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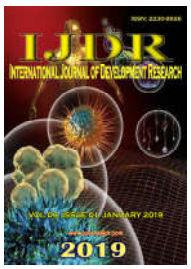

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

A PROPOSAL FOR INSTALLATION, OPERATIcON, AND PERFORMANCE QUALIFICATION PROTOCOL FOR HOT CELLS FOR RADIOPHARMACEUTICALS PRODUCTION

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ABSTRACT

Background: According to the International Organization for Standardization (ISO), "quality assurance" is an all planned and systematic set of actions that are necessary to guarantee that a product or service will satisfy the requirements as to quality. As such, it is comprehensive and covers all relevant procedures, activities, and actions. This article aims to present a proposal for a checklist to be performed in the installation, operation and performance qualification for hotcells in agreement with the relevant standards recommendations. **Methods:** The checklist was applied during the installation of a hot cell in a cyclotron facility in Brazil. It was done a compilation of different guidelines for the qualification of hot cells proposing a comprehensive list of aspects to be verified during their installation, operation, and performance in a cyclotron facility, which is useful worldwide. **Results**: During the test, it was possible to identify unappropriated conditions in operation and performance qualification, allowing the team to take actions and make adjustments before acceptation and full use of the hot cell. **Conclusion:** The use of the proposed questionnaire during the installation of the hot cell can be applied worldwide, allowed us to spot the problems and solve them, shortening the equipment approval time for use in the routine production of sterile positron emitting radiopharmaceuticals for human use.

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INTRODUCTION

Until the early 1980s, around 90% of the radiopharmaceuticals used in diagnostics were technetium-99m (^{99m}Tc) complexes, prepared at nuclear medicine departments from lyophilized cold kits and ^{99}Mo/^{99m}Tc generators. The remaining 10% were mainly ^{67}Ga, ^{111}In, and ^{201}Tl compounds, produced by a few nuclear companies and distributed around the world. Still, during the 1980s, this scenario started to change due to an increase in radioisotopes production in cyclotrons as well as the correspondent ^{11}C and ^{18}F radiopharmaceuticals. Some Universities were the first to produce the compounds in cyclotrons, mainly for research purposes. However, some compounds like Fludeoxyglucose (^{18}F-FDG) proved to be cost-effective, and the companies started to operate cyclotron facilities to produce Positron Emission Tomography (PET) radiopharmaceuticals and new rules for good manufacturing practices (GMP), and radiation protection was established (ANVISA, 2010). The main changes observed in radiopharmaceuticals production were the adequacy of the installations – to attend pharmaceuticals production rules – and the development of commercial hot cells and synthesis modules, instead of the homemade equipment. Still, during the 1980s, the hot cells used were made from lead blocks – piled one over the other and covered at the top with a gas extractor, like a fume hood – to protect workers from radiation (Schubiger *et al*., 2007). Thus, they could be easily rebuilt in the laboratories to cope with new equipment, methodologies or processes. However, when PET radiopharmaceuticals started to be produced under pharmaceutical regulations, it became necessary to apply procedures and to use equipment to protect the materials being manufactured, avoiding injecting patients

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with biologically contaminated products (IAEA, 2004). The basic requirements were established such as the cell dimensions that must be compatible with the work to be done, allowing enough room inside for synthesis modules, liquid chromatography modules, heating plates, peristaltic pumps, a pneumatic system for lifting, etc; the system must be sealed to avoid contamination from the external environment allowing the preparation of injectable products as well as external contamination or radioactive exposition from internal sources keeping the occupational radiation dose limits within the values set by the national regulatory agencies (CNEN, 2011); the lead thickness must be calculated considering the type, the energy and activity of the radioisotope to be handled; whenever possible, the packaging of dose calibrators, waste containers - among other devices - beneath the handling area of the cell to maintain the area clear and facilitate handling, regarding a specific shielding configuration, must be considered; and, finally, the doors need to be equipped with interlocks to avoid opening during the operation, reducing the risk of exposure and contamination of workers and the radiopharmaceutical produced.

The hot cells aforementioned are usually made of carbon steel, covered with stainless steel, with smooth walls, waterproof, with uninterrupted and rounded corners to provide easy decontamination and aseptic conditions, which are the basic requirements for GMP. The hot cell operations are conducted through one of its largest faces using handlers. It usually has a door allowing access for maintenance and cleaning purposes. Due to radiation protection and GMP, hot cells should be installed in positive pressure rooms (+ΔP) whereas pressure within the cells should be negative (-ΔP), maintaining the surroundings within the standards established for the production of injectable drugs. The exhaustion system from hot cells and the room must use the same duct to the treatment systems or retention of radioactive effluents. The hot cells must have their air flow control (with filtered in air and exhaust air system), assurance of at least 20 cycles per hour and an average incoming air velocity of 0.5 m/s (ANVISA, 2010; CNEN, 2013; IAEA, 2012) for systems operating in dynamic mode. In Brazil, the production and handling of radioactive materials have been regulated by the National Nuclear Energy Commission (CNEN) since 1956 (EMC–56, 2007).

However, radiopharmaceuticals production started to be regulated by the National Health Surveillance Agency (ANVISA) only in 2009 (ANVISAa ,2011; ANVISAb, 2011), through regulations covering general aspects of production as well as aspects of product registration rules, some specificities of material quality, their use, and rules for generic pharmaceutical production (EMC–49, 2006). Therefore, there is a relevant need for the qualification of the equipment involved, considering the specificity of each device. However, at this moment, there are no purely national standards establishing the requirements for the installation, operation and performance qualification of equipment, like hot cells (ANVISAa ,2011; ANVISAb, 2011). A mixture of some national standards, literature recommendations, and manufacturer instructions is, usually, applied. The research reported in this paper is related to the compilation of different guidelines for the qualification of hot cells proposing a comprehensive list of aspects to be verified during their installation, operation, and performance in a cyclotron facility. We believe that the guidelines presented are useful worldwide.

MATERIALS AND METHODS

To perform the qualification procedures the following equipment and materials were used:

- A 10.8 Ci source produced in a Cyclotron GE PETtrace 860 with maximum proton energy of 16.5 MeV, maximum single beam current of 75 μA, and a maximum dual beam current of 100 μA;
- Hot cell BBS2 from *Costruzioni Meccaniche Certificate* (Comecer);
- Dose rate monitor: Geiger-Muller (Radalert 100);
- Standard radioactive source of ^{137}Cs with an activity of 6.77 MBq (183 μCi).
- A private company with certified equipment and standard material was contracted to perform the test of particles count.

A. Installation Qualification (IQ): For IQ eight questions were established as the minimum requirement to verify if the area and facilities were in agreement with the manufacturer specifications for installation of the hot cell. All questions are from the hot cell manufacturer requirements, but questions a.3 and a.4 attend the national requirements or local needs.

a.1 Regarding the area designed for the installation of the hot cell, has any building work being finished and is it clean?
a.2 Are the area dimensions following the recommendations of the manufacturer?
a.3 Is the area adequate to receive and store boxes containing hot cell parts?
a.4 Is there any appropriate equipment to move hot cell parts from storage to the production laboratory?
a.5 Is the infrastructure for special gases and electrical mains prepared/installed according to the manufacturer's specifications?
a.6 Is the electric current stable enough for the installation to be fully operational?
a.7 Has the exhaust system been properly installed?
a.8 In case of a radioactive gases leakage, is the monitoring system working properly?
a.9 Are both room temperature and humidity in agreement with the specifications?
a.10 Is there any non-compliance with the project?
a.11 Is there any of the specifications by the manufacturer that has not been fulfilled?

B. Operation Qualification (OQ): Once the installation of the hot cell is over, it is necessary to check the operational conditions of the equipment. At least nineteen questions need to be addressed for safety and proper work with this equipment. These questions are necessary to fulfill the requirements of the manufacturer, CNEN, ANVISA and those established by us.

b.1 Was the hot cell installed properly?
b.2 Is there any visually perceptible abnormality?
b.3 Is the positioning of the equipment and devices suitable?
b.4 Were all the labels and warning signs placed correctly?
b.5 Have the starters and controllers been identified?
b.6 Are the signs and identification in the local language?
b.7 Is the door opening and closure appropriate?
b.8 Are the visual alarms working?
b.9 Are the shutdown emergency systems fully operational?

b.10 Have the radiation monitoring systems been properly installed?
b.11 Do the radiation monitoring control systems work correctly?
b.12 Is the exhaust system working properly?
b.13 Is the exhaust control working properly?
b.14 Is the internal cell manometer adequate and working?
b.15 Are the cell shield material and thickness suitable, by the design and practice to be performed?
b.16 Were all the interlocks installed and tested?
b.17 Was the filter system installed properly?
b.18 Is there any manufacturer's specification which was not accomplished?
b.19 Does the cell finishing meet the GMP and the radiation protection requirements?

Questions b.1 to b.3 and b.14 to b19 were proposed exclusively by us; questions b.4 to b.6 are necessary to attend ANVISA as well as our requirements; questions b.7 to b.8, are from the manufacturer and the CNEN requirements; whereas questions b.9 to b.13 are CNEN only requirements. Protocols for the tests are described in the manufacturer´s manual or national standards.

C. Performance Qualification (PQ): The PQ procedure ratifies that the equipment fulfills all the requirements necessary for the intended use. In this case, the equipment authentication is performed by analyzing the accuracy of the results, which were previously determined in compliance with the manufacturer's manual, and with the international and national standards. The following questions were established for PQ:

c.1 Are the cell material and the thickness of the shielding built suitable for the practice to be performed?
c.2 Is the exhaust interlock efficient?
c.3 Is the door opening interlock working?
c.4 Do the manipulator devices (if there is any) work properly?
c.5 Is there any indication of structural damage to the filters (visual inspection)?
c.6 Do the filters have the same absorption capacity, as described by the manufacturer?
c.7 Was the cell approved for the air flow, inlet, and outlet airspeed tests?
c.8 Was the hot cell approved in the air quality classification test?
c.9 Did the hot cell pass the radiometric survey test?
c.10 Are there radiation leakage points in the hot cell?
c.11 Is there any non-compliance with the project?
c.12 Is there any specification by the manufacturer that has not been fulfilled?

We proposed questions c.1, c.2, c.11 and c.12; questions c.3 and c.4 are requirements established by the manufacturer and by us; questions c.5 and c.8 to c.10 are CNEN requirements, and questions c.6 and c.7 fulfill CNEN and ANVISA requirements. PQ was carried out under real operational conditions. A sample of 10.8 Ci of ^{18}F-FDG was introduced inside the hot cell at positions C (Figure 1) to verify the radiation shielding. At the end of the Qualification process, a general report was produced, containing all the results concerning the IQ, OQ, and PQ, plus all the standard certificates used as well as any event that occurred. It is important to consider that the manufacturer technician under the supervision of customer staff can perform the Installation and Operation Qualification; whereas, experts or private companies, rather than the manufacturer, with traceable standards, must do part of the Performance Qualification, ensuring high-quality performance and a reliable process.

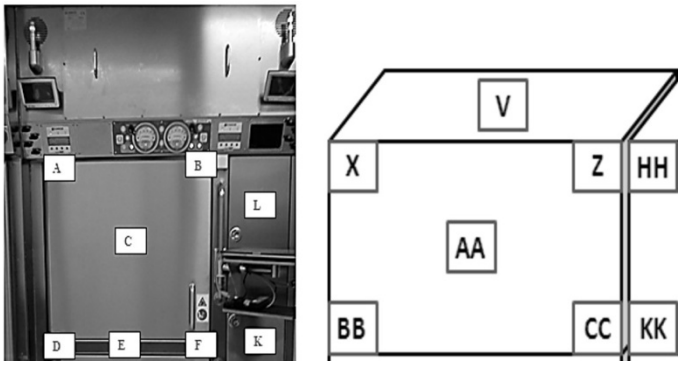

Figure 1. Locations where the dosimetric screening was carried out in the hot cell, considering the manipulation room. The letters show the monitoring points

RESULTS AND DISCUSSION

Our objective was to propose a set of questions to be addressed when carrying out Installation, Operation and Performance Qualification of a hot cell in cyclotron facilities or other sites where high doses of radionuclides for radiopharmaceutical production or research are manipulated. Although sometimes IQ is considered of minor importance, some questions need to be considered before acquiring a hot cell, mainly regarding room and door size when taking the equipment in and the structure of the floor, which will have to support some tons/m^2. Before applying this questionnaire in the cyclotron facility as IQ, the site needs to be well planned and constructed to attend all the requirements from the radiopharmaceutical sector so that unexpected events did not take place when carrying out the IQ. With this step concluded, the installation of the hot cell was authorized. After installation, an OQ questionnaire was applied. It helped in detecting an unconformity for item a.3, that is, the outsourced gas service was connected to the main valve, but the technician from the manufacturer had not connected the hot cell gas tubing to the valve. The cyclotron staff quickly fixed this unconformity. All other requirements were met adequately, and PQ then started.

The PQ was carried out in two steps: first, the functioning conditions of the filter system and quality of the air inside of the hot cell were checked. A specialized company performed the tests in agreement with ANVISA regulations. The system performance is presented in Table 1, and all values were within limits established by ANVISA and in agreement with hot cell manufacturer´s specifications. According to the classification ISO 7 - less than 3.52 x 10^5 particles with a maximum size of 0.1 µm, 8.32 x 10^4 particles with a maximum size of 1 µm, and 2.9 3x 10^3 particles with a maximum size of 5 µm - means approved for production of injectable products. Those data are equivalent to the class 100/1.000/10.000 of the ABNT NBR ISO 14644 (ABNT, 2005). A radiometric survey was performed with a dose rate meter positioned as indicated in Figure 1. A source containing 10.8 Ci of ^{18}F-FDG (the maximum activity planned to be used into the hotcell) was positioned at the cave indicated as C.

Table 1. Laminar flow performance qualification

Air velocity (m/s)	Filter Differential Pressure (Pa)	Class 2	Classification
0.47 ± 0.06	171	$T_f = 1.15 \cdot 10^{-3}$	ISO 7

Table 2. Results from the radiometric survey, considering fixation of 10.8 Ci of into de cave at position C.

Monitoring Points		Dose rate (μSv/h)	
A	V	0.5	4.5
B	X	1.9	1.3
C	Z	0.7	1.3
D	AA	5.2	0.5
E	BB	1.1	1.3
F	CC	0.8	1.2
K	HH	2.0	2.0
L	KK	0.2	1.0
Transfer channel		1100	

However, the radiation interlock using the standard radioactive source of ^{137}Cs was tested beforehand. The acceptable limit for this test is 5 mSv/year, with an occupancy factor of 0.5 for the manipulation room and 0.125 for the maintenance area, corresponding to values of 4.8 μSv/h and 19.2 μSv/h, respectively. The measurements are presented in Table 2, subtracting the background in the room (0.3 μSv/h), which had been measured without any radioactive source in the room. The values for all locations were within limits, except for position D. Nonetheless, the difference to the limit is within the uncertainty of the Geiger-Muller. The compilation of requirements established by the hot cell manufacturer and those prescribed by the regulatory authorities in Brazil (CNEN and ANVISA) allowed de addressing of key questions during hot cell Installation, Operation, and Performance Qualification processes. The use of the proposed questionnaire during the installation of the hot cell that can be applied worldwide, also allowed us to spot the problems promptly and quickly solve them, thus shortening the equipment approval time for use in the routine production of sterile positron emitting radiopharmaceuticals for human use.

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