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AIR SYSTEM IN THE HOT CELL FOR INJECTABLE RADIOPHARMACEUTICAL PRODUCTION: REQUIREMENTS FOR PERSONNEL AND ENVIRONMENT SAFETY AND PROTECTION OF THE PRODUCT

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ABSTRACT

Radiopharmaceuticals are applied in Nuclear Medicine in diagnostic and therapeutic procedures and must be manufactured in accordance with the basic principles of Good Manufacturing Practices (GMP) for sterile pharmaceutical products. In order to prevent the uncontrolled spread of radioactive contamination, the processing of radioactive materials requires an exhausted and shielded special enclosure called hot cell. The quality of air inside the hot cell must be controlled in order to prevent the contamination of the product with particulate material or microorganisms. On the other hand, the hot cell must prevent external contamination with radioactive material. The aim of this work is to discuss the special requirements for hot cells taking in account the national rules for injectable pharmaceutical products and international standards available. Ventilation of radiopharmaceutical production facilities should meet the requirement to prevent the contamination of products and the exposure of working personnel to radioactivity. Positive pressure areas should be used to process sterile products. In general, any radioactivity should handle within specifically designed areas maintained under negative pressures. The production of sterile radioactive products should therefore be carried out under negative pressure surrounded by a positive pressure zone ensuring that appropriate air quality requirements are met. Some of the recent developments in the use of radioisotopes in medical field have also significantly impacted on the evolution of handling facilities. Application of pharmaceutical GMP requirements for air quality and processing conditions in the handling facilities of radioactive pharmaceuticals has led to significant improvements in the construction of isolator-like hot cells and clean rooms with HEPA filtered ventilation and air conditioning (HVAC) systems. Clean grade A (class 100) air quality hot cells are now available commercially, but in a high cost. Nevertheless, the application of clean room requirements in radioisotope laboratories in general and hot cells is technically not an easy task. The required negative pressure inside the hot cell depends on the operations to be performed inside the cell, on the type of radionuclide and their total activity. Hot cells works in negative pressure that ranges typically from 200 Pa to 500 Pa below room pressure. The new rules for radiopharmaceutical production will be soon published by ANVISA in order to regulate the GMP in this area. This make urgent the development of national models for hot cells that combines GMP and radioprotection concepts and attempt for the radiopharmaceutical process lines as in development at IPEN.

1. INTRODUCTION

Radiopharmaceutical or “radioactive drug” is a drug which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons. Radiopharmaceuticals are applied in Nuclear Medicine in diagnostic and therapeutic procedures. Diagnostic radiopharmaceuticals are used to image or otherwise identify an internal structure or disease process, while therapeutic radiopharmaceuticals are used to effect a change upon a targeted structure or disease process. The action of most radiopharmaceuticals is derived from two components: a nonradioactive delivery component (a carrier and/or ligand) and a radioactive component (a radionuclide). The ligands and

carriers direct the radionuclide to a specific body location or process, where the radionuclide component can be detected. The imaging component usually is a short-lived radioactive molecule that emits radioactive decay photons having sufficient energy to penetrate the tissue mass of the patient. The emitted photons are detected by specialized devices that generate images (nuclear medicine cameras, Single Photon Emission Computer Tomography – SPECT or Positron Emission Tomography-PET) or radiation detection probe devices.
Radioactive drugs may be administered orally, by inhalation and mainly by injection and must be manufactured in accordance with the basic principles of Good Manufacturing Practices (GMP) for sterile pharmaceutical products as recommended by the World Human Organization (WHO) [1].
Good Manufacturing Practices (GMPs) is a system designed to ensure that pharmaceuticals are consistently produced and controlled according to quality standards, with a view to eliminating the risks involved in drug production. The compliance of GMP is directed to minimize the risks presented in the pharmaceutical production that can not be detected with the analysis of the final product: cross-contamination, contamination with particulate material and change or mixture of products [2,3].
Because of their short half-lives, many radiopharmaceuticals are released and administered to patients shortly after their production, so that quality control (e.g. tests for sterility, endotoxin, radionuclide purity, etc) may sometimes be retrospective. The implementation and compliance with the quality assurance programme are therefore essential [4,5].
The GMP in Brazil is published in the Resolution RDC 210, August 04, 2003 by the National Sanitary Agency (ANVISA) of the Health Ministry [2]. This Resolution does not include any particular reference to radiopharmaceuticals. Recently, at the end of 2007, ANVISA proposed a special regulation for GMP applied to radiopharmaceutical production, that was not published yet (CP 94, 2007) [6].
In radiopharmaceutical production, special facilities are required to shield the radiation emitted and to prevent contamination of the environment by the radioactive materials released during handling and processing. In production laboratories the processed activities are high and therefore the requirements for shielded facilities with well-controlled ventilation and remote handling devices are greater [7].
In order to prevent the uncontrolled spread of radioactive contamination, the processing of radioactive materials requires an exhausted and shielded special enclosure called hot cell. Hot cells are arranged in the production laboratory in series, in blocks or individually with provision accessibility to maintenance. Control devices placed in the front of the hot cells serve for operating the technological equipment and measuring instruments [7].

The Energy and Nuclear Research Institute (IPEN-CNEN-SP) produces and distributes radiopharmaceuticals for more than 300 Nuclear Medicine services in Brazil. The installations for radiopharmaceutical productions at IPEN possess many dedicated hot cells, most of them developed and constructed at IPEN.
Hot cells can be considered as a containment enclosure applied in radiopharmaceutical production. The quality of air inside the hot cell must be controlled in order to prevent the contamination of the product with particulate material or microorganisms. On the other hand, the hot cell must prevent external contamination with radioactive material. So, the ventilation system in a hot cell must be developed in order to ensure (ISO 11933-4:2001) [8]:

- the enhancement of safety, by helping keep personnel and environment free from contamination;

- the protection of materials and handled products, indirectly contributing to safety, by keeping the internal atmosphere (temperature, humidity, physical/chemical composition) in a status compatible with their proposed use.

2. OBJECTIVE

The aim of this work is to discuss the special requirements for hot cells taking the national rules into account for injectable pharmaceutical products based on international requirements for standards available.

3. MATERIAL AND METHODS

- The discussion proposed in this study is based on the national and international rules for the production of injectable pharmaceuticals:
- Resolution RDC 210 by the National Sanitary Agency (ANVISA) About Good Manufacturing Practices (GMP) to radiopharmaceutical production [2].
- Draft of the resolution for GMP in radiopharmaceutical production (ANVISA) [6].
- Draft of the resolution for GMP for criticals and suggestions relative to Resolution RDC 210 (ANVISA) [9].
- WHO-World Health Organization- Good Manufacturing Practices for pharmaceutical production [3].
- This work also takes in account the contents of some ISO (the International Organization of Standardization) International Standards as follow:
- ISO 14644:2005 -Cleanrooms and Associated Controlled Environments [10].
- ISO 10648-1:1997-Containment Enclosures-Part 1:Design Principles [11].
- ISO 10648-2:1994 - Containment Enclosures-Part 2:Classification According to Leak Tightness and Associated Checking Methods [12].
- ISO 11933-4:2001 -Components for Containment Enclosures-Part 4:Ventilation and Gas-Cleaning Systems Such As Filters, Traps, Safety and Regulation Valves, Control and Protection Devices [8].
- NSF/ANSI 49-2008 - Biosafety Cabinetry: Design, Construction, Performance And Field Certification [13].

4. DISCUSSION

4.1. Manufacture of Sterile Medicinal Products

As a general principle of GMP, buildings must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories for the handling of radioactive materials must be specially designed to take into consideration aspects of radiation protection in addition to cleanliness and sterility [5].
Radioactive materials are produced typically in small batch sizes using materials in small quantities. Cross contamination should be prevented by the adoption of “closed systems” of manufacture, avoiding the manufacture of different products at the same place or even at the same time, unless they are effectively segregated [5].
As radioisotope handling facilities are generally big halls equipped with heavy machinery (e.g. cranes for lifting and transporting containers) which generate particles, and because the

target treatment includes several dirty mechanical operations (e.g. target crushing, cutting) as well as several target processing technologies requiring operations with acid addition and evaporation, powder treatment, high temperatures, etc, these operations should be separated from further processing (e.g. bulk dilution, adjustment of radioactive concentration, dispensing, autoclaving, packaging) to allow aseptic conditions to prevail [7].
Medicinal or medical products should be protected from microbiological contamination by their environment. As the direction of the potential microbiological contamination is from the environment and towards the material the ideal protection is to hinder movement of the surrounding air towards the product. This can be achieved by providing filtered airflow towards the product from the environment. Basically, such a system creates overpressure in the production area so clean rooms operate with positive pressure relative to the environment [7].
Ventilation of radiopharmaceutical production facilities should meet the requirement to prevent the contamination of products and the exposure of working personnel to radioactivity. Positive pressure areas should be used to process sterile products. In general, any radioactivity should be handle within specifically designed areas maintained under negative pressures. According to WHO recommendations, the production of sterile radioactive products should therefore be carried out under negative pressure surrounded by a positive pressure zone ensuring that appropriate air quality requirements are met [5].
Some of the recent developments in the use of radioisotopes in medical field have also significantly impacted on the evolution of handling facilities. Application of pharmaceutical good manufacturing practice (GMP) requirements for air quality and processing conditions in the handling facilities of radioactive pharmaceuticals has led to significant improvements in the construction of isolator-like hot cells and clean rooms with HEPA filtered ventilation and air conditioning (HVAC) systems. Clean grade A (class 100) air quality isolator-like hot cells compliant with GMP requirements for handling radiopharmaceuticals are now available commercially, but in a high coast. Nevertheless, the application of clean room requirements in radioisotope laboratories in general and hot cells in particular is technically not an easy task. [7].
Harmonized solutions for the aseptic processing of radioactive pharmaceuticals are:
- Placing conventional hot cells (with - ΔP) in clean rooms (with + ΔP) where exhausted hot cells are supplied with filtered air from the surrounding clean room.
- Using hot cells with own air flow control (supplied with filtered in/air and exhaust air systems), designed and operated as negative pressure isolators (- ΔP). Such hot cells must be airtight to avoid air sucking from the surrounding. These hot cells, with grade A or C depending on the type of product are recommended for radioactive materials similar to cytotoxic products in the conventional pharmaceutical industry [7].

Normally such conditions are provided by a laminar air flow workstation. Laminar airflow systems should provide a homogeneous air speed in a range of 0.36-0.54 m/s (guidance value) at the working position in open clean room applications. But in according RDC 210 ANVISA, the speed must be 0.45 m/s +/- 20 %.
The maintenance of laminarity should be demonstrated and validated. An unidirectional airflow and lower velocities may be used in closed isolators and glove boxes.
Clean rooms and clean air devices should be classified in accordance with EN ISO 14 644-1. The classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in following tables [10].

TABLE 1- Air Classification

Comparison Table in **"at rest"** occupancy state

Maximum permited number of particles per m^3 or ft^3 equal to or greater than the tabulated size											
ISO 14644-1			GMP (new:2008)			GMP (old: 2003)			FS 209D		
Class	(Part./m^3)		Grade	(Part./m^3)		Grade	(Part./m^3)		Class	(Part./m^3)	
	0.5µm	5.0µm		0.5µm	5.0µm		0.5µm	5.0µm		0.5µm	5.0µm
5&4.8*	**3 520**	***20**	**A**	**3 520**	***20**	**A**	**3 500**	**1**	**100**	**100**	**N.A.**
5	**3 520**	**29**	**B**	**3 520**	**29**	**B**	**3 500**	**1**	**100**	**100**	**N.A.**
7	**352 000**	**2 930**	**C**	**352 000**	**2 900**	**C**	**350 000**	**2 000**	**10 000**	**10 000**	**70**
8	**3 520 000**	**29 300**	**D**	**3 520 000**	**29 000**	**D**	**3 500 000**	**20 000**	**100 000**	**100 000**	**700**

* For Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥5.0µm.

Comparison Table in **"in operation"** occupancy state

Maximum permited number of particles per m^3 or ft^3 equal to or greater than the tabulated size											
ISO 14644-1			GMP (new:2008)			GMP (old: 2003)			FS 209D		
Class	(Part./m^3)		Grade	(Part./m^3)		Grade	(Part./m^3)		Class	(Part./m^3)	
	0.5µm	5.0µm		0.5µm	5.0µm		0.5µm	5.0µm		0.5µm	5.0µm
5&4.8*	**3 520**	***20**	**A**	**3 520**	***20**	**A**	**3 500**	**1**	**100**	**100**	**N.A.**
7	**352 000**	**2930**	**B**	**352 000**	**2 900**	**B**	**350 000**	**2.000**	**10 000**	**10 000**	**70**
8	**3 520 000**	**29300**	**C**	**3 520 000**	**29 000**	**C**	**3 500 000**	**20.000**	**100 000**	**100 000**	**700**
/	/	/	**D**	Not defined	Not defined	**D**	Not defined	Not defined	/	/	/

* For Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥5.0µm.

For classification purposes in Grade A zones, a minimum sample volume of 1 m³ should be taken per sample location. For Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥ 5.0 µm. For Grade B (at rest) the airborne particle classification is ISO 5 for both considered particle sizes (Table 1).
Cleaning and sanitation are important preparations to provide aseptic conditions for production. However, hot cells generally cannot be opened regularly for cleaning. Although, effective sanitation agents and decontamination agents are available, there is no easy-to-use applicator, unless hydrogen peroxide spraying head is installed. In the absence of hydrogen peroxide, isopropyl or ethyl alcohol may be generally applied onto the surfaces. The efficiency of cleaning and sanitation methods need to be validated [7].

4.2. About negative pressure level into the HOT CELLS

The hot cells constructed for the production of radioactive pharmaceuticals need to meet the requirements for a negative pressure isolator. The hot cells should be tight fitting taking into account the international technical standard. The walls of the hot cells should be smooth, impervious and unbroken and the corners should be curved. The installation of permanent components, which cannot be sufficiently cleaned, should be avoided [7,11,12,13].
Stainless steel and organic glass are recommended as construction materials. The stainless steel surface inside the hot cell should be polished. The hot cells need to meet the general recommendations for rooms according to the GMP regulation [7,11,12,13].
There is a specific normative document (ISO 11933-4:2001) that considers the negative pressure level into the hot cells and specifies the characteristics of various components used

for ventilation and gas-cleaning in the containment enclosures such as filters, traps, safety and regulation valves, control and protection devices [8].
As described in ISO 11933-4:2001, the role of ventilation in containment is to [8]:

- Contain and protect the operator against the radioactive contamination.
- Protect the radiopharmaceutical sterility from the external environment.

For handling of radioactive products, the enclosure is required to be at a negative pressure in relation to the room. The required negative pressure inside the hot cell depends on the operations to be performed, on the type of radionuclide and their total activity manipulated inside the cell.
The negative pressure is expressed in Pascals (Pa) or decaPascals (daPa). Shielded isolators (hot cells) work in negative pressure that ranges typically from 200 Pa to 500 Pa below room pressure. This requirement is coming from the radiation safety provisions that a typical cell should provide, to minimize the risk of sucking external air (and particles) in the case of a leak in hot cell.

So, the first test that must be done is to ensure the classification according to leak tightness and associated checking methods.
The ventilation system act dynamically in order to determine a negative pressure gradient between different containment enclosures and between the enclosure and the external ambient.
In this pressure gradient the diffusion of the air through efficient filters prevents contamination. The quality of the air can be continuous by monitored.
Finally, after the commissioning of all the system, must be qualified and the production process must be validated. The ANVISA foresee in the public consult No 94, a draft guidance for quality assurance in radiopharmaceutical production, item 8 - Guarantee of the Quality and Control of the Quality: “To assure that the monitoring of the environment, the qualification of the equipment and the validation of the processes are lead in appropriate way, in order to allow the evaluation of the adequacy of the manufacture conditions”.

5. CONCLUSIONS

Some special considerations must be done in the project of a hot cell for radiopharmaceutical production to ensure the enhancement of personnel and environment safety as well as the protection of materials and handled products.
Although GMP hot cell are available in the international market, the final cost is very high. Another fact that must be considered is that these hot cells generally are not in agreement with the production process and production scale of radiopharmaceuticals at IPEN and must be adapted. This fact contributes to increase the final cost of the hot cell.
The new rules for radiopharmaceutical production will be soon published by ANVISA in order to regulate the GMP in this area. This make urgent the development of national models for hot cells that combines GMP and radioprotection concepts and attempt for the radiopharmaceutical process lines as in development at IPEN. This study discussed the principal factors involved in the hot cell conception and represents a punctual contribution for the development of this important area in Brazil.

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