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QUALIFICATION OF DESIGN (DQ) AND INSTALLATION (IQ) OF CYCLOTRONS FOR RADIOPHARMACEUTICALS PRODUCTION

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ABSTRACT

The rapid increase of radiopharmaceutical units in Brazil after the monopoly flexibilization in 2006, together with the requirements of the National Nuclear Energy Commission (CNEN) and the National Agency of Sanitary Surveillance (ANVISA), have raised the need for a proposal of Design (DQ) and Installation (IQ) Qualification for Cyclotrons by applicable national standards, manufacturer's guide and international literature recommendations. The objective of this study was to present a proposal for the DQ and IQ for low and medium energy cyclotrons according to national standards and international recommendations. Our proposal was evaluated for two facilities that underwent the referred qualification requirements. We showed that our methodology fits the needs of national regulations and international recommendations for the evaluated cyclotrons in these qualifications. Indeed, our proposal will support new facilities in Brazil and worldwide to evaluate their cyclotron during the design and installation process.

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INTRODUCTION

In the early 1940s, the cyclotrons were already used in the production of radioisotopes and studies of the structure of matter and degradation of materials (1). Cyclotrons were pivotal in uranium research, building nuclear reactors, and, unfortunately, the atomic bomb (2). However, with the advent of nuclear reactors, cyclotrons remained confined to academic institutions, reaching only 17 units around the world until the 1970s. As the radioisotope productions were made exclusively for medical purposes, the number of cyclotrons in the world increased significantly, mainly in Europe and the United States, surpassing the number of 350 cyclotrons in 2006. Nowadays, there is a high demand for cyclotrons worldwide to produce radioisotopes for medical purposes, i.e., nuclear medicine (3), aiming both SPECT (single photon emission computed tomography) and PET (positron emission tomography) (4). Currently, the radioisotopes of interest for PET are those that allow the labeling of biomarkers, antibodies, molecules, nanoparticles, among others (5). Notably, the clinical demand is compounds labeled with ^{11}C, ^{15}O, ^{13}N, ^{68}Ga, and, mainly, with the radioisotope $^{18}F^-$. The dependency of nuclear medicine on the radioisotopes produced by cyclotrons makes the underlying methodologies extremely necessary to assure the high quality needed for medical application, mainly, in the initial phases, such as design and installation. The objective of this study was to propose methods for (DQ) and (IQ) of low- and medium-energy cyclotrons according to national standards and international recommendations.

MATERIAL AND METHODS

Our proposal was concepted on the evaluation of two cyclotron facilities which underwent the steps of design and installation:

- Cyclotron PETtrace 860 (GE Healthcare, Uppsala) with maximum proton energy of 16.5 MeV, maximum beam current of 75 μA in single beam and 100 μA in dual beam, capable of producing 10 Ci of ^{18}F- in 2 hours of irradiation;

Target: Gen II niobium (GE Healthcare, Uppsala);

- Cyclotron PETtrace 880 (GE Healthcare, Uppsala) with maximum proton energy of 16.5 MeV, maximum beam current of 75μA per beam and 130 μA in dual beam, capable of producing 14,5 Ci of ^{18}F- in 2 hours of irradiation;

Target: Gen II niobium (GE Healthcare, Uppsala);

The materials below were used in the evaluation and verification of the cyclotrons:

- Enriched water (^{18}O 98% purity) for nuclear reactions ^{18}O (p,n)^{18}F.
- Hydrogen gas (> 99,95% Purity) for proton beam and
- Helium gas (> 99,95% Purity).

Design Qualification (DQ): The DQ demonstrates that the equipment to be purchased is in accordance with the specifications created by the user and good manufacture production (GMP) standards. The DQ verifies that the proposed design for the facility, system and equipment are suitable for the intended purpose.

We proposed the following question guide for qualifying the cyclotron design:

1. Is the place suitable for receiving the equipment?
2. Are the dimensions of the site according to the manufacturer's recommendations?
3. Was the floor prepared according to the manufacturer's specifications?
4. Was the shielding of aqueous boron solution, concrete shielding or vault chamber adequately prepared for the cyclotron?
   a. In this study the shielding of both cyclotrons was verified with radiometric survey and according to the manufacturer's specification (*6,7*).
5. Have the gas points been prepared/installed according to the manufacturer's specifications?
6. Was the power grid monitored?
7. Does the power supply show any instability higher than recommended for machine operation?
8. Was the water cooling system installed according to the manufacturer's recommendation?
9. Was the radiological system installed?
10. Has the design qualification protocol been finalized?

If the above requirements have been achieved, the accelerator is eligible for the next qualification step as the operation and performance qualification.

Installation Qualification (IQ): The purpose here is to ensure that the installation procedure meets the requirements recommended by the manufacturer.

We proposed the following question guide for qualifying the cyclotron installation:

1. Is there any non-compliance with the project?
2. Is there any need for manufacturer's specifications that have not been met?
3. Have the equipment's master files (equipment manual, software, maintenance manual, among others) been delivered as specified?
4. Have the components and accessories of this equipment been shipped as specified?
5. Have all security and alarm systems on the equipment been delivered in a way that allows the equipment to function correctly and safely?
6. Is the equipment compatible with the purchase order, including software, components and accessories?
7. Does the equipment show any damage to its structure?
8. Are the electrical modules of the equipment correctly working when connected to the power source?
9. Have the software been installed on the processing units and worked correctly?
10. Have the peripheral components (printer, secondary modules, no breaks, etc…) been installed?
11. Has a list containing a description of all equipment components and accessories been drawn up?
12. Was a logbook created for this equipment and was its installation recorded?
13. Has the installation qualification protocol been finalized?

If the above requirements have been achieved, the accelerator is eligible for the next qualification step.

RESULTS

Design Qualification

The Table 1 shows the results obtained from the Design Qualifications (DQ) for both cyclotrons:

Installation Qualification

The Table 2 shows the results obtained from the Installation Qualifications (DQ) for both cyclotrons:

DISCUSSION

In this study we proposed a guide, developed within national and international standards for evaluating the design and installation of low and medium energy cyclotrons dedicated to the radioisotope production. This methodology was evaluated using two cyclotrons from different facilities in Brazil. The cyclotrons that underwent our evaluation were the PETtrace 860 and PETtrace 880. In the DQ and IQ step for both cyclotrons all questions were fulfilled. The radiometric survey did not show values above the advocated by national (CNEN) and international standards (IAEA) under normal operation conditions.

Table 1. Results of Design Qualification (DQ) for cyclotron PETTrace 860 and PETtrace 880

Questions	Results for both Cyclotrons
Is the place suitable for receiving the equipment?	Yes
Are the dimensions of the site according to the manufacturer's recommendations?	Yes
Was the floor prepared according to the manufacturer's specifications?	Yes
Was the shielding of aqueous boron solution, concrete shielding or vault chamber adequately prepared for the cyclotron?	Yes. The radiometric survey performed in the bunker of one of the cyclotrons of this study showed radiation levels below 2μSv/h under normal operating conditions. We didn't measure exposure levels higher than advocated by national and international standards in the radiometric survey around water shielding under irradiation conditions of 40 μA in the ^{18}O target for $^{18}F^-$ production.
Have the gas points been prepared/installed according to the manufacturer's specifications?	Yes
Was the power grid monitored?	Yes
Does the power supply show any instability higher than recommended for machine operation?	Yes. We measured 7% of instability. However 5% is the limit of manufactures specifications. A capacitor was installed in the electrical cabin to solve this problem. This problem was observed in the two installations evaluated.
Was the water cooling system installed according to the manufacturer's recommendation?	Yes.
Was the radiological system installed?	Yes.
Has the design qualification protocol been finalized?	Yes.

Table 2. Results of Installation Qualification (DQ) for cyclotron PETTrace 860 and PETtrace 880

Questions	Results for both Cyclotrons
Is there any non-compliance with the project?	No.
Is there any need for manufacturer's specifications that have not been met?	No.
Have the equipment's master files (equipment manual, software, maintenance manual, among others) been delivered as specified?	Yes.
Have the components and accessories of this equipment been shipped as specified?	Yes.
Have all security and alarm systems on the equipment been delivered in a way that allows the equipment to function correctly and safely?	Yes.
Is the equipment compatible with the purchase order, including software, components and accessories?	Yes.
Does the equipment show any damage to its structure?	No.
Are the electrical modules of the equipment correctly working when connected to the power source?	Yes.
Have the software been installed on the processing units and work, correctly?	Yes.
Have the peripheral components (printer, secondary modules, no breaks, etc…) been installed?	Yes.
Has a list containing a description of all equipment components and accessories been drawn up?	Yes.
Was a logbook created for this equipment and was its installation recorded?	Yes.
Has the installation qualification protocol been finalized?	Yes.

We measured 7% of instability of the electrical grid. However, 5% is the limit of manufactures specifications. A capacitor was installed in the electrical cabin to solve this problem. This problem was observed in the two installations evaluated.

Conclusion

We proposed a methodology for qualification of design and installation of low and medium-energy cyclotron for radioisotope production. In our study, two cyclotrons with five and ten years of operation in Brazil underwent our approach. The methodology did not fail to contemplate any situations due to the experience of these facilities. Therefore the guide for DQ and IQ has proved to be effective by national regulations and international recommendations for the evaluated cyclotrons. Therefore, the qualification proposal is effective and it will certainly support new facilities in Brazil and worldwide to evaluate their cyclotrons.

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