# Radiopharmacy

# 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 $^{99}$Mo-$^{99m}$Tc generator, PET, SPECT, and betta emitters ready to use radiopharmaceuticals for diagnostic and therapy and lyophilized kits 99m for labeling with 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 cyclotron produced radioisotopes.

The highlights of this period were:

– The reform of facilities with financial resources from Ministry of Health in order to comply with the needs arising from the regulatory agencies, CNEN and ANVISA;

– new hot cells and glove boxes acquisition for the production area;

– the research and development projects shifted with time to new products for therapy with $^{177}$Lu, for PET ($^{18}$F, $^{68}$Ga, $^{64}$Cu) and diagnosis with $^{99m}$Tc;

– the synthesis and quality control conditions for the routine production of $^{18}$F-Choline and $^{18}$F-FLT;

– certification and maintenance of the ISO Quality Management System;

– delivery to ANVISA of 37 radiopharmaceuticals dossiers with the market registration objective;

– implementation of cGMP applied to radiopharmaceutical production (RDC 63, December, 2009) and

– validation plan implemented in $^{131}$I-NaI solution and capsules, $^{18}$F FDG, and lyophilized kits production lines.

**The Production of Radiopharmaceuticals is divided in 3 different areas**

- **Radioisotopes: ($^{99m}$Tc generator, PET, SPECT ready to use)**
- **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. These radiopharmaceuticals are distributed to approximately 430 Nuclear Medicine Clinics. The main product specifications are described as follows:

## A Radioisotopes

### Genervator:

**GERADOR-IPEN-TEC $^{99m}$Tc Generator - IPEN-TEC**
The $^{99m}$Tc - Generator is a system which produces Technetium-99m for labeling lyophilized "kits" and it also is used in nuclear medicine for thyroid and salivary glands scintigraphy. Approximately 400 generators are delivered weekly.

### Radioisotopes ready to use

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

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

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

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

**GAL-IPEN $^{67}$Ga - Gallium citrate**
Indicated for localization and detection of soft tissue tumors

and inflammatory process.

**CARD-IPEN $^{201}$Tl - Thallium chloride**
For cardiac function studies.

**FOSFATO DE SÓDIO-32**
**$^{32}$P – Sodium phosphate**
Used in treatment of polycythaemia vera and biotechnology.

**SULFATO DE SÓDIO-35 $^{35}$S - Sodium sulfate**
Used in metabolic investigation.

**FLUR-IPEN $^{18}$F – Sodium Fluoride**
Used in bone image in PET and PET-CT.

## B Labeled compounds

**SAMAR-IPEN $^{153}$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.

**GUAN-IPEN-131 $^{131}$I-MIBG – (Meta-iodobenzylguanidine)**
Diagnostic and therapeutic agent of neural crest-derived tumors.

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

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

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

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

**HIPUR-IPEN $^{131}$I-Hippurate – (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.

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

**ALB-IPEN-51 $^{51}$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.

**DAT-IPEN $^{51}$Cr -EDTA – (ethylendiaminotetracetic acid)**
For study of glomerular filtration rate.

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

**HAT-IPEN-153 $^{53}$Sm-HA - (hydroxiapatite)**

**HAT-IPEN-90 $^{90}$Y-HA - (hydroxiapatite)**
For synovectomy, treatment of rheumatic arthritis.

**DOT-IPEN-68 $^{68}$Ga-DOTATATE (DOTA-Octreotate)**
Diagnostic agent for neuroendocrine tumors.

## C Lyophilized ‘kits” for labeling with $^{99m}$Tc

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

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

**DMSA-TEC - Dimercaptosuccinic Acid**
For renal cortical imaging.

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

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

### $^{99}$Mo/$^{99m}$Tc Generator

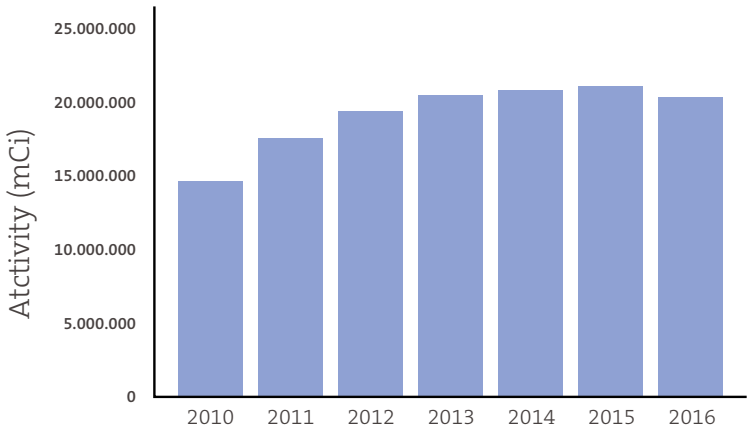



Figure 1 - Distribution of $^{99}$Mo/ $^{99m}$Tc generators at IPEN

### $^{18}$F-FDG

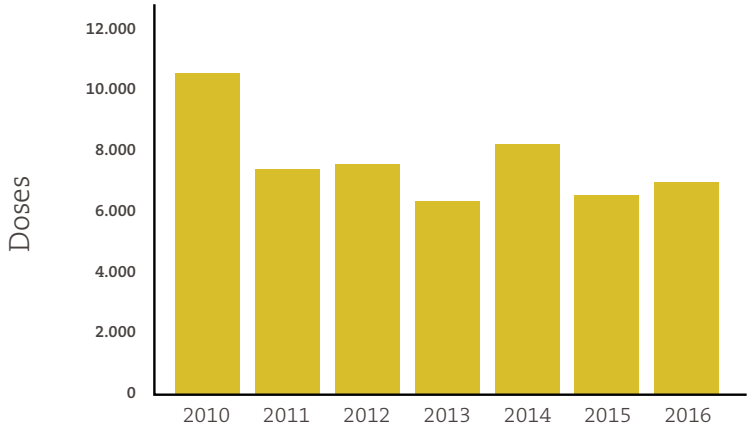



Figure 2 -Distribution of $^{18}$F-FDG doses

### $^{131}$I-NaI Solution

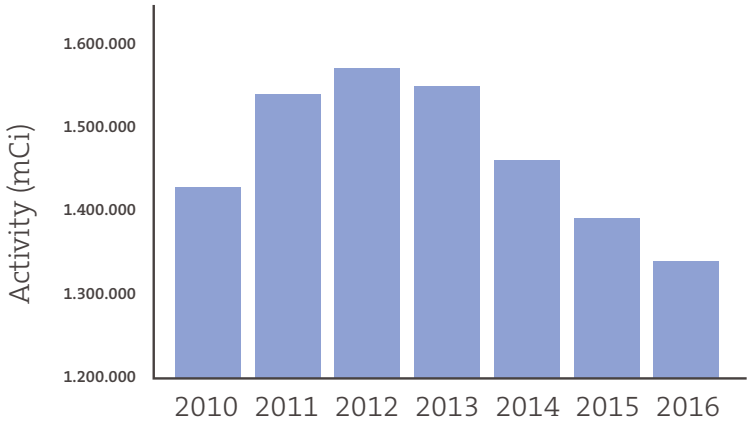



Figure 3 - Distribution of $^{131}$I-NaI solution

**DEX-70-TEC - Dextran–70**
Used in sentinel node scintigraphy.

**DEX-500-TEC - Dextran–500**
Used in sentinel node scintigraphy.

**CIS-TEC– Ethylene dicysteine**
For renal function study.

**ECD-TEC – 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.

**SAH-TEC Human Serum Albumin**
Used in cardiovascular studies in the diagnosis of pericardial effusion, intracardiac shunts, ventricular or

## $^{131}$I-Na Capsule

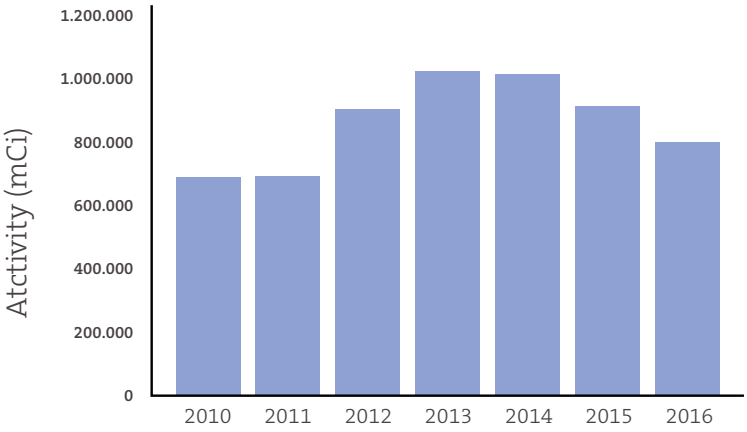



Figure 4 - Distribution of $^{131}$I-NaI capsule

## $^{68}$Ga-Dotatate

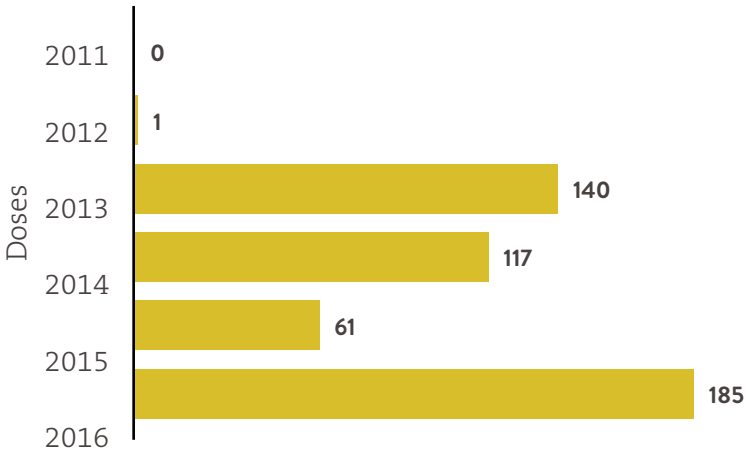
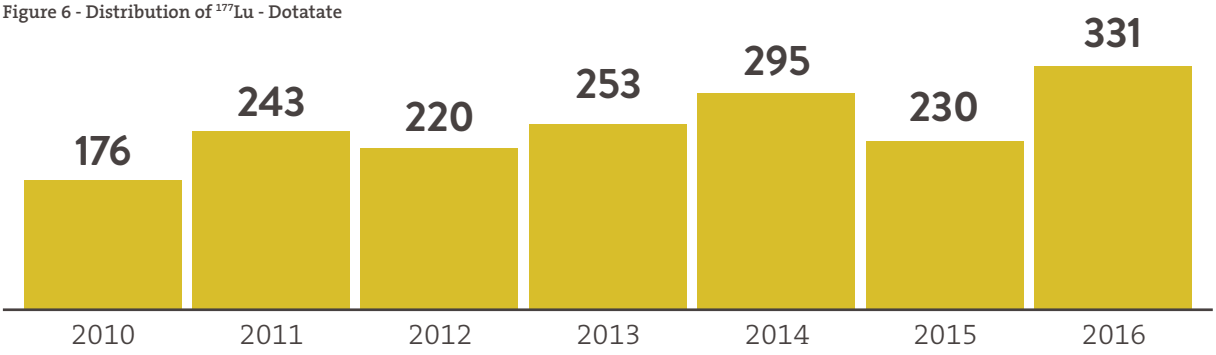



Figure 5 - Distribution of $^{68}$Ga- Dotatate

## $^{177}$Lu-Dotatate

Doses

Figure 6 - Distribution of $^{177}$Lu - Dotatate



major vessel aneurysm, major vascular pathway obstruction, congestive heart failure and midline mediastinal masses. It is also helpful in confirming suspected placenta previa.

**PUL-TEC Macroaggregated Albumin**
Used as a lung imaging agent for the detection of regional disturbances of pulmonary arterial blood flow in a variety of lung disorders. The major application lies in the diagnosis and management of pulmonary embolism.

**GLUCO-TEC Glucoheptonate**
For visualization of the kidneys, investigation of renal perfusion and morphology, evaluation of renal transplants, and imaging of 99m brain tumors and other brain lesions.

**TIN-TEC– Stannous colloid**
Indicated for imaging, localization and evaluation of liver and spleen pathology.

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

**MIBI-TEC- Sestamibi**
Indicated for myocardial perfusion analysis, breast scintigraphy, parathyroid scintigraphy.

During this period of time, the total number of generators sent to clinical and hospitals was slightly increased (Figure 1). The production of $^{18}$F-FDG was stable (Figure 2) even with the private PET production centers producing $^{18}$F-FDG. Besides, the $^{131}$I-NaI solution and capsule production was decreased (Figure 3 and 4 respectively).

The radiopharmaceuticals for diagnosis and therapy for neuroendocrine tumors was increased (Figure 5 and 6 respectively)

# Quality control of radiopharmaceuticals

Quality Control is part of the 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 radiopharmaceutical drugs are not released for use by the responsible radiopharmacist until their quality is guaranteed. Radiopharmaceuticals are transported to the nuclear medicine services in accordance with the radiation protection regulation. Nowadays, about 80,000 assays are executed in radionuclides including eluates from radionuclide generators, ready to use radiopharmaceuticals, non-radioactive components for labeling with a radionuclide, starting materials, packaging materials and environmental monitoring at the Radiopharmacy Center of IPEN-CNEN/SP. In order to evaluate if radiopharmaceuticals comply with the specifications of national and international pharmacopoeias and official standards for oral and parenteral human administration(,) 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, 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 9001-2015 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.

# Research and Development

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

- Study of high activity $^{99}$Mo- $^{99m}$Tc generators
- Study of different Sep-PaksÆ filters for using in $^{99}$Mo/$^{99m}$Tc generators

## Primary radioisotopes

- Production method for $^{64}$Cu.
- New target for $^{123}$I

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

- Studies pre-clinicals with $^{18}$F-Choline;
- Labelling of PSMA-11 with $^{68}$Ga using synthesis module
- Labelling of PSMA 617 and Rituximab with $^{177}$Lu
- Labelling of Cetuximab with $^{111}$In and $^{89}$Zr
- Trastuxumab with $^{111}$Lu and $^{64}$Cu
- Development of: a production method for MAG3 labeling with $^{99m}$Tc

## Lyophilized kits –

- Development of a production method for PSMA-11 lyophilized kit labeling with $^{68}$Ga

## IAEA Projects

- RLA 6074-006- Curso Regional de Capacitación sobre Validación
- BRA 6027- Improving protocols in nuclear medicine services and in the development of new radiopharmaceuticals

The Project IAEA – BRA 6027 - "Improving protocols in Nuclear Medicine Services and in the Development of new Radiopharmaceuticals" started on 2016 and is coordinated by Lorena Pozzo. It is a collaborative work among four national institutions: IPEN, CRCN, CDTN and InsCer – PUCRS. During four years, these institutions will work to develop and provide new Radiopharmaceuticals for PET/CT to the Brazilian society, like FLT, FCholine FES, PIB and FMISO.

Two events were organized in the scope of the Project to spread the knowledge about the Development of new Radiopharmaceuticals and pre-clinical tests, including imaging:

- National Course: Theoretical and practical techniques on synthesis and quality control on new PET tracers, Dr. Philip Elsinga, Dr. Regina Célia Carneiro, Mr. Marcos Vinícius Fortes Alba, Dr. Lorena Pozzo. 3 - 7th October – IPEN – CNEN/SP.
- Training on Preclinical Assays for Radiopharmaceuticals, Dr Michael Maria Welling, Dr. Lorena Pozzo, Dr. Danele Faria, MSc. Paula Feltes, Dr. Marcos Lima. 21 – 25th November. IPEN – CNEN/SP.

## REBRATS - NAT – IPEN

Since late 2016, IPEN is an oficial Nucleus of Health Techtology Assessment (NAT, from Portuguese: Núcleo de Avaliação de Tecnologias) of REBRATS, the Brazilian net for Health Technology Assessment (from Portuguese: Rede Brasileira de Avaliação de Tecnologias em Saúde), of Ministry of Health.

http://rebrats.saude.gov.br/membros-cat/440-instituto-de-pesquisas-energeticas-e-nucleares-ipen-cnen-sp

## Preclinical Imaging Laboratory IPEN/USP

The Faculty of Pharmaceutical Sciences of University of São Paulo (FCF – USP) and IPEN had firmed an agreement on 2013 to manage the Preclinical Imaging Laboratory at Center of Radiopharmacy, IPEN. This core facility is composed by an experimental bioterium, a room for animal preparation, surgeries and radioactive materials manipulation and a dedicated imaging room equipped with a PET/SPECT/CT scanner for small animals (Albira-Bruker).

Since then, the laboratory has developed different researches in a collaborative approach with FCF – USP and other centers from IPEN and USP, as well as other national institutions for research.

In the period from 2014 to 2016, about 10 projects were developed using this facility,

resulting in at least 3 finalized doctorates and other still in progress.

## 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 cannot 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 70). 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. From 2014 to 2016, the validation was applied in the Production process as It $^{131}$I-NaI solution and capsules, $^{18}$F FDG, lyophilized kits. production lines.

## 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 was finished 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 70, December 2014), the Quality Assurance send the 37 final dossiers to the regulatory organ in order to obtain the market authorization for the radiopharmaceuticals produced at IPEN. The quality assurance has also been working in the elaboration of the dossiers for clinical trials with new radiopharmaceuticals.

# Cyclotron Installation

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

## Cyclone 30

The cyclotron, Cyclone 30 model, manufactured by Ion Beam Applications-Belgium, is a compact, fixed-field, fixed-frequency, 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, $^{64}$Cu. Figure 7 shows the Cyclone 30.

Figure 7 - 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 there 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 $6^0$ 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 cost 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 $^{124}$Xe 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 8 shows the Cyclone 18.

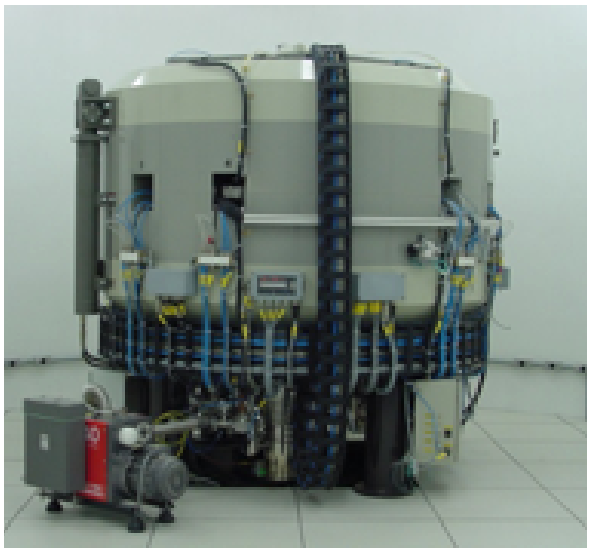


**Figure 8 - Cyclone 18**

## Clean Rom

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 9. 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).

**Figure 9 – Hot Cells**

Inside these hot cells synthesis modules are installed: two Synthera model, from Ion Beam Applications (Figure 10a) and three TraceLab MX model from GE (Figure 10b). These synthesis modules allow the routine production of $^{18}$F-FDG, $^{18}$F-NaF and experimental production of another radiopharmaceutical labelled with $^{18}$F.

Figure 10a – Synthera module

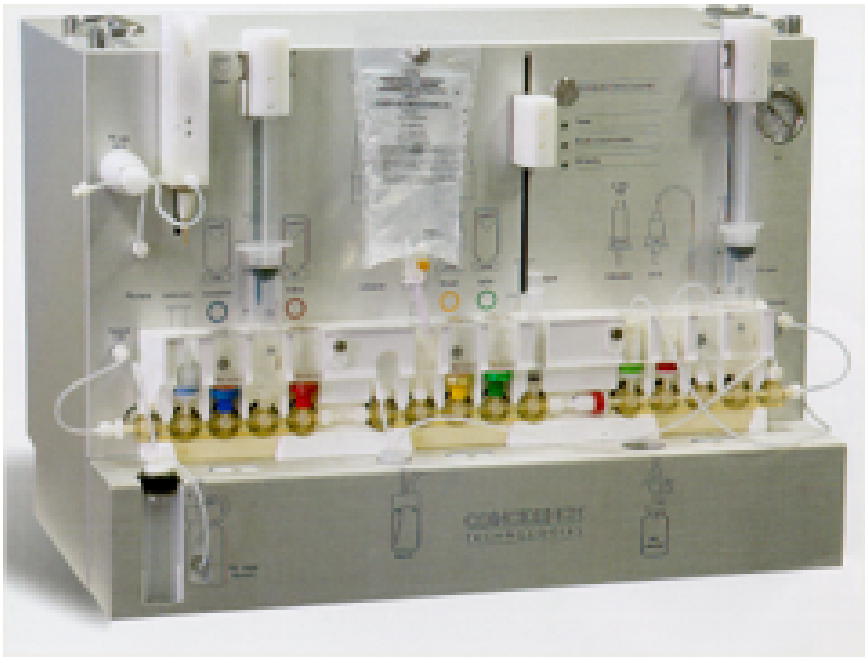


Figure 10b– TraceLab MX (GE) module

# Radiopharmacy facility infrastructure management

Figure 11 - New freeze dry production facility


Figure 14 - New Radiopharmacy Center electrical supply cabin

Figure 12 - New freeze dryers

Figure 13 New Radiopharmaceutical consumables warehouse

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-70 (which refers to radiopharmaceutical registry), the CR has been developing and managing several projects. From 2014 to 2016, the projects below were accomplished:

New freeze dry production facility (Figure 11) with 2 news freeze dryers; -that can quadruple the current lyophilized kits production (Figure 12).

Figure 15; - New R&D laboratory

New Radiopharmaceutical consumables warehouse (Figure 13) and Center electrical supply cabin (Figure 14).

For the research and production a new laboratory (Figure 15) and

modern hot cells to attend the GMP rules (Figure 16a and 16b)

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 out-sourcing companies.

Figure 16a and 16b- New radiopharmaceutical production fractionating hot cells

# Program Team

## Research Staff

Dr. Bluma Linkowski Faintuch; Dr. Dulcila Maria Lessa Bernardes; Dr. Elaine Bortoleti de Araújo; Dr. Henrique Barcellos de Oliveira; Dr. Lorena Pozzo; Dr Luís Alberto Pereira Dias Dr. Margareth Mie Nakamura Matsuda; Dr. Maria Tereza Colturato; Dr. Patrícia de Andrade Martins; Dr. Regina Célia Gorni Carneiro; Dr. Vanessa Gomes Batista; MSc. Afonso dos Santos Tomé Lobão; MSc. Carlos Leonel Zapparoli Júnior; MSc. Efrain Araujo Perini; MSc. Hylton Matsuda; MSc. Jair Mengatti; MSc. Neuza Taeko Okasaki Fukumori; BSc. Antonio Augusto Zanchetta; BSc. Carlos Farias Felgueiras; BSc. Enocles Melo de Oliveira; BSc. Geraldo Alves Pereira; BSc. Rosana Herrerias; BSc. Tonisson Lima de Azevedo; Tech. Ademar Cerqueira Filho; Tech. Adilson Abolafio; Tech. Adilson Guerrero; Tech. Adriano Aparecido de Souza; Tech. Aguinaldo Donizete Negrini; Tech. Antônio Carlos Freire; Tech. Antônio Carlos Gomes; Tech. Benedito Aragão de Araújo Dias; Tech. Celso Dias de Oliveira; Tech. Claudia Elisabete Castanheira; Tech. Claudia Regina Pereira; Tech. Cléo de Sousa Batista; Tech. Clovis dos Santos; Tech. David Antonio de Resendes; Tech. Decio Borges de Souza; Tech. Domingos Gomes de Campos; Tech. Edivaldo Caetano da Silva; Tech. Edmilson Bambalas; Tech. Edson Soares França; Tech. Eli Suares de Almeida; Tech. Eliel Domingos de Oliveira; Tech. Eliseu Santana da Silva; Tech. Everaldo José dos Santos; Tech. Fabio Lazzarutti; Tech. Francisco Carlos Ferraz; Tech. Geraldo Magela de Azevedo; Tech. Ideli Moraes de Oliveira; Tech. Irene Vicente; Tech. Jeremias Luiz Correia; Tech. João Alves dos Santos; Tech. José Alberto de Castro; Tech. José Alcides Silva Lima; Tech. José Antônio Trindade Pires; Tech. José Augusto de Oliveira; Tech. José Luiz da Silva; Tech. Josevaldo Clemente de Oliveira; Tech. Jurandi Silva Azevedo; Tech. Jurandir Alves de Sousa; Tech. Laércio da Silva; Tech. Ligia Benito da Silva Ricco;; Tech.; Tech. Luiz Antônio Villela; Tech. Luiz Fernando Soares Moracci; Tech. Manoel Varela Leite; Tech. Marcelo P. de Souza Santos; Tech. Marcos dos Santos; Tech. Mario Figueiredo Eusébio; Tech. Mauro Kioshi Miyahira; Tech. Mauro Veiga Fernandes; Tech. Natanael Gomes da Silva; Tech. Nestor Conceição da Silva; Tech. Orlando Oliveira da Silva; Tech. Osvaldo Alves de Araujo; Tech. Paulo Sergio G. Meneghetti; Tech. Pedro José Ricardo; Tech. Regina Ribeiro de Lima Bezerra; Tech. Reginaldo Felix de Lima; Tech. Reginaldo Pereira da Silva; Tech. Renato Arthur Benvenutti; Tech. Renato Brito; Tech. Rivadávia Bergara Sobrinho; Tech. Rubens Frederico Millan; Tech. Tarcísio Souza Alves; Tech. Vanderlei Inocencio Souto; Tech. Vivian Mendonça; Tech. Vladimir Lepki; Tech. Wagner Fonseca; Tech. Wagner Nieto; Tech. Waldir Mauch de Carvalho; Tech. Wellington Coelho de Carvalho; Tech. Wilson Aparecido Bruzinga; Fatima das Neves Gili; Iltemar Santana; Neli Pires da Silva.

## Graduate Students

Alyne Eloise Lafratta; Ana Cláudia Camargo Miranda; Arian Perez Nario; Cristian Antonio W. Villa Boas; Débora Franco Correa Pereira; Jefferson de Jesus Silva; Luiza Mascarenhas Balieiro; Marcelo Thaad; Maria Cícera Cardoso Viana Matos; Maria Renata Valente Brandão Freire; Mariana D´Angelo Martins K. El-Corab; Martha Sahyli Ortega Pereira; Raquel Benedetto; Renan de Azevedo Silva; Thais Oliveira Mendes de Castro;

## Postdoctoral Fellow

Dr. Sofia Nascimento dos Santos