Radiopharmacy

The radiopharmaceuticals allow the diagnosis and treatment of a several diseases, and the products go through a series of quality control procedures before being sent to the hospitals and clinics all over the country

Radiopharmacy

Introduction

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 activities areas: Production; Quality Assurance; Quality Control; Research, Development and Innovation; Infrastructure and Maintenance Support; and Cyclotron Accelerator.

The highlights of this period were:

- All the efforts related to overcome the ^{99}Mo supply crisis that begun in 2009. A fast solution was achieved by a two countries agreement with Argentine and the implementation of a new schedule of production of ^{99m}Tc generators, three times a week.
- A new scheme of importation of ^{99}Mo was initiated, with the possibility of receiving the radioisotope from 3 different suppliers.
- The project of nationalizing the production of ^{99}Mo by the fission of LEU targets was started, together with the new reactor (RMB) project.
- The reform of the installations in 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 acquiring the GMP in radiopharmacy. The actions required to comply with these regulations were implemented.
- The increase in the demand of ^{18}F-FDG that lead 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.
- The effects of the modification in the law that regulates the production of radioisotopes in Brazil lead to the assembling of new producers and subsequently a decrease in the demand of ^{18}F-FDG produced by IPEN. Anyway IPEN acts as a back up for the producers and continues its role of transferring technologies of producing new PET radiopharmaceuticals.
- 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.
- An environmental monitoring plan was established to evaluate clean areas.
- A validation master plan was prepared considering the whole production process, personnel and material flow procedures were implemented and new equipments have permitted the introduction of modern analytical methods in the quality control.

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Production

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; and 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 300 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.

Dextran70 and Dextran500
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 increase, while the total activity of ^{99}Mo used in the preparation of generators decreases (Figure 1). Otherwise, the total number of generators sent to clinical an hospitals was increased. The production of ^{18}F-FDG was decreased (Figure 2) due to the assembling of new PET production centers.

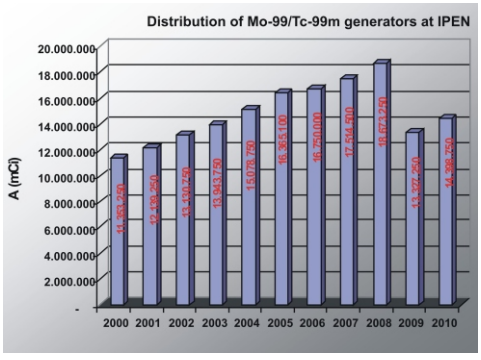

Figure 1. Radioactivity of ^{99}Mo-^{99m}Tc generators

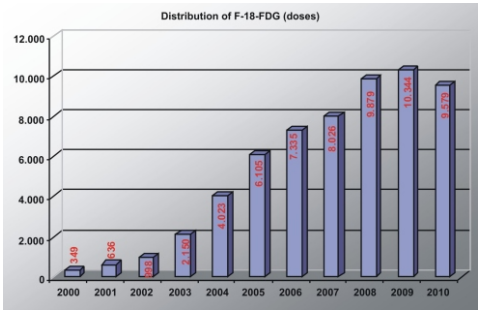

Figure 2. Distribution of ^{18}F-FDG doses

Quality Control of Radiopharmaceuticals

Annually, about 40,000 assays are executed in primary radioisotopes, labeled molecules, lyophilized reagents, starting materials, packaging materials and intermediate products at the Radiopharmacy Directory of IPEN-CNEN/SP. Figure 3 shows the distribution of the quality control tests during the year of 2010.

Specific tests that ensure the purity, potency, product identity, biologic safety and efficacy include physicochemical and biological tests: physical appearance of the sample, pH, humidity and particle size measurements, determination of radionuclidic and radiochemical purities, chemical impurities, dissolution test, sterility, bacterial endotoxin test, biodistribution and toxicity.

The quality control staff improves analytical methods for new products together with the research and development group and participates actively in the maintenance of the ISO 9001-2000 Certification.

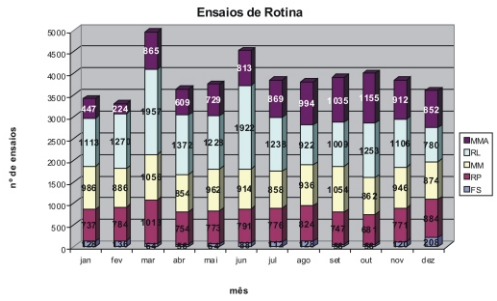

Figure 3. Number of quality control tests (2010)

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Research and Development related to Radiopharmacy

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 and ^{90}Sr-^{90}Y generators.
- Study of high activity generators.

Primary radioisotopes

- Development of a production method for ^{64}Cu.
- A project is under way aiming a new production method for ^{67}Ga.
- Project aiming the production of ^{99}Mo through the fission of LEU targets with the assistance of IAEA (CRP).
- Purification of ^{123}I and ^{131}I.
- Improvements in the gas target for the production of ^{123}I.

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

Research projects have been developed aiming the preparation of the following radiopharmaceuticals:

- A research project sponsored by IAEA (CRP) is under way and it has the objective of developing labelling methods for the Therapeutic Radiopharmaceuticals based on ^{188}Re and ^{90}Y.
- Labelling of octreotide with ^{68}Ga.
- Labelling of antibodies with radiometals and lantanides: studies concerning the derivation of the antibody.
- Labelling of substance P with ^{177}Lu.
- Labelling of DMSA with ^{188}Re.

Lyophilized kits

The synthesis of compounds not commercially available and the development of new lyophilized kits are necessary to introduce new ^{99m}Tc-based radiopharmaceuticals. Lyophilized kits allow the instant preparation of the labeled molecules with ^{99m}Tc without purification steps prior to administration.

- Labelling of the peptide ubiquicidine with ^{99m}Tc for oncology.
- Development of ^{99m}Tc radiopharmaceuticals for Sentinel Node detection and Cancer diagnosis (CRP-IAEA).

Quality control analytical methodologies

- Gram tests for classification of microorganisms.
- Radiochemical quality control of labeled kits: comparison of methodologies.
- Evaluation of total organic carbon in the water used in the Radiopharmacy.

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Quality Assurance in Radiopharmaceutical Production

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 sum of the organized arrangements made with the object of ensuring 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, endotoxin, radionuclidic purity, etc) may sometimes be retrospective. The implementation of 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 the National Sanitary Agency (ANVISA) of the Health Ministry. Specific regulations and registration of radiopharmaceuticals were published by ANVISA (Resolution RDC 63 and 64 of 18 December, 2009).

The Brazilian Pharmacopoeia constituted the "Technical Comission of Radiopharmaceuticals" to prepare the radiopharmaceuticals monographs to integrate the Brazilian Pharmacopoeia. IPEN has participate in these work groups which reflect 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 cGMP 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 process validation, analytical procedures, cleaning procedures and personnel training. Validation program is in course for utilities (water and air) and attention has been given to process validation, including validation of sterilization process, process control and the monitoring of the established parameters, especially from the environment, particularly when the product should be released before the conclusion of all the quality control assays.

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. Some projects for improving the Radiopharmacy Instalation are in course in order to attend the GMP requirements for radiopharmaceutical production.

Regularization of the radiopharmaceutical in Health Ministry
Considering the new ANVISA Resolution for radiopharmaceuticals registration (RDC 64), the Quality Assurance group works in the development of final dossies to be submitted to the regulatory organ in order to obtain the register of the radiopharmaceutical in the Health Ministery.

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 μA) 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 4. 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 6º 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 10 mm x 100 mm, 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. If occasionally there is a rupture in the first window, the ^{124}Xe gas will be trapped in the helium cooling system and the mixture can be transferred to the storage bottle. 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 that lead 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 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 5 shows the Cyclone 18.

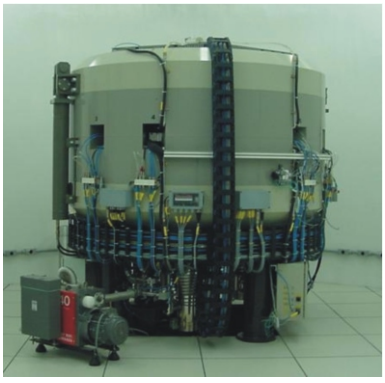

Figure 5. Cyclotron Cyclone 18