute filters;

– for rooms where activities involving manipulation of radionuclides are carried out, a dedicated extraction system must be provided: the extracted air, before being released into the environment, must be filtered through a system composed of prefilters, active carbon (specific for radioisotopes) and absolute filters, possibly ULPA filters (UNI, 2010).

This system is also used to extract air from the manipulation cells and to release it into the environment.

In order to reduce the risk of radioactive contamination, the filter block system should be positioned in a specific classified room, with access limited to authorized personnel only.

The exhaust air duct must be separate from the building's normal duct, made of non-flammable materials, in such a way that it can be easily cleaned and replaced.

After filtration, the air must be discharged through stacks of a height that ensures sufficient dilution of the gaseous effluents in the atmosphere before reaching the ground. When necessary, according to the evaluations of the radiation protection expert, it is desirable to provide for suitable devices for monitoring and sampling the air discharges before they are released into the atmosphere after filtering.

It is also necessary to provide fire alarm systems, as well as leakage detection systems for the gases used in the quality control laboratory or in cooling systems involving risks of flammability (such as hydrogen) or lowering of the oxygen content (*e.g.* helium).

As there are a lot of reference parameters to take into account in the ventilation system design (air flow, pressure gradients, relative humidity, microbiological and radioactive contamination), in order to reduce the risk of contamination it is necessary to periodically check the correct functioning of the systems and equipment referring to the technical standards mentioned above (UNI, 1995a, 2016, 2010; WHO, 2011).

3.4.4 Safety and control systems

The routine environmental monitoring of external irradiation must be continuous in the areas where sources of radiation are present or activities with radiological risk are carried out, with the aim of controlling the levels of ambient dose equivalent and verifying possible anomalous situations and risks. Depending on the radionuclides and the activities handled, the environmental monitoring of external irradiation can be carried out with portable instrumentation. According to the assessments of the radiation protection expert, it may be necessary to supply devices for monitoring and sampling the effluents, which must be placed inside the exhaust air duct, downstream of the filtration systems.

In addition, uninterruptible power supplies must be provided in order to guarantee the continuous operation of all systems and equipment also in case of emergency.

3.4.5 Biological protections

Around areas with risk of exposure to ionizing radiation appropriate shielding must be provided, of material and thicknesses suitable for confining radioactive emission.

Therefore, paying attention to floor-loading requirements, at the design stage adequate protective measures should be provided such as:

– shielded storage for radioactive sources;
– shielded temporary storage for both solid and liquid radioactive waste;
– structural (wall, floor and ceiling shielding) and ancillary barriers to protect workers where significant external exposure might occur and to shield sensitive instruments (so as to keep a low background), such as well counters, probes and imaging equipment.

Mobile shields can be provided in the "hot" waiting room if the regular presence of operators is assumed.

The combination of containment devices, shields and tools for handling radioactive materials must be appropriate to the type and quantity of materials to be used, as well as the type and duration of the operations to be performed. Hence, the planning of activities and workload has a decisive role, and it is necessary to establish in advance the amount of activity to be handled and the number of patients per year.

Depending on the type of incident radiation and the attenuation required, the design of a barrier requires three further aspects to be considered:

– material (elements, composition, density, etc.);
– dimensions (thickness, lateral and vertical extension);
– stratification (different layers, order of the layers).

The best material (or the best combination) depends on the radiation: the ideal shielding material for x and gamma radiation is lead or even heavier materials such as tungsten. In the case of beta emitters the use of heavy materials would cause the production of *Bremsstrahlung* radiation, therefore mixed screens are used consisting of a first layer of lighter material (for example polyethylene) followed by heavier materials to stop the x-radiation produced in any case.

Dose constraints must also be set in the design phase, which guarantee compliance with legal dose limits.

4 Conclusions

For the design and subsequent construction of facilities for the manufacturing of radiopharmaceuticals, also in the context of organizing a "complex" NM service, it is necessary to comply with the regulatory provisions and the standards for good practice applicable in this field, in order to ensure adequate conditions of safety and radiation protection for workers and the population. This way it is possible to pursue solutions that allow both the maximum organizational effectiveness of the activities and an adequate radiation protection strategy. With this aim in mind, some operational indications have been reviewed in the present work for the design stage, which should be useful to build a radiopharmacy laboratory, thus ensuring an efficient organization of human and technical resources and a constant condition of risk minimization.

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References

Decree of the Ministry of Health. 2005. Approvazione e pubblicazione del I supplemento alla XI edizione della Farmacopea ufficiale della Repubblica italiana. G.U. 168, 21/07/2005.

European Commission. 2008. EudraLex – Volume 4 – Good manufacturing practice guidelines. Brussels: European Commission.

IAEA. 2009. Technical reports series, No. 471 "Cyclotron produced radionuclides: guidelines for setting up a facility". Vienna: IAEA.

IAEA. 2010. Human health series, No. 11 "Planning a clinical PET centre". Vienna: IAEA

IAEA. 2018. Safety standards series, No. SSG-46 "Radiation protection and safety in medical uses of ionizing radiation". Vienna: IAEA.

ICRP Publication 57. 1989. Radiological protection of the worker in medicine and dentistry. *Ann. ICRP* 20(3). Oxford: Pergamon Press.

UNI 7496. 1975. Nuclear plants – Efficienty testing of particulate filters in ventilation ducts.

UNI 10491. 1995a. Criteria for construction of installations for handling of unsealed radioactive sources.

UNI 10339. 1995b. Air-conditioning systems for thermal comfort in buildings – General, classification and requirements – Offer, order and supply specifications.

UNI EN 1822-1. 2010. High efficiency air filters (EPA, HEPA and ULPA) – Part 1: classification, performance testing, marking.

UNI EN ISO 14644-1. 2016. Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration.

WHO. 2011. Technical report series, No. 961. Geneva: World Health Organization.

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