Radiopharmacy

Introduction

The use of radioisotopes in medicine is certainly one of the most important social applications of Nuclear Energy. IPEN, and 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 and constant increase in the demand for these products over the years and nowadays more than 30 products are listed at the 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 Production area carries out the everyday 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 tests needed to release products for human use. Research, Development and Innovation develops new radiopharmaceuticals and improves production processes and applications. The Cyclotron Accelerator Division is responsible for the operation of the Cyclotron and carries out the irradiation for obtaining the cyclotron produced radioisotopes.

The highlights of this period were:

- Development of some new radiopharmaceuticals for diagnostics and therapy: ^{111}In-DTPA-octreotide, ^{90}Y-hidroxyapatite and ^{177}Lu-DOTA-Tyr^{3}-octreotate;
- The increase in the demand of ^{18}F-FDG that led to the modification of the law regulating the production of radioisotopes in Brazil and also to the purchase of a new Cyclotron that will be dedicated only to ^{18}F production and new possibilities for positron emission radioisotopes;
- Certification and maintenance of the ISO Quality Management System;
- A new installation project was conceived with the expectation of cGMP compliance;
- 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.

Production and Quality Control of Radiopharmaceuticals

The Production of Radiopharmaceuticals is divided in 3 different areas: Radioisotopes (Tc-99m generator and Primary Radioisotopes); Labeled Compounds for diagnosis (PET and SPECT) and for therapy; and Lyophilized Kits for Labeling with Tc-99m. 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. 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.

^{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.

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.

^{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 Tc-99m

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 - Phytic 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 production group has validated and introduced in routine production two new radiopharmaceuticals for diagnosis and therapy of neuroendocrine tumors: ^{111}In-DTPA-Octreotide and ^{177}Lu-DOTA-Tyr^{3}-octreotate, respectively. In 2007, it was distributed 30,784 MBq of ^{111}In-DTPA- Octreotide and 502,645 MBq of ^{177}Lu-DOTA-Tyr^{3}-octreotate to nuclear medicine centers in São Paulo and other states. The evaluation of revenue of radiopharmaceuticals is illustrated in Figure 1.

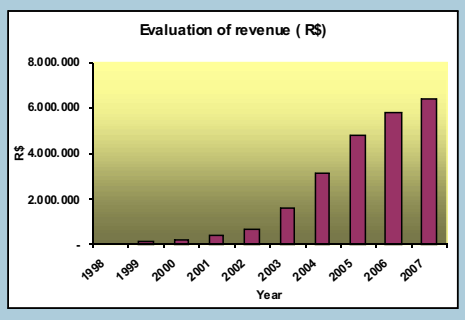

Figure 1. Evaluation of revenue (R$) since 1998

Quality Control is that part of Good Manufacturing Practice (GMP) which is concerned with sampling, specifications and testing, and with the 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 or supply, until their quality has been judged to be satisfactory.

In order to evaluate if radiopharmaceuticals comply with the specifications for oral and parenteral human administration according to the GMP and pharmacopoeias, strict quality control tests must be performed. 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. Annually, about 30,000 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 2 shows the distribution of the quality control tests during the year of 2007.

The Quality Control Laboratory has adequate facilities which were improved as several modern analytical equipments were acquired. Special attention has been given to the validation of the analytical methodologies. Metal impurities can be determined by the ICP (Inductively Conducted Plasma) and UV-Vis spectrophotometer; residual solvents from the F18-FDG production in a gas chromatograph; paper and thin-layer chromatography have been used to determine radiochemical purity and the radioactivity is measured in a gamma counter or a scanner; high performance liquid chromatography has been applied to analyze lyophilized reagents labeled with Tc-99m. Sterility tests are performed according to the microbiology procedures stated in the pharmacopoeias and the Limulus amebocyte lysate (LAL) test is used for the detection of bacterial endotoxin. The clean room environments have been monitored to assess particulate and microbial contamination for GMP purposes. Air sampling, culture medium plate exposure, surface and operator monitoring ensure the manufacturing process and quality control test conditions.

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.

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

- A research project sponsored by IAEA (CRP) is under way and it has the objective of developing production methods for the ^{188}W-^{188}Re and ^{90}Sr-^{90}Y generators.

- A research project was developed aiming the purification of high activity ^{99}Mo-^{99m}Tc generators. The use of an alumina SepPak cartridge has given very good results, and now it is being used in the routine production of the generators.

- A concentration unity is being studied for increasing the radioactive concentration of ^{99m}Tc eluted from gel type generators.

Primary radioisotopes

- The optimization of the parameters for the production of ^{131}I by the irradiation of TeO2 in the reactor and the dry distillation method of ^{131}I separation were completed. Two hot cells were assembled and are currently in use for the routine production of ^{131}I.

- The project for the nationalization of the production of ^{201}Tl was completed and this radioisotope can now be fully produced at IPEN.

- A project aiming the evaluation of the routine production of Lu-177 is being developed, using both the direct and indirect reactions for the production at IEA-R1 Nuclear Reactor.

- The recovery of enriched water used in the production of ^{18}F is being studied in order to minimize the costs of production.

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

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

[^{177}Lu]-DOTA-Tyr^3-octreotate - optimization of labeling conditions of the peptide DOTA-Tyr^3-octreotate (somatostatine analog) with ^{177}Lu to produce a radiopharmaceutical applied in the therapy of neuroendocrine tumors. The work is part of a project sponsored by IAEA (Coordinated Research Programme) started in 2002.

[^{131}I]-DOTA-Tyr^3-octreotate - optimization of labeling conditions of the peptide DOTA-Tyr^3-octreotate (somatostatine analog) with ^{131}I to produce a radiopharmaceutical applied in the therapy of neuroendocrine tumors. The work is part of a project sponsored by IAEA (Coordinated Research Programme) started in 2002.

[^{131}I]-Anti-CD20 antibody - optimization of labeling conditions, quality control and purification procedures to produce radioiodinated anti-CD20 antibody applied in the therapy of non-Hodgkin lymphoma.

[^{188}Re]-HEDP - optimization of labeling conditions, quality control and purification procedures to produce a phosphonate labeled with ^{188}Re for bone pain palliation.

[^{90}Y]- citrate and hydroxiapatite - preparation of radiopharmaceuticals for therapeutic applications in radiosynoviortesis.

[^{166}Ho]-microspheres - development of methods of preparation of resin and polymer based microspheres for therapy of liver cancer.

[^{188}Re]-Anti CD20 antibody - optimization of labeling conditions, quality control and purification procedures to produce anti-CD20 antibody labeled with ^{188}Re for therapy of non-Hodgkin lymphoma.

[^{177}Lu]-bombesin - development of bombesin analogs labeled with ^{177}Lu for therapy of prostate cancer.

Development of therapeutic radiopharmaceuticals based on ^{177}Lu for radionuclide therapy - International Atomic Energy Agency (IAEA) Coordinated Research Programme.

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.

Development of ^{99m}Tc based small bio-molecules using novel ^{99m}Tc cores - International Atomic Energy Agency (IAEA) Coordinated Research Programme - New ligands as peptide with sequence RGD, annexine, glucose analogue, and quinazoline analogue will be labeled with the Tc cores and evaluated for tumor uptake *in vivo* (2003-2006).

^{99m}Tc-anexin-V - labeling of anexin-V for apoptosis studies.

^{99m}Tc-glucoheptonate - preparation of kits for in vivo labeling of leukocytes with ^{99m}Tc.

^{99m}Tc-antimyosin - labeling of fragments of the antimyosin antibody for cardiac evaluation.

^{99m}Tc-DMSA-V - preparation of a direct kit for labeling of DMSA-V for tumor localization.

^{99m}Tc-BFCA-HYNIC-[Tyr^3]-Octreotide - labeling of octreotide with ^{99m}Tc for diagnosis of neuroendocrine tumors.

^{99m}Tc-thymidine - labeling of timidine with ^{99m}Tc for tumor localization.

Quality control analytical methodologies

Determination of Sn(II) using polarography - application in the routine quality control of lyophilized kits.

HPLC technique for quality control of ^{99m}Tc-radiopharmaceuticals - application in the routine quality control of lyophilized kits.

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 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 210 of 04 August, 2003 of the National Sanitary Agency (ANVISA) of the Health Ministry. This Resolution does not include any particular reference to radiopharmaceuticals. A specific regulation for radiopharmaceuticals is in course in Brazil. A “Radiopharmaceutical Group” is being coordinated by ANVISA in order to establish the rules governing radiopharmaceutical products in Brazil. Also recently, the Brazilian Pharmacopoeia constituted the “Sub-commission of Radiopharmaceuticals” to prepare the radiopharmaceuticals monographs to integrate the Brazilian Pharmacopoeia. IPEN has participated in these work groups which reflect the importance of the radiopharmaceuticals in the context of pharmaceutical production in Brazil.

In the Radiopharmacy Directory of IPEN, the Quality Assurance Management is responsible for maintenance and improvement of the Quality Management System (according to ISO-9001-2000) 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 checks the production and quality control operations to ensure that a radiopharmaceutical of sufficient quality is produced. 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:

Personnel
To ensure the safe manufacture of radiopharmaceuticals, personnel was trained in GMP, safe handling of radioactive materials and radiation safety procedures. Periodic courses and training have kept abreast of the latest developments in the field, according to a previous and annual training plan.

Production, quality control and research equipments
A calibration program has been continuously developed at regular intervals and equipments are checked daily or before production is started. A specific plan for qualification of production and quality control equipments was elaborated and has been implemented.

Contamination control
Clean areas should be maintained in an appropriate cleanliness standard and supplied with air, which has passed through filters of an appropriate efficiency. This condition protects the product from microbiological contamination by the environment. A planning to improve the conditions of the hot cell was started and an "Environmental Monitoring Program" was introduced in the production and quality control installations, which included elaboration of specific procedures, personnel training and acquisition of equipments and materials.

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. The Project of a new installation for the Radiopharmacy Center was concluded and sent to the sanitary authority for appreciation. In parallel, some rebuilding is in course to adapt the actual clean areas of the production to GMP conditions.

Regularization of the radiopharmaceutical in Health Ministry
All the directions of some radiopharmaceuticals (lyophilized reagents for labeling with technetium-99m) were reformulated to attend the regulatory instructions. Technical report for the register of the products is in course.

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. The ions are produced by a multicusp external source, located above the cyclotron. They are axially injected and inflected in the medium plane of the cyclotron and are subjected to a fixed magnetic field and gain energy due to a high voltage alternating electric field induced on the Dees. The beam is extracted by means of a carbon foil, which can be adjusted at different radii. The stripping foils are mounted on two stripping probes, one for each beam line and can be radially and azimuthally adjusted, allowing the extraction of two different beams at different energies or current simultaneously. That means, two radioisotopes can be produced at the same time. Figure 2 shows the Cyclotron Cyclone 30.

Figure 2. 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. These target facilities are described as follows:

Solid Target

This system 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. A cylindrical steering magnet rotates the beam by an adjustable AC field. The target material (^{68}Zn or ^{203}Tl) is electrodeposited on an elliptical area measuring 10mm x 100mm, giving a typical thickness of 150 - 170μm. On the back of the target there are fins to increase the water cooling efficiency. Irradiation with current up to 250μA is possible.

Liquid Target

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 (Figure 3) 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 50μm respectively), a water cooled semi hemispherical niobium body of 5 mL 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 50μA.

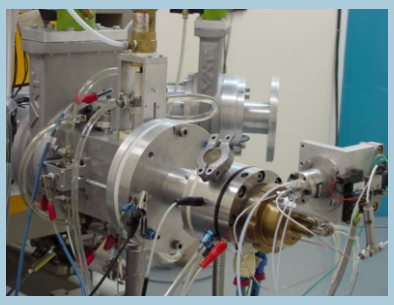

Figure 3. Liquid target system

Gas Target

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 (Figure 4) includes a water cooled target ^{124}Xe chamber, a double Mo window (50μm) 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. In the

unlikely event of a dual window failure, the Xe-124 gas will be expanded in the beam alignment system and will be trapped in a safety volume cooled with liquid nitrogen and the beam gate automatically will be closed. 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.

Typical values:

target volume: 75 mL;
P_{Xe} = 2 bar (without beam);
P_{Xe} = 4.5 bar (during irradiation);
E = 30 MeV; i = 50μA;
Yield (EOB) = 8mCi/μAh

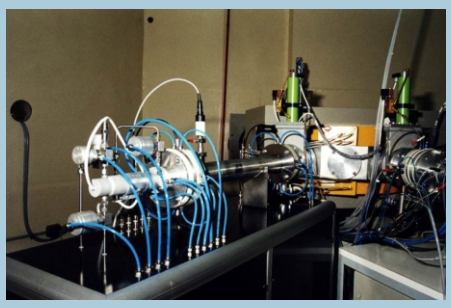

Figure 4. ^{124}Xe target system

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Honor Mention and Awards

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