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SCIENTIFIC REVIEW

Radiopharmaceuticals Industry Based On the Brazilian Regulations

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Summary

The present work is concerned with all requirements recommended by the Brazilian Good Manufacturing Practices for Pharmaceuticals and Occupational Safety and Health Regulations required for Health Services. Due the fact that Brazilian regulations are not specific to radiopharmaceutical production, the facility presented in this work will provide a national standard in this area. This facility is intended to produce radiopharmaceuticals completely capable of being certified under the most rigorous worldwide standards. The most important aspects and requirements of air quality control, radiation protection, cleaning rooms, personnel and Quality Assurance are covered in this work to create a prototype of an installation that is capable of producing radiopharmaceuticals for use in state-of-art diagnostic procedures.

Key Words: *Civil engineering, radiopharmaceutical industry, layout, design, PET radiopharmaceuticals.*

Radyofarmasötik Endüstrisinde Brezilya'da Uygulanan Yasal Düzenlemeler

Özet

Bu derlemede, Brezilya'da ilaçlar için İyi Üretim Uygulamaları ve Sağlık Hizmetleri için İş Güvenliği ve Sağlık Düzenlemelerince gereken koşullardan bahsedilecektir. Brezilya'nın radyofarmasötik üretimi için özel yönetmelik ve kuralları olmadığı için, bu çalışmada sunulan tesis, bu alan için ulusal standartları karşılamaktadır. Bu tesis dünyaca kabul edilmiş, çok kesin standartlarla sertifikalanan/ ruhsatlanan radyofarmasötikleri üretmeyi amaçlamaktadır. En son teknoloji teşhis yöntemlerinde kullanılacak radyofarmasötikleri üretebilecek bir model tesis yaratmak için hava kalite kontrolü, radyasyondan korunma, temiz odalar, personel ve kalite güvencesi ile ilgili en önemli noktalar ve karşılanması gereken koşullar bu çalışmanın kapsamındadır.

Anahtar kelimeler: *İnşaat mühendisliği, radyofamasotik endustrisi, plan, tasarım, PET radyofarmasötikler*

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INTRODUCTION

Radiopharmacy is scientifically recognized as a branch of the pharmacy profession that gives service to nuclear medicine. Without radiopharmaceuticals, the "food" of nuclear medicine, no radiodiagnostic or radiotherapeutic procedures could be performed, and without progress in radiopharmacy, this medical speciality would ultimately wither and die. The radiopharmaceuticals used around the world are essentially the same, with some minor differences (1,2).

Radiopharmaceuticals are used for two purposes; the first and most important is as a traceable compound administered to a patient to observe physiologic alterations or abnormal distribution in the body (diagnosis); the second is as a compound for therapeutic action in clinical medicine (3). The practices of nuclear medicine and radiopharmacy require the preparation of radioactive drugs for injection into patients (4).

Radiopharmaceuticals have a very special role to play in research. In a noninvasive manner, radiopharmaceuticals may be used to produce kinetic information on a drug and metabolite and to enhance our knowledge of human pathology, pathophysiology or biochemistry, while respecting the health and safety of the human subject. Radioactive tracers are playing an increasingly important role in the study of drug formulation and drug delivery systems, ranging from the discovery of new drugs to the in vivo evaluation of drug delivery in humans(5).

Although radiopharmaceuticals have been produced in Brazil for over 50 years, only in 2006 the first steps in regulation were taken in Brazil. The results of these steps created the Brazilian Regulation on Radiopharmaceuticals Production. This regulation was inserted in the RDC 210/03 (the GMP legislation for pharmaceuticals in Brazil) as an addendum. However, no single comment was made regarding the construction aspects.

In this direction all national and international regulation guidelines were searched and analyzed to create the most modern PET radiopharmaceuticals facility in Brazil. The PET industry was established following the recommendations concerning this specification (PET radiopharmaceuticals).

In this study, we discuss the main questions raised in our project and the regulations and specifications that should be prepared to produce safe and effective radiopharmaceuticals.

ACCOMODATION

The production of PET radiopharmaceuticals has some peculiarities and involves two basic aspects: radiation protection and the aseptic condition of the workplace. Working with PET radiopharmaceuticals is potentially dangerous and subject to radioactivity-related rules. The risk level depends particularly on the type of radiation emitted and the half-life of the radioisotope used. Special attention must be given to the risk of cross-contamination, as well as the wastes created at the end of each production5. Radiopharmaceuticals have two components, a radioactive part and a pharmaceutical part. Therefore, they have to fulfill the quality specifications for both the radioactive part (radionuclidic purity, radiochemical purity, radioassay, etc.) and the pharmaceutical part (pH, organoleptic properties, sterility, apirogenity, chemical purity, dosage related properties, etc.) These quality control tests are necessary for finished radiopharmaceutical products before the licensing of the finished product can be obtained. In addition, another license is necessary for the production area. For this reason, the production environment and quality control must be classified as to what is made using laminar flow and HEPA (high efficiency particulate air) filters, beyond procedures of adequate cleanliness and sterilization (6,7). Due to the importance of these conditions for the patients and quality of the final product, a design based on the clean-room concept is fundamental for engineers and researchers.

The first stage in planning was to identify the functions and scope of operation. The radiopharmaceutical production lab has to have a special layout attested by the National Nuclear Energy Commission and the entrance to the production area has to be forbidden except for the authorized staff. The engineers

decided to locate all services within the roof and the basement in such a way that maintenance staff would not have to enter the laboratory areas. The routes for staff and materials were designed to have a unique and different flow in order to respect the Brazilian regulation, Resolution 210/03 of the National Health Surveillance Agency (RDC210/03) and to minimize cross-contamination8. In addition, a separate delivery entrance with a packaging (dispatch) area and bulk storage beside it was decided to be used.

The production area and quality assurance area were completely separated. Entry could only be made through a single access point. That access was made using doors with air locks that maintained air pressure and an advanced system of permission levels. This allowed only the regular laboratory staff to have access.

To minimize or lessen claustrophobic reactions on the part of staff personnel, glazed panels in internal walls were utilized wherever possible. In the production area the glazed panels were made with a special type of glass having a high concentration of lead to avoid radioactive cross-contamination in case of an accident with the radioactive material.

The production of radiopharmaceutical materials has pharmaceutical and radioactivity requirements that differ from traditional pharmaceutical production. To fulfill all the radiation protection aspects, a number of precautions were taken. All laboratory doors were made of lead. A high-security system against intruders was installed. The building was divided into two inner areas using card-operated electronic doors with an access system, so that staff would not be required to carry a large number of keys, and that this type of entrance control is more effective. Within the laboratory area, all external windows are non-opening and are fitted with passive infrared intruder detectors.

The non-laboratory or administrative area was made using the same system. It was connected by one door to the laboratory area. This connecting door, similar to the other laboratory entrance, used an electronic entry system, permitting only laboratory staff to pass. The resulting floor plan is shown in Figure 1.

SHIELDING

Extremity doses are often high enough to warrant that an individual be designated a classified radiation worker. Any worker who receives or is likely to receive $3/10^{th}$s of any dose limit should be classified. The dose limit applied to the extremities and to the skin is 500 mSv. In addition, under the ionising radiations regulations (IRR 99) (10) this dose limit is applied to the most exposed 1 cm^2 of skin; this was a change from previous legislation where the dose to the skin could be averaged over 100 cm^2. Radiopharmaceuticals are prepared in a radionuclide dispensary and are then administered to patients for a variety of diagnostic procedures in nuclear medicine departments. Dispensaries may serve one or several nuclear medicine departments. Doses to the hands and other parts of the body are kept as low as possible using the accepted methods of radiation protection, namely time management, distance management and shielding. Manipulations were put into practice so that they could be performed as quickly as possible. The syringe was held by the plunger at the end of the barrel in order to maximise the distance from the radioactive liquid. There are different options for shielding, for example, both the vial and the syringe may also be used. There is an interdependence of the various protection strategies, for example the use of shielding around a syringe requires a change in the position adopted by the fingers and may increase the time required to perform the manipulations (11).

In order to avoid excessive exposure to radiation a self-shield hot cell was used in the project. Still, high density concrete was used in the construction. For personnel use, cotton clothes, which are more absorbent and washable were preferred. Extra care in personnel exposure was applied particularly by the use of personal protection, like glass and gloves. A monitoring system was implemented and personnel dosimeters of all staff were started to be checked monthly in the building, not only the ones related to the production.

AIR SYSTEM

All laboratory areas, including the production area and the quality control area, were required to

have a Class I (British Standard 5295) air system according to the Brazilian regulation of injectable pharmaceuticals (12).

The main air-conditioning was located on the roof and contained panel and bag pre-filters followed by a HEPA filter in order to maximize the life of the terminal room filters. The air supply was fed through a duct located in the roof, where it was directed to terminal HEPA filters above the room vents. The uniform distribution of air into the areas of the building was achieved using louvres. The use of louvres also prevented the operators from experiencing draughts.

The air return was performed using ducts located at floor level. The returned air was conducted by ducts to the upper portion of the discharge tower.

In the pharmaceutical environment where the prime considerations are the protection of the product and the avoidance of cross-contamination, clean rooms are vital. The maintenance of a clean room is performed through the use of air pressure. For this purpose, positive pressure was used in all laboratory areas. An agreement was reached between the engineering group and the pharmacist group to operate the laboratories at 30Pa overpressure. This pressure was maintained by self-operating baffles in the return ducts, driven by a computerized control unit which obtained information from pressure sensors located in each laboratory area and related these to ambient pressure. The RDC 210/03 states that all laboratory areas must have 35 air changes per hour, and for that, each laboratory must do it.

WORKSTATION

In the quality control laboratory, a laminar flow work station was used. The vertical flow work stations were chosen because a horizontal flow work station expels air from the cabinet towards the operator. Although it makes no difference with regard to product safety, it is very undesirable for operators, because they can be contaminated by the radioactive material. The chosen cabinet type was the laminar flow type with a recirculating system. To prevent cross-contamination in case of accident, the air exhaust from each laminar flow cabinet was directed separately into the roof space and was passed through two filters. The first one was a HEPA type filter that removed all particulate matter, either particulate in nature or microbial. The second, with activated charcoal, absorbed any gaseous or volatile materials, either radioactive or non-radioactive.

In addition to the RDC 210/03, the Regulamentary Norm 32 – NR32 on Occupational Safety and Health on Health Services (13) and the Guidelines on Good Radiopharmacy Practices for Radiopharmaceuticals in Nuclear Medicine (11), additional precautions were taken. In the laboratories, the floors were covered with 2 mm welded vinyl covering, called pavifloor. The walls were covered with a metallic sheet called styropainel III® which did not form junctions. This kind of covering material has on its surface a solvent-based impervious and water-resistant finish which allows it to be washed with disinfectants. The air vents/returns, light fixtures, switches, sockets and intercoms were all flush fitting. The workbench surfaces were covered with granite and formic, offering a continuous impervious surface. In case of spillage of radioactive material, blocks of lead are to be used to isolate the contaminated area, and special agents are to be used to enclose the material.

SECURITY AND CONTROL

Each duct was fitted with a radiation monitor that would ring an alarm if any escape was detected. Monitor alarms were dispersed throughout all laboratories even in the administrative area, and were ready to ring the alarm in case of cross-contamination. Wearing personal dosimeters in radioactive labs was made obligatory for the staff, in order to monitor personal exposure to radioactivity, through the use of dosimeters and Geiger-Müller equipment.

The facility was connected to the main system located at the administrative area, in the protection officer's office. These are under the control the electrical engineer and technician's responsibility and transmit appropriate alarm conditions to the workstation. The external security monitoring was made by a surveillance company contracted for this purpose.

CONCLUSION

In Brazil, the production of radiopharmaceuticals is very difficult because of the pharmaceutical as well as radioactivity regulations to be followed. This project is the first one to comply with all the necessary requirements and will be a guide to other radiopharmaceutical companies to construct a radiopharmaceutical production facility that can offer a service to the users in routine and research activities, as well as produce radiopharmaceuticals with quality and safety.

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