Radiopharmacy

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introduction

The use of radioisotopes in medicine is certainly one of the most important social applications of Nuclear Energy. IPEN, and more particularly the **Radiopharmacy Program**, has a special place in the history of Nuclear Medicine in Brazil.

The production of radioisotopes and radiopharmaceuticals for use in Nuclear Medicine started in the late 50's at IPEN. There has been a significant increase in the demand for these products over the years and nowadays more than 30 products are listed at IPEN catalogue.

The Radiopharmacy Program is organized in six areas: Production; Quality Assurance; Quality Control; Research, Development and Innovation; Infrastructure and Maintenance Support; and Cyclotron Accelerator.

The Production area carries out the routine production of primary radioisotopes, labeled molecules and lyophilized kits for labeling with ^{99m}Tc. Quality Assurance is responsible for the quality system management. The Quality Control executes all the necessary tests to release products for human use. Research, Development and Innovation develops new radiopharmaceuticals and improves production processes and applications. The Cyclotron Accelerator is responsible for the operation and maintenance of the cyclotrons and carries out the irradiation for production of cyclotron produced radioisotopes.

The highlights of this period were:

- The efforts to overcome the ^{99}Mo supply crisis that began in 2009. An immediate solution was achieved by an agreement between Brazil and Argentine. A new scheme for ^{99}Mo import was initiated with three different suppliers and a new schedule for the production of ^{99m}Tc generators was implemented three times a week;
- The project of nationalizing the production of ^{99}Mo by the fission of LEU targets was started, together with the new Brazilian multipurpose reactor (RMB) project;
- The reform of facilities is on the way with financial resources from CNEN and FINEP in order to comply with the needs arising from the regulatory agencies, CNEN and ANVISA;
- ANVISA published the regulations for registration of radiopharmaceutical products and for obtaining the GMP accreditation in radiopharmacy. The actions required to comply with these regulations were implemented;
- The purchase of a new cyclotron dedicated only to ^{18}F production has opened several possibilities for the development of new positron emission radioisotopes;
- The research and development projects shifted with time to new products for therapy (with ^{177}Lu, ^{90}Y and ^{166}Ho) and for PET (^{18}F, ^{68}Ga, ^{64}Cu);
- Certification and maintenance of the ISO Quality Management System;
- A validation master plan was prepared considering the production process and related areas, personnel and material flow procedures were implemented and new equipments have allowed the introduction of modern analytical methods in the quality control.

The Production of Radiopharmaceuticals is divided in 3 different areas:

- Radioisotopes: (^{99m}Tc generator and Primary Radioisotopes);
- Labeled Compounds: for diagnosis (PET and SPECT) and for therapy;
- Lyophilized Kits for labeling with ^{99m}Tc.

The Commercial Department (SAC) is responsible for receiving the product order from the clients weekly or by demand. The main product specifications are described as follows:

Radioisotopes

Generator

^{99m}Tc Generator - IPEN-TEC
The ^{99m}Tc - Generator is a system which produces Technetium-99m for labeling lyophilized "kits" and it is used in nuclear medicine for thyroid and salivary glands scintigraphy. More than 350 generators are delivered weekly.

Primary Radioisotopes

^{131}I-Na - Sodium iodide solution
For oral study of thyroid gland and therapy of thyroid cancer and metastases.

^{131}I-Na - Sodium iodide capsules
For therapy of hyperthyroidism and therapy of thyroid cancer and metastases.

^{123}I-Na - Sodium iodide solution
For oral study of thyroid gland.

^{51}Cr – Sodium chromate
Used in nuclear medicine for study of red blood survival and spleen scintigraphy.

^{67}Ga - Gallium citrate
Indicated for localization and detection of soft tissue tumors and inflammatory process.

^{201}Tl - Thallium chloride
For cardiac function studies.

^{32}P – Sodium phosphate
Used in treatment of polycythaemiavera and biotechnology.

^{35}S - Sulphuric acid
Used in metabolic investigation.

^{18}F – Sodium fluoride
Used in bone image in PET and PET-CT.

Labeled Compounds

^{153}Sm-EDTMP - (ethylenediamine-tetramethylene-phosphonic acid)
Therapeutic agent indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions in breast and prostate cancer.

^{131}I-MIBG - Meta-iodobenzylguanidine
Diagnostic and therapeutic agent of neural crest-derived tumors.

^{177}Lu-DOTATATE (DOTA-Octreotate)
Therapeutic agent for neuroendocrine tumors.

^{111}In-DTPA-TOC (DTPA-Octreotide)
Diagnostic agent for neuroendocrine tumors.

^{131}I-Lipi - (Lipiodol)
Treatment of hepatocellular carcinoma (HCC), the selective retention suggests its potential as chemotherapeutic or radiotherapeutic agents.

^{123}I-MIBG - (Meta-iodobenzylguanidine)
Diagnosis of pheochromocytoma, neuroblastoma and myocardial studies.

^{131}I-Hipp - (o-iodo-hippurate)
Used for the investigation of kidney function, gives information about the renal blood flow, urinary tract potency and urinary flow in nuclear medicine.

^{131}I-HSA - (Human serum albumin)
For determination of plasma volume and total blood volume.

^{51}Cr-HSA - (Human serum albumin)
For the measurement of proteins lost by gastro intestinal tract, it is an ideal radionuclide for long time studies in nuclear medicine.

^{51}Cr -EDTA - (ethylendiaminotetracetic acid)
For study of glomerular filtration rate.

^{18}F-FDG - (fluoro-2-deoxy-D-glucose)
In oncology, cardiology and neurology studies.

^{53}Sm-HA - (hydroxiapatite)
^{90}Y-HA - (hydroxiapatite)
For synovectomy, treatment of rheumatic arthritis.

Lyophilized "kits" for labeling with ^{99m}Tc

DTPA - Diethylenetriaminepentaacetic Acid
For brain imaging, renal flow study and glomerular filtration rate measurement.

MDP - Methylene Diphosphonate
To demonstrate areas of altered orthogenesis as seen, in metastatic bone disease and osteomyelitys.

DMSA (III) - Dimercaptosuccinic Acid
For renal cortical imaging.

DISIDA - Diisopropyliminodiacetic Acid
Commonly used as hepatobiliary agent to evaluate hepatic and biliary duct function, also in cholescingraphy.

PYRO - Pyrophosphate
For localization of primary bone tumors, metastatic tumors and metabolic bone diseases, also in myocardial infarct.

Dextran-70 and Dextran-500
Used in sentinel node scintigraphy.

EC - Ethylene dicysteine
For renal function study.

ECD - Ethylene dicysteine diethyl ester
Used for cerebral perfusion studies, and detection of intra-cerebral inflammatory conditions; detection of an abnormal focus in patients with head trauma and cerebral-vascular accidents; differentiation of Alzheimer's disease from multi-infarct dementia.

Sn-colloid - Stannous colloid
Indicated for imaging, localization and evaluation of liver and spleen pathology.

Fitato - Fitic acid
Indicated for imaging areas of functional reticuloendothelial cells in liver, spleen and bone marrow and in lynphoscintilography study.

During this period of time, the demand for therapeutic radiopharmaceuticals increased, while the total activity of ^{99}Mo used in the preparation of generators decreased. However, the total number of generators sent to clinical and hospitals was increased. The production of ^{18}F-FDG was decreased due to the assembling of new PET radiopharmaceuticals production centers. Besides, the ^{131}I solution production was stabilized while the production of ^{131}I capsule was increased.

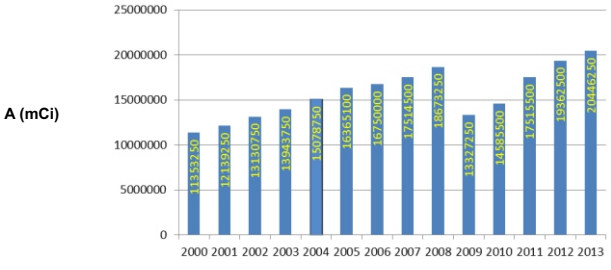

Figure 1. Distribution of ^{99}Mo/^{99m}Tc generators at IPEN.

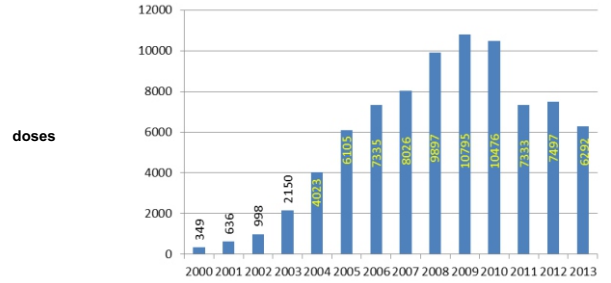

Figure 2. Distribution of ^{18}F-FDG doses.

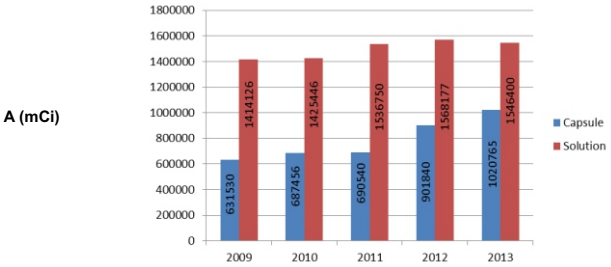

Figure 3. Distribution of ^{131}I solution and ^{131}I capsule.

Quality control of radiopharmaceuticals

Quality Control is part of Good Manufacturing Practices (GMP) which is concerned to sampling, specifications and testing, and also to organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and the materials are not released for use, nor products released for sale until their quality is guaranteed. After approval by the responsible person the products are released in the computerized system and the radiopharmaceuticals are transported to hospitals and clinics.

Nowadays more than 45,000 assays are executed in primary radioisotopes, labeled molecules, lyophilized reagents, starting materials, packaging materials and intermediate products at the Radiopharmacy Center of IPEN-CNEN/SP. Figure 4 shows the number of quality control tests during the last two years (2012-2013) and in Figure 5 the contribution of each group of products can be seen.

In order to evaluate if radiopharmaceuticals comply with the specifications for oral and parenteral human administration according to GMP, pharmacopoeias and official standards, strict quality control tests are performed.

Specific tests that ensure purity, potency, product identity, biologic safety and efficacy include physicochemical and biological tests: organoleptic characteristics, pH, moisture content, particle size measurement, determination of radionuclidic, radiochemical and chemical purity, capsules dissolution testing, sterility, bacterial endotoxin test, biodistribution and toxicity studies, among others. The Quality Control has adequate facilities with modern analytical equipment for its activities. Instrumental techniques as gamma counters, IR spectrophotometry, GC, ICP-OES, HPLC and gamma spectrometry with HPGe detector are used.

Environmental monitoring is conducted in the production areas (hot cells and clean areas) by collecting and measuring airborne particles as well as microbiological contamination is assessed with passive and active air sampling. The quality of water used in different processes is also examined.

Training of professionals of Nuclear Medicine also takes place in the laboratories of the Quality Control. The staff of the Quality Control (QC) Laboratory is trained and qualified and participates actively with all the other groups in the maintenance of the ISO 9001-2008 Certification, in compliance with GMP for radiopharmaceuticals. The QC group is also engaged in the qualification of equipment, development and validation of analytical methodologies, validation of production processes, observing the requirements of the National Sanitary Surveillance Agency (ANVISA) and it has also been participating in the development of new products.

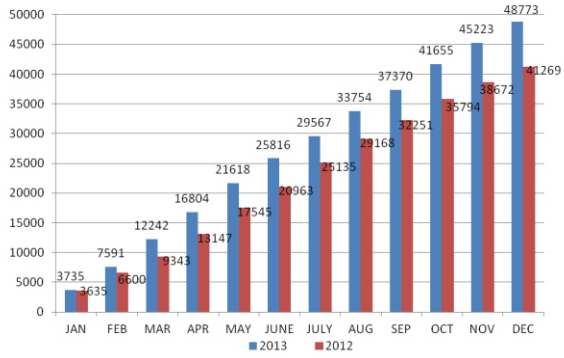

Figure 4. Quality control tests (2012-2013).

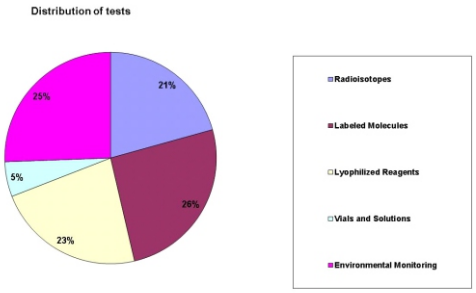

Figure 5. Distribution of tests.

The area of Research and Development applied to Radiopharmacy at IPEN is divided into 6 different fields: Radionuclide generators; Primary radioisotopes; Labeling of molecules for diagnosis (PET and SPECT) and therapy; lyophilized kits and quality control analytical methodologies. The main achievements are described as follows:

Radionuclide generators

- Research project are under way with the objective of development of ^{68}Ge-^{68}Ga generator.
- Study of high activity ^{99}Mo-^{99m}Tc generators.

Studies on the development of the production process of ^{99}Mo

^{99m}Tc, daughter of ^{99}Mo, is the tracer element most often used in nuclear medicine, because of its favorable nuclear properties, accounting for about 80% of all diagnostic procedures *in vivo*. Currently the supply of this important radioisotope is deficient due to the numerous shutdowns of the reactors in Canada and Belgium, the largest world producers.

The production of ^{99}Mo is one of the most important points within the enterprise RMB (Brazilian Multipurpose Reactor). With that Brazil intends to become self-sufficient and independent from international producers, with a production estimated in 1,000 Ci per week. The development process in laboratory scale has started in 2009, and in the three years 2011-2013 amounted to some important settings for further studies. The chosen process for the production of ^{99}Mo from ^{235}U fission was that following an alkaline dissolution of UAl_x LEU (Low Enriched Uranium) targets and purification of ^{99}Mo in chromatographic columns, according to the process developed mainly in Argentina, which is based on the process developed by researcher Dr. Sameh Ali (KfK, Germany), in the 1980's. Another important point in this development, which is not made by other producers, is the recovery of ^{131}I radioisotope, important for the diagnosis and treatment of thyroid tumors. The studies on the development of the production process of ^{99}Mo are divided into two parts: (a) dissolution and (b) separation/purification of ^{99}Mo and ^{131}I. During the evaluation studies of parameters influencing the dissolution in both lines of research, only Al-samples were used, mainly because aluminum corresponds to about 80% of the total mass of the targets.

Dissolution of Al: Two lines of research for obtaining ^{99}Mo via fission of ^{235}U have been studied. The surveys cover targets with low enrichment (<20% ^{235}U). The first one studies the dissolution of the targets with NaOH/$NaNO_3$ alkaline solutions, and the second one studies the dissolution with NaOH solution, aiming to achieve the best dissolution conditions for defining the chemical process to be implemented in the project RMB. During alkaline dissolution studies various experimental arrangements were used in that different parameters were evaluated. The following parameters were evaluated in both lines of research: Dissolution time; volume / composition of dissolved gases; loss of ^{99}Mo in the filtrate; contamination of the product solution; minimization of the formation of H_2 during dissolution.

Separation and purification of fission ^{99}Mo and ^{131}I: This research involves the study of retention and recovery of Mo ions from simulated solutions of alkaline dissolution of UAl_x-Al targets by chromatographic materials. Adsorption and desorption behaviors of Mo and the main contaminants have been investigated on the acidic and neutral aluminas and Dowex 1x8, AG 1x8 and Chelex 100 resins, which are used on the Argentine process and ROMOL-99 process (Molybdenum Rossendorf technology - developed in Germany) as classic chromatographic materials. Moreover, an iron oxide, the magnetite, and the AG 50Wx8 cation exchanger resin have been investigated as adsorbents of Mo and contaminants, respectively. All experiments has been conducted with the element carriers and their radioactive tracers added in pure acid and base solutions as well as in solutions prepared from the alkaline dissolution of Al plates.

In period 2011-2013, the adsorption and desorption of Mo in the presence of Al and contaminants as ^{131}I, ^{123m}Te, ^{95}Zr and ^{103}Ru were studied. Variables of separation and purification of Mo by the batch tests and subsequently by the column tests were evaluated. Influences of pH, nitrate ions and aluminium ions, as well as the kinetics and isotherms of Mo were investigated. The ions of sulfate, bisulfate, carbonate, bicarbonate, sulfide, chloride, nitrate and hydroxyl were tested as Mo desorbents. Study of formation of the molybdenum thiocyanate complex for retention on the Chelex 100 was carried out. The acidic and neutral aluminas adsorbed more than 99% of Mo in the pH range from 0.1 to 10 while the Dowex 1x8 and AG 1X8 resins in the range from 3 to13. Aluminium ions did not affect the Mo retention. Magnetite showed a similar behavior to the alumina where it was highly efficient for Mo adsorption in the pH range from 0.5 to 9 and about 80% was desorbed by hydroxyl ions. More than 90% of iodine ions were adsorbed on the Dowex 1x8 and AG 1x8, so that the desorption with tetrabutylammonium ions and nitrate ions has been investigated. The recovery was about 80% in both cases, indicating the possibility of obtaining ^{131}I as a byproduct from the process of production of fission ^{99}Mo.

Tests were carried out in chromatographic columns aiming the selective elution of Mo in relation to the contaminants, specially the iodine, using different eluents in various concentrations and temperature. In laboratory scale, a process consisting of Dowex 1x8 and acidic alumina columns in series, including steps of washing, acidification and elution, was investigated. A final product was obtained with Mo yield greater than 90% and ions of I, Ru, Zr and Te below the detectable limit of the analysis. This process showed to be very promising, and a detailed study of decontamination for each contaminant and iodine recovery is being developed. Similar results were found in the simulation of the Argentine process consisting of columns of Dowex 1x8, Chelex 100 (2x) and acidic alumina. A prototype study of the separation and purification process was initiated using load volumes from 1 to 4 L, dimensions of two columns closed to the actual dimensions and a peristaltic pump. The first studies of the controlled bottom-up flow for loading, washing and elution were investigated. Also, the last step of purification by sublimation using a tubular furnace with controlled atmosphere and temperature to obtain the Mo radiochemical purity was initiated.

Primary radioisotopes

- Development of: a production method of ^{99m}Tc solvent extraction; a production method for ^{64}Cu.
- Project aiming the production of ^{99}Mo through the fission of LEU targets with the assistance of IAEA (CRP).
- Improvements in the gas target for the production of ^{123}I.
- Purification of ^{123}I and ^{131}I.

Labeling of molecules for diagnosis (PET and SPECT) and therapy

- Labelling of: ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC; Choline with ^{18}F [^{18}F-FCH]; Fluorothymidine with ^{18}F [^{18}F-FLT]; ^{64}Cu-ATSM; peptide ubiquicidine with ^{99m}Tc for oncology; antibodies with radiometals and lantanides: studies concerning the derivation of the antibody.
- Bombesin derivatives as molecular markers for tumor diagnosis by SPECT and PET.
- Development of: a production method for MAG3 labeling with ^{99m}Tc; a production method for Glass and Polymeric Microspheres loaded with ^{166}Ho.

Lyophilized kits

- Development of a production method for HYNIC-TATO lyophilized kit labeling with ^{99m}Tc.

Quality control analytical methodologies

- Radiochemical quality control of labeled kits: comparison of methodologies.
- Gram tests for classification of microorganisms.
- Evaluation of: total organic carbon in the water used in the Radiopharmacy; the effectiveness of the cleaning processes - GMP process.
- HPLC-MS method for determination degradation products.

Preparation of radiopharmaceuticals for injection involves adherence to regulations in radiation protection as well as to appropriate rules of working under aseptic conditions that should follow the regulations on current Good Manufacturing Practices (cGMP). Good Manufacturing Practices (GMP) 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 in the analysis of the final product: cross-contamination, contamination with particulate material and change or mixture of products.

Quality Assurance is a wide ranging concept which covers all matters that individually or collectively influence the quality of a product. It is the total arrangements to ensure that medicinal products have the required quality for their intended use. Quality assurance therefore incorporates GMP and thus Quality Control. 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 and radionuclidic purity) may sometimes be retrospective. The implementation and compliance with the quality assurance program are therefore essential.

Manufacturing practices are the methods, facilities, and controls used in the preparation, processing, packaging, or holding of a drug. The GMP in Brazil is published in the Resolution RDC 17 of 16 April, 2010 of ANVISA. Specific regulations for GMP and marketing authorization of radiopharmaceuticals were published by ANVISA (Resolution RDC 63 and 64 of 18 December, 2009, respectively).

The “Technical Committee of Radiopharmaceuticals” from the Brazilian Pharmacopoeia is elaborating the monographies of radiopharmaceuticals produced in Brazil. IPEN participates in this work group which reflects the importance of the radiopharmaceuticals in the context of pharmaceutical production in Brazil.

In the Radiopharmacy, the Quality Assurance Management is responsible for maintenance and improvement of the Quality Management System (according to ISO-9001-2008) and the implementation of all the aspects related to GMP in production and quality control of radiopharmaceuticals. There is a group responsible for control, maintenance and improvement of data generated in the production and quality control process and all documents of the Quality Management System. The accompaniment of non-conformities generated in the System and the attention to the fulfillment of ISO 9001 are also attributions of this group. The Quality Assurance Management coordinates the Instrument Calibration, Equipment Qualification, Process Validation and also the implementation of other GMP requirements.

The Quality Assurance Management can oversee the production and quality control operations to ensure that a radiopharmaceutical is produced according the specifications. It is the responsible for approving or rejecting components, in-process materials and finished product to ensure compliance with procedures and specifications affecting the identity, concentration, quality and purity of the radiopharmaceutical.

In the last years, the maintenance of the ISO 9001 Quality Management System Certification was very important and contributed to the introduction of the GMP concepts. Some aspects of the GMP applied to the Quality Assurance Program are of special interest and have been discussed and introduced in the radiopharmaceutical production context at IPEN, including:

Validation
It was elaborated the “Validation Master Plan”, including utilities (water and air), process analytical methods, cleaning process and softwares.

Installations
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 especially designed to take into consideration aspects of radiation protection in addition to cleanliness and sterility. A big infrastructure project is in course to adequate the radiopharmaceutical production areas to attend the GMP requirements, including the “hot” area for production of labelled molecules and primary radioisotopes and the area for production of lyophilized kits for labelling with 99m-tecnethium. New laboratories for quality control of radiopharmaceuticals were constructed.

Regularization of the radiopharmaceutical in Health Ministry
Considering the new ANVISA Resolution (RDC 64, 2009), the Quality Assurance group works in the development of final dossiers to be submitted to the regulatory organ in order to obtain the market authorization for the radiopharmaceuticals produced at IPEN. The quality assurance also works in the elaboration of the dossiers for clinical trials with new radiopharmaceuticals.

To produce specific radioisotopes, in IPEN are installed two cyclotrons:

Cyclone 30

The cyclotron, Cyclone 30 model, manufactured by Ion Beam Applications-Belgium, is a compact, fixed-field, fixed-frequence, that can accelerate H-ions with energies between 15 and 30 MeV. This energy range and its high external beam current available (350 A) is optimum for production of the most important SPECT and PET cyclotron radioisotopes used in nuclear medicine: ^{18}F, ^{11}C, ^{13}N, ^{15}O, ^{67}Ga, ^{201}Tl, ^{123}I, ^{111}In, ^{124}I and ^{64}Cu. Figure 6 shows the Cyclone 30.

Figure 6. Cyclotron Cyclone 30.

The Cyclone 30 cyclotron has two external beam lines. One is dedicated to irradiation of solid target where ^{67}Ga and ^{201}Tl can be produced. At the end of the other beam line, a switching magnet with five exit ports is installed. In two of these positions liquid targets are installed and in another exit is a gas target, which allows the production of ^{18}F and ^{123}I, respectively.

The target system for production of ^{67}Ga and ^{201}Tl was manufactured by Ion Beam Applications-Belgium, and it uses a target at 6° with respect to the beam axis, resulting in an enlargement of the beam by a factor of 10. The target material (^{68}Zn or ^{203}Tl) is electrodeposited on an elliptical area measuring 10mm x 100mm, giving a typical thickness of 150 - 170 µm. On the back of the target there are fins to increase the water cooling efficiency. Irradiation with current up to 250 µA is possible.

At IPEN, ^{18}F is produced by the ^{18}O(p,n)^{18}F reaction using enriched water as target material. The liquid target system was manufactured by Ion Beam Applications - Belgium and it basically consists of four main parts: a conical collimator of 10 mm diameter, a window holder with two windows cooled by helium gas, one for the vacuum side and one for the target side (Havar of 25 and 50 µm respectively), a water cooled semi hemispherical niobium body and a high pressure valve for remote-controlled filling, unloading and purging of the target. In front of the target there is a four sector collimator, which helps the optimization of the cyclotron parameters. The production is made with protons of 18 MeV and current of 50 µA.

For ^{123}I production, due to the high coast of acquisition, IPEN has decided to develop its own system to produce ^{123}I *via* ^{124}Xe irradiation. This system includes a water cooled target ^{124}Xe chamber, a double Mo window (50 µm) cooled by helium gas, an alignment system, which consists of a pair of four sectors collimators and a safety volume cooled with liquid nitrogen and a valve manifold for vacuum and transference of the ^{124}Xe gas from the storage vessel to the irradiation chamber and recovery. The ^{124}Xe transfer from the storage bottle to the target and the recovery of the gas after irradiation to the bottle is made cryogenically with liquid nitrogen, through stainless steel pipes. The control system uses a PC and a PLC with a Siemens SIMATIC S5. A friendly software permits to control the process in manual mode selecting the desired action (valve open/off, pump on/off, and so on) by pointing the appropriate icon on the screen. The fully automated operation mode can be selected via keyboard and makes the process flexible.

Cyclone 18

The increase in the demand of ^{18}F-FDG led to the modification in the law that regulates the production of radioisotopes in Brazil and also to the purchasing of a new Cyclotron, dedicated only to ^{18}F production and new possibilities for positron emission radioisotopes.

Cyclone 18, manufactured by Ion Beam Applications-Belgium, is a fixed-energy cyclotron, accelerating H^- ions up to 18 MeV. The beam intensity is 150 µA. It includes eight independent exit port allowing eight targets to be simultaneously mounted on the cyclotron. Figure 7 shows the Cyclone 18.

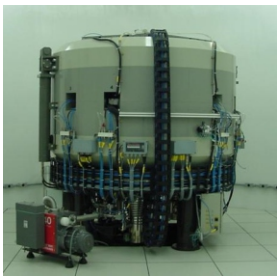

Figure 7. Cyclotron Cyclone 18.

Clean Room

In the cyclotron facility there is a clean room, class 10,000, with two double hot cells for synthesis modules and a laminar flow hot cell for reception of the final product, as shown in figure 8. The cells were acquired from Comecer-Italy. This clean room was constructed according to regulations in radiation protection as well as to appropriate rules of working under aseptic conditions (GMP).

Inside these hot cells synthesis modules are installed: two Synthera model, from Ion Beam Applications (Figure 9a) and one TraceLab MX model from GE (Figure 9b).

Figure 8. Hot cells.

These synthesis modules allow the routine production of ^{18}F-FDG and experimental production of another radiopharmaceutical labelled with ^{18}F, such as ^{18}F-FLT, ^{18}F-Acetate and ^{18}F-choline.

Figure 9a. Synthera module.

Figure 9b. TraceLab MX module.

Radiopharmacy facility infrastructure management

The Radiopharmacy Facility Infrastructure Management at the Radiopharmacy Center is in charge to support and make the arrangements for the radiopharmaceutical production following the cGMP standards which includes activities such as project management, maintenances programs, consumables storage and support to public procurements.

In order to fulfill the cGMP standards and sanitary regulations required by ANVISA (Brazilian Health Surveillance Agency) by the public resolutions RDC-63 (which refers to radiopharmaceutical cGMP production) and RDC-64 (which refers to radiopharmaceutical registry), the CR has been developing and managing several projects, such as:

- Radiopharmaceutical production laboratory adequation to cGMP standards;
- Radiochemistry laboratory adequation to cGMP standards;
- New HVAC systems for radiopharmaceutical and radiochemistry productions;
- R&D new laboratory;
- New radiopharmaceutical production and fractionating hot cells;
- New Tc-99m generator production line;
- Whole facility adequation to people, products and waste flow;
- New dry freeze production facility;
- New Radiopharmaceutical consumables warehouse;
- New Radiopharmacy Center electrical supply cabin;
- Developments on the Tc-99m generator package;
- New biological and microbiological quality control laboratories.

The preventive maintenances program is applied to all the Radiopharmacy Center equipment and the tasks are split into the “in house” maintenances and the contracted services. Due to the continuing decreasing IPEN crew (for retiring reasons), most of the maintenances has been carrying out by outsourcing companies.

Research Staff

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