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Analysis of the Production Routine of Iodine^{123} at IEN and an Adaptation Proposal for a New Radiopharmaceuticals Production Facility

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Abstract

The Brazilian Nuclear Energy Commission (CNEN) is the main manufacturer of radiopharmaceuticals in Brazil. The Nuclear Engineering Institute (IEN), located at Rio de Janeiro, is one of its main research and production centers, supplying public and private hospitals in the country. This radiopharmaceutical production is used in diagnostic and therapy procedures and allows one and a half million nuclear medicine procedures annually. However, IEN facilities were designed in the 60's and today its structure is inadequate in relation to the good manufacturing practices established by sanitary regulator (ANVISA) for the production of radiopharmaceuticals, leading to the need for a new project. In order to adapt and increase production in the country, a new plant will be built and integrated to the existing facilities with a new 30 MeV Cyclotron. Thus, it is proposed an analysis of the productive capacity of this plant in accordance with the principles of good manufacturing practices in order to define daily production and propose an optimized routine. As a result, the IEN / CNEN will in the future have a well-defined and standardized production process, with the flexibility to produce several radioisotopes required in nuclear medicine, obtaining a greater efficiency in its operation.

Keywords: Radiopharmaceuticals; Radiopharmaceuticals Production; Cyclotron; Optimization

Introduction

Radiopharmaceuticals have a short history compared to other drugs and medicinal products. The widespread use of radioactive nuclides for medical applications came as a direct result of the development of the atomic bomb during the Second World War. The construction of nuclear reactors in this context, opened up for the possibility of producing a whole range of new radionuclides by neutron activation of non-radioactive targets. Radionuclides that were not found in nature could now be produced artificially. According to the International Atomic Energy Agency (IAEA), radiopharmaceuticals are radioisotopes linked to biological molecules capable of integrating with specific organ, tissue or cell functions of the human body [2]. This new generation of short half- life radioisotopes, produced in particle accelerators, allows more accurate diagnoses and more effective therapies, mainly in the oncological and cardiological areas, with lower radiation doses for the patients, as well as lower levels of contamination of the environment.

However, the production of radiopharmaceuticals involves the handling of large quantities of radioactive substances and chemical processing. While still on a relatively small scale in comparison to the production of conventional pharmaceuticals, it involves a number of aspects that can be quite demanding for small-scale manufacturers. These include the operation and maintenance of processing facilities, complying with the codes of current good manufacturing practices (GMP), ensuring effective quality assurance and quality control systems, radioactive material transport, and registration of the products with the relevant health authorities [3].

As with any medicine, radiopharmaceuticals should be produced under carefully controlled conditions and tested for quality before being given to patients using standardized and validated operating procedures [3].

Currently, IEN's radiopharmaceutical division plays an important role in providing radiopharmaceuticals to public and private hospitals throughout Brazil, and produces only one type of radioisotope, ^{123}I, which gradually replaced ^{131}I as the isotope of choice for radiopharmaceuticals of diagnostics containing radioiodine, as it entails a lower dose of radiation for the patient and gamma ray energy of 159 keV is ideal for use in a gamma camera, in addition to being used as a marker in several radiopharmaceuticals, of which IEN provides two: Sodium iodide ($Na^{123}I$), Metaiodobenzylguanidine ($M^{123}IBG$) [4].

However, because of its installation and the Cyclotron were designed in the 1960s and built in the 1970s, its structure is currently unsuitable for the good manufacturing practices recommended by ANVISA (National Sanitary Surveillance Agency), and there is a fundamental need for an upgrade project. Thus, the IEN as a supplier of these radiopharmaceuticals has the fundamental need to conform to good manufacturing practices and increase its production and research capacity through a new radioisotope and radiopharmaceutical production facility with a new 30 MeV cyclotron accelerator. The remainder of this article is subdivided as follows. Section 2 is dedicated to the presentation of the floor plan of a new installation that will integrate to the existing installations in the IEN, to the Cyclotrons CV-28 and Cyclone 30XP, and to the system of iodine-123 production along with the GMP that will be met. Section 3 describes the

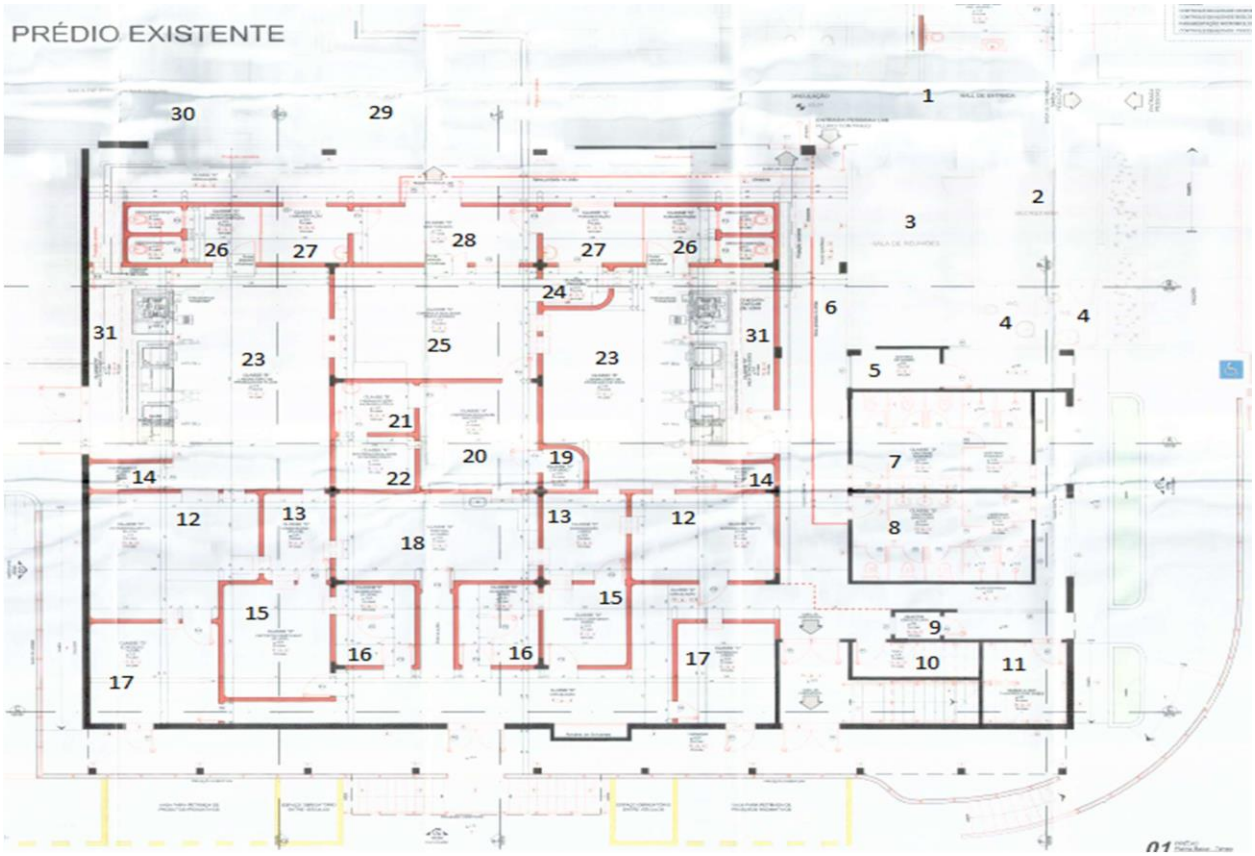
process of production of iodine-123 in the IEN, in addition to the inputs and human resources needed for its proper functioning. Section 4 will address the flow of people and materials from the proposed facility and new routine. Section 5 will discuss the results of the comparative analysis between the cyclotrons performances. Finally, Section 6 will conclude this work with the conclusions that have been drawn.

The Proposed Radiopharmaceutical Production Facility

The National Nuclear Energy Commission (CNEN), a federal authority, is the main supplier of radiopharmaceuticals in Brazil. The Institute of Nuclear Engineering (IEN), located in Rio de Janeiro, is one of the main centers of research and production, providing in total the accomplishment of approximately one and a half million nuclear medicine procedures per year in the country, which reveals the great importance of the nuclear sector in medicine [5].

The layout shown in (Figure 1) reveals how the new facility is designed to be incorporated into the existing IEN building, making the most of the available space for construction, taking into account the characteristics of the site.

Figure (1): Layout of the new production plant that meets ANVISA requirements for GMP



From the layout presented, it is possible to observe the following present areas, highlighted in (Table 1).

Table (1): Area framework

Area	Feature	Number
Entrance Hall	Common Usage	1
Secretary	Common Usage	2
Meeting Room	Common Usage	3
WC.	Common Usage	4
Gas Central	Restricted Use	5
Bathroom Circulation	Restricted Use	6
Women's Bathroom	Restricted Use	7
Men's Bathroom	Restricted Use	8
Waste Room	Restricted Use	9
Cleaning Materials Deposit	Restricted Use	10
Reservation of Gas Cylinders	Restricted Use	11
Conditioning Room	Restricted Use	12
Hygiene Room	Restricted Use	13
Proofread Room	Restricted Use	14
Component Storage Room	Restricted Use	15
Quarantine	Restricted Use	16
Expedition	Restricted Use	17
Preparation and Washing	Restricted Use	18
Cleanse	Restricted Use	19
Biological Quality Control	Restricted Use	20
Changing Room for Microbiological Work	Restricted Use	21
Microbiological Quality Control	Restricted Use	22
Production Laboratories	Restricted Use	23
Weighing Room	Restricted Use	24
Physical-Chemical Quality Control	Restricted Use	25
Monitoring and Decontamination Room	Restricted Use	26
Changing Room	Restricted Use	27
Monitoring Room	Restricted Use	28
Control Room	Restricted Use	29
Power Room	Restricted Use	30
Technical Area	Restricted Use	31

This work analyzes the production process, describing the step-by-step of how the ^{123}I, currently the flagship of the IEN, is elaborated, clarifies the time of each step of the process along the procedures by which this radioisotope will pass until becoming a radiopharmaceutical, and compares the average time with what is expected to be with the new 30 MeV cyclotron of the facility presented. In this way, some characteristics of the CV-28 cyclotron, which are currently used in the institute, and the Cyclone 30XP of IBA Radiopharma ™ Solutions, chosen to meet the needs of the IEN with the new installation are presented below. In addition, the way Iodine-123, using the KIPROS system (Karlsruhe Iodine Production) is also demonstrated.

Features of IEN Cyclotron CV-28

The Cyclotron CV-28 of 24 MeV of protons manufactured by "The Cyclotron Co.", (Figure 2), was assembled and installed in the Institute of Nuclear Engineering (Island of Fundão) during 1974, being at the time the first compact cyclotron of variable energy. It was inaugurated on December 31, 1974. Its main characteristics are:

- Type: isochronous;
- Weight: 23 tons;
- Polar diameter: 96 cm;
- Extraction radius: 40,64 cm;
- Number of sectors: 3;
- Average magnetic field: 18,500 gauss;
- Stability of the magnetic field: 10-5;
- Number of Dee's: 2;
- Sources of ions: penning.

The operation of the IEN Cyclotron CV-28 is controlled through a control table and instrument racks located in the Operating Room.

Figure (2): Detail of the CV-28 control desk and main irradiation line.

The main control and operation systems are [6]:

- Vacuum Measurement Panel - Indicates the pressure in the cyclotron acceleration chamber. An interlock device does not allow the operation of the radio frequency system when the acceleration chamber pressure reaches a value above the operating limit value;
- Ion Source Control Panel - Indicates the arc current and voltage and the gas pressure for the ion source. This control allows adjustment of current, gas flow rate, and the mechanical position of the puller;
- ON-OFF Panel General - "Ready" and "ON" Status Indicators and On-Off Switches are available for cooling water, oscillator filament, ion source gas, and the power supplies of the magnet, the profile coils, the anode, the arc of the ion source, and the electrostatic deflector;
- Power Distribution Control Panel - Provided with protection and control circuit breakers for individual control circuits of 115 volts AC;
- Operating Time Measurement Panel - Indicates the total integrated operating time for the ion source and oscillator valve filament;
- Beam Current Measurement Panel - Measures the current of the particle beam using selector switch and scale;
- Deflector Control Panel - Measures and

adjusts the position and voltage of the electrostatic deflector;
- Magneto Current Panel - Indicates and allows for fine and coarse adjustment of magneto main coil currents;
- Harmonic Coil Control - Adjusts the azimuth and magnetic bump magnitude caused by harmonic and center coils;
- Ion Source Position Control - Adjusts the position of the ion source;
- Position Control - Control for position adjustment of probe and magnetic channel;
- Frequency Meter - Digital display indicating the radiofrequency of operation of the cyclotron;
- RF Voltage Meter - Monitors the voltage of the Dee's and oscillator and the DC voltage and current of the oscillator valve plate. It also allows the adjustment of the Dee's voltage level;
- Radio Frequency Control - Allows remote adjustment of oscillator and resonator tuning parameters;
- Profile Coil Control - Digital displays indicate the profile, harmonic, center and main coil currents. Allows the adjustment of the chains of each of the four sets of profile coils;
- Controls are arranged for sequential operation, with interlocks to prevent damage and ensure safe operation with minimal operator training.

In addition to the cyclotron specific panels and controls above, the following other control instruments are available [6]:

- Vacuum Measurement Panel of Irradiation Lines - Indicates the measurement of the pressure in the irradiation lines;
- Integrator - Measures the integrated load of the particle beam;
- Quadrupolar Lens Power Supplies - Allows adjustment of position and focusing of the particle beam;
- Distributor Magnet Panel - Controls and positions the beam in one of seven available irradiation lines;
- 4 Sectors Collimator Panel - indicates, for each irradiation line, the distribution of the beam current in the 4 sectors of the collimators.

Features of Cyclone® 30XP Cyclotron

The need to exchange the CV-28 for a new cyclotron is due to the fact that it is already at the end of its life, with limitations of an obsolete technology and without specialized technical support (the company that supplied this equipment declared bankruptcy in the 80's) therefore, due to these threats, the installation of a new Cyclotron was proposed, and Cyclone 30XP was also ideal because of its ability to produce bundles of alphas, as well as protons.

According to the IBA, Cyclone® 30XP is a variable-energy cyclotron that accelerates protons of 15 to 30 MeV and is capable of delivering a double beam of protons, deuterium and alpha beams, as well as upgradeability for higher currents, necessary case. In addition, it offers guaranteed intensities of 400μA, 750μA and 1500μA. The 30 MeV alpha beam is suitable for producing isotopes such as ^{211}At, a promising alpha emitter for radiotherapeutic use. While the proton and deuterium are accelerated in the mode of negative ions and extracted with the stripping system, the positive alpha beam (He ++) is accelerated and extracted in positive ionic mode using an electrostatic deflector. In addition, because of the energy range of 15 to 30 MeV, the cyclotron has the flexibility to produce a series of radioisotopes such as ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{64}Cu, ^{67}Ga, ^{111}In, ^{123}I, ^{201}Tl, ^{68}Ge, among others [7].

KIPROS System for Production of Ultra-Pure Iodine123

The ^{123}I is produced by the nuclear reaction ^{124}Xe(p,2n)^{123}Cs → ^{123}Xe → ^{123}I in

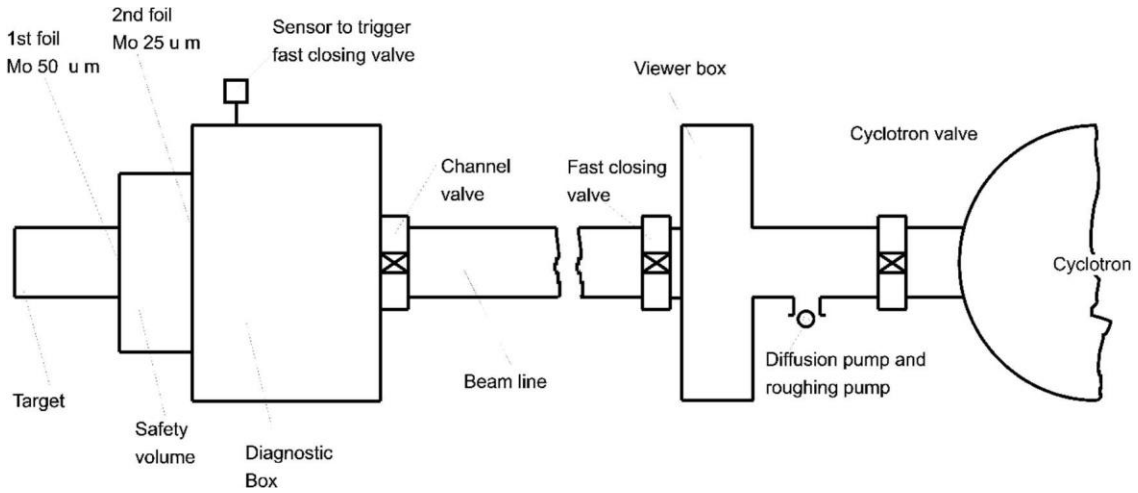
IEN's CV-28 Cyclotron using the KIPROS (Karlsruhe Iodine Production) system. The basic structure of this system is composed of a beam diagnostic box, a chemical unit, a target chamber, a rack with electronic control based on the programmable logic controller and two computer terminals [8].

As the enriched xenon gas is expensive input and difficult to obtain, in addition to meeting a safety philosophy, KIPROS works with a gaseous "multi-trap" system, Figure 3, in order to reduce losses. The target chamber is sealed by a 50 μm molybdenum window. The safety volume in front of the target chamber is additionally vacuum sealed by a 25 μm molybdenum sheet [8].

In order to the cyclotron proton beam reach the target it will have to pass through the safety volume and two sheets (windows), which are indirectly cooled. In case the target sheet ruptures, the gas expands in the safety volume. The Xe gas can then be recovered by the standard cryogenic transfer procedures for the storage bottle [8].

The worst-case scenario would be the second window breaking simultaneously with the first. In this case the gas would expand in the diagnostic box and in the beam line. In order to prevent gas expansion towards the pump system and cyclotron, there is a sensor that monitors the pressure in the diagnostic box. Upon detecting a pressure increase, the programmable logic controller sends a command to the KIPROS quick shutdown valve (13 ms) and to the cyclotron beam gate, ensuring gas retention in the diagnostic box and blocking the beam [8].

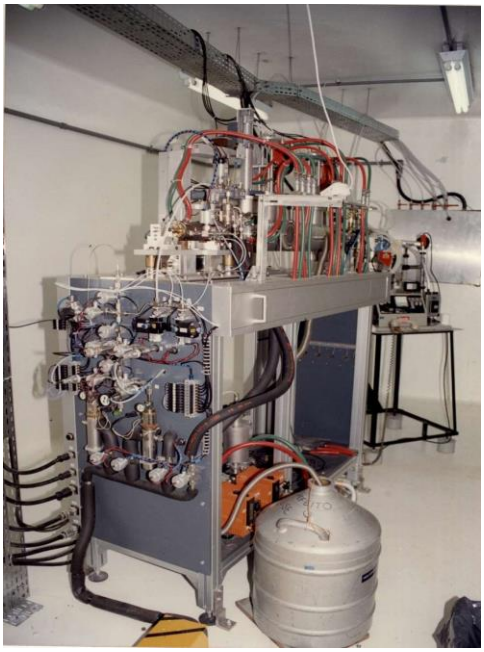
Figure (3): KIPROS System Security Philosophy



Working Principle

In the KIPROS' casemate is located the beam diagnostic box and the high-pressure target chamber with the automatic window changer, (Figure 4). The electronic control rack is installed in the control room of the cyclotron as well as one of the computer terminals. The chemical unit for concentration of produced ^{123}I activity is located within the respective processing cell in the radiopharmaceutical production laboratory, as well as the second computer terminal [8].

Figure (4): KIPROS high-pressure gas target system for the production of I-123. A sophisticated beam diagnosis system in front of the target ensures adequate beam alignment.



The SIMATIC S5 Programmable Logic Controller from Siemens (located in the control rack), which is used in the Control System of the production process of the ^{123}I, uses the programming language STEP 5 specific language for automation of industrial processes [8].

The beam diagnostic box consists of two collimators of four sectors, a beam stop, the target chamber, a safety volume, all of these components are cooled with ice water, to meet the operational needs, that comes from the continuous system integrating the facilities of the cyclotron. The control of this effluent is done by a capacitive sensor through a fan that detects the flow of water and the SIMATIC controls this signal [8].

The KIPROS vacuum system is connected to a filter system, and this to the casemate exhaust system. In addition, the pump responsible for the purification of xenon gas is connected to a molecular sieve trap responsible for the capture of impurities that may have formed in the system [8].

Cave 5, KIPROS' casemate, and the processing cell containing the chemical unit are completely watertight and an under pressure of at least 40 mm c.a. in relation to the environment. The sealing of the cave 5 is guaranteed by the installation of airtight doors [8].

The input and output of materials of any kind in the cave 5 or in the processing cell are performed without loss of confinement and remotely via the programmable logic controller (SIMATIC) and in some unit operations in the cell with clamps [8].

The cryogenic unit responsible for the supply of liquid nitrogen and the helium gas used in the process are located in the experimental area of the facility, having their entry and exit in the process controlled by SIMATIC [8].

At the front of the cell is installed the reagent station of the system, (Figure 5). In it we have the ultrapure water tank for dissolution of the ^{123}I produced, a peristaltic pump that makes its transfer through a 1/8" teflon tube outside diameter to the target chamber in the cave 5, the sodium hydroxide for elution of 123I after its concentration on an ion exchange column inside the cell and a metering pump [8].

In order to retain ^{123}I in the event of teflon tube rupture, they pass through a ¾" galvanized iron pipe outside diameter installed in the walls of the casemates [8].

Figure (5): Reagent Station

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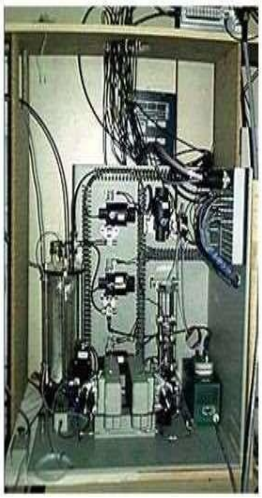
The chemical unit, (Figure 6), for concentration of ^{123}I stored inside the processing cell receives the iodine dissolved in water from the target station by the capillary to the shielded ion exchange columns, (Figure 7) [8].

Figure (6): Chemical Unit of KIPROS inside the cell on the left, on the right details of the Millipore filter.



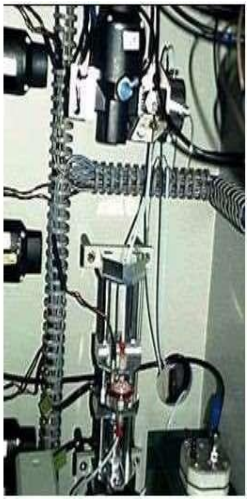
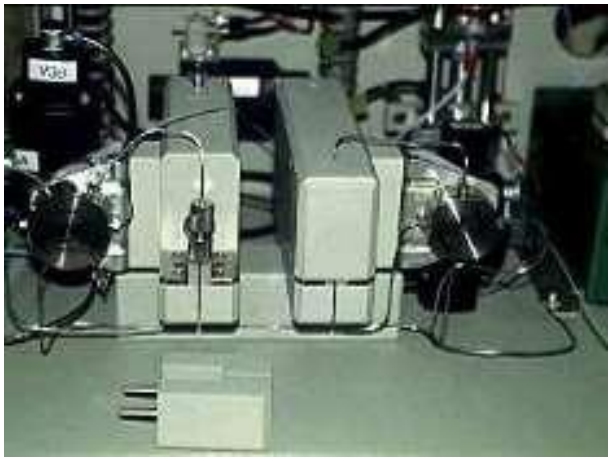


Figure (7): Shielded ion exchange columns.



A dose calibrator, a dispensing wheel, a sample aliquotator (teleburet), an equipment to unseal pencilin-type bottle and sealer are also located inside the processing cell [8].

National and International Guidelines on Good Manufacturing Practices for Radiopharmaceutical Products

ANVISA Resolution RDC No. 63 of December 18, 2009 has the objective of establishing the minimum requirements to be observed in the manufacture of radiopharmaceuticals, which must comply with Good Radiopharmaceutical Manufacturing Practices (GMP) and also with the principles GMP Medicines [9].

About the good manufacturing practices, the key points for the new facility be in compliance are:

- Personnel;
- Premises and Equipments;
- Production;
- Documentation;
- Quality Assurance and Quality Control.

Personnel

To ensure the safe manufacture of radiopharmaceuticals, an ongoing personnel training program should be established that

includes training in Good Manufacturing Practices, safe handling of radioactive materials and radioprotection procedures [9].

The production site and its personnel must be under the responsibility of a pharmacist with proven academic background and demonstrated experience in radiopharmacy and radiation protection. In addition, batch release for use should only be approved by this responsible professional, who must have experience in the production of radiopharmaceuticals [9].

Personnel performing radioactive product handling operations or performing tasks in clean or aseptic areas should be carefully selected to ensure that GMP principles are followed and should not present any disease or condition that could compromise product integrity. In clean or aseptic areas only the minimum personnel required to perform the work should be presente [9].

Training records should be maintained and evaluations of the effectiveness of the training program should be performed. All personnel involved in the production, maintenance and quality control activities of radioactive products should strictly follow the Standards for the handling of these products and should be monitored for possible radiation contamination or exposure [9].

Premises and Equipment's

As a general principle, buildings must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them [10].

Specific disposal systems should be mandatory for radioactive effluents. These systems should be effectively and carefully maintained to prevent contamination and exposure of personnel to the radioactive waste both within and outside the facility [9].

Sinks should be excluded from aseptic areas and lighting, air conditioning and ventilation systems should be designed to maintain satisfactory temperature and relative humidity, ensuring the thermal comfort of personnel working in protective clothing [9]. Buildings should be in a good state of repair. The condition of the buildings should be reviewed regularly and repairs carried out when and where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not compromise products [9].

Ventilation of radiopharmaceutical production facilities should meet the requirement to prevent the contamination of products and the exposure of working personnel to radioactivity [10].

Dedicated facilities and equipment should be used for the manufacture of any radiopharmaceutical product derived from human blood or plasma [10].

Autoclaves used in production areas for radiopharmaceuticals may be placed behind a lead shield to minimize the radiation exposure of the operators [9].

All containers of radiopharmaceutical substances, regardless of the stage of manufacture, should be identified by securely attached labels. Cross-contamination should be prevented by the adoption of some or all of the following measures [10]:

- Processing and filling in segregated areas;
- Avoiding the manufacture of different products at the same time, unless they are effectively segregated;
- Containing material transfer by means of airlocks, air extraction, changing clothes and careful washing and decontamination of equipment;
- Protecting against the risks of contamination caused by recirculation of untreated air, or by accidental re-entry of extracted air;
- Using "closed systems" of manufacture;
- Taking care to prevent aerosol formation;
- Using sterilized containers.

In general, any radioactivity should be handled within specifically designed areas maintained under negative pressures [10].

Separate air-handling units should be used for radioactive and non-radioactive areas. Air from operations involving radioactivity should be exhausted through appropriate filters that are regularly checked for performance [9].

Pipework, valves and vent filters should be properly designed to facilitate validated cleaning and decontamination [10].

Production

Radioactive products must be manufactured in controlled areas and all operations performed must have their Standard Operating Procedures (SOPs) [9].

Raw material specifications shall include details of their source, origin and, where applicable, production method and quality control assays used to ensure their suitability for their intended use [9].

Special consideration should be given to the validation process of sterilization methods. Chromatography equipment should generally be dedicated to the preparation and purification of one or more products labeled with the same radionuclide to avoid radioactivity cross-contamination [9].

Special consideration should be given to cleaning, sterilization and operation of lyophilizer equipment used in the preparation of lyophilized reagents. For labeled lyophilized reagents, the lyophilization process should be performed under aseptic conditions [9].

There is also a need to draw up a list of the most critical equipment (such as scales, dose calibrators, sterilizing filters, etc.) whose reading or operating errors could potentially cause harm to the patient receiving the final product [9].

Specific equipment and devices for measuring radioactivity, as well as radioactive reference standards, should always be available for use. The packaging and transport of radiopharmaceuticals must be carried out according to current health surveillance and radioprotection standards [9].

Documentation

The documentation system must follow the guidelines contemplated in ANVISA's Resolution that disciplines the good practices of drug manufacturing [9].

Separate records of the receipt, storage, use and disposal of radioactive materials, in accordance with applicable radioprotective legislation, should be maintained outside the distribution records of all products [9].

Quality Assurance and Quality Control

Radiopharmaceuticals are nearly always used before all quality control testing (e.g. tests for sterility, endotoxin, radionuclidic purity, etc.) has been completed. The implementation of and compliance with the quality assurance programme are therefore essential [10].

The Quality Assurance and Quality Control areas should have the following duties [9]:

- Prepare detailed instructions for each test and analysis;
- Ensure proper identification and segregation of test samples to avoid mixing and cross contamination;
- Ensure that environmental monitoring, equipment qualification and process validation are carried out appropriately to enable assessment of suitability of manufacturing conditions;
- Release or reject raw materials and intermediate products;
- Release or reject packaging and labeling materials;
- Release or reject each batch of finished product;

- Assess the suitability of the conditions under which raw materials, intermediate and finished products are stored;
- Assess the quality and stability of finished products and, where appropriate, raw materials and intermediate products;
- Establish expiration dates based on shelf life related to specific storage conditions;
- Establish and review control and specification procedures;
- Take responsibility for radiopharmaceutical retention samples;
- Take responsibility for proper maintenance of radiopharmaceutical distribution records.

The Quality Control laboratory should be located separately from the production area and all qualitative and quantitative testing established in the raw material specifications may be replaced by reviewing the certificates issued by the supplier of these materials, provided that the following conditions are met [9]:

- There is a reliable production history;
- All raw material manufacturers/ suppliers must be qualified and must be regularly audited;
- At least one specific identification test is performed by the manufacturer of the radiopharmaceutical.

Samples of the intermediate and final products should be retained in sufficient amounts and under appropriate storage conditions to allow repeated testing or verification of a batch control. These samples should be kept for an appropriate period in accordance with the shelf-lives of the radioactive components concerned. However, this may sometimes not be applicable, e.g. for radiopharmaceuticals with a short half-life [10].

Analysis of the Iodine-123 Production Routine in the Current Radiopharmaceuticals Production Facility

The relationship of CNEN's radiopharmaceutical units with their customers is formalized through a service contract, the price of products being established by CNEN for all of its units. These units have a customer service, by e-mail or telephone, which is the main channel for requesting the supply of radiopharmaceuticals. Because the requested frequency and activity depend on scheduled exams in clinics or hospitals, requests are made continuously by clients.

Therefore, every need for production starts from the request of a customer, made through the IEN website, in the radiopharmaceuticals tab, after selecting the option "To order radiopharmaceuticals click here". In this window, the requester fills in the login and password fields to then access the request window, where it is possible to inform all desired characteristics for a certain date, such as the activity.

In the intranet dashboard the technician can plan the production by following all the orders made in the week with their respective delivery dates, so that by Friday the entire production plan of the following week has already been defined. It is also possible to visualize the quantity requested and quantity supplied, registered after the shipment, the number of the service order, the Tax Code of Operations and Services of goods exits (intermunicipal and interstate), in addition to presenting the individual contact of each one of the hospitals to report any unforeseen events that could lead to delays in delivery. After having the production plan

defined, the preparations for the beginning of production of ^{123}I begin, which has three stages:

- Irradiation;
- Chemical Processing with the KIPROS Production System;
- Quality control.

Irradiation

The first stage of the production process is the irradiation of the Xe target with proton beams in the week after the production plan. The irradiation process needs to precede the quemical procedure by at least 6 hours due to the radioactivity decay sequence, since the production of ^{123}I starts from a stable Xenonium-124 core, a rare material in nature with an abundance of 0.0952% being necessary to take the isotopic enrichment of this material to 99.9% for its use, thus becoming the first great input needed for the final product (already enriched).

Before starting the irradiation, several parameters need to be checked to ensure the safety and efficiency of the process, starting with the employee, usually technician in mechanics, who checks the utilities such as the air conditioning system, ventilation and exhaust, water cooling, compressed air, filtering system, electric panel, among others. A second professional, usually an engineer, is the cyclotron operator, who connects the voltage sources of the coils that generate the magnetic field, the ions source device, vacuum pumps and adjust all the parameters related to the control table. He ensures that the target is being irradiated in the right conditions.

The third professional is responsible for the radiation protection aspects. He is not necessarily the radiation protection supervisor, but has a specialization in the area and participates in monitoring during the irradiation process, ensuring that all dose levels are controlled and within normal conditions, established in the radiation protection plan.

Finally, there is the KIPROS System operator. Thus, there are a total of four professionals working together in this stage of production. Both the KIPROS operating stage and the irradiation process are performed simultaneously. The KIPROS operator supplies the target with Xe gas, performing a cryogenic step that involves the cooling of the target chamber before he opens specific valves to transfer the xenon gas inside it. After that he can heat the chamber, so that the irradiation can be done. All these preparations mentioned above, for the irradiation using the cyclotron, involving the four professionals, takes around thirty minutes. During this procedure, this professional take notes of some parameters such as temperature, gas pressure, target incident current and irradiation time.

In this way, the production sequence starts from Xenon-124 bombardment with protons, thought the nuclear reaction "$^{124}Xe(p,2n)^{123}Cs$", in which a proton enters, but almost immediately two neutrons emerge, thus obtaining the Cesium-123 as a result of the first reaction, which has a half-life of 5.9 minutes. Cesium-123 decays to Xenon-123 with 2.06 hours of half-life. The ^{123}I is obtained from its decay and has 13.2 hours of half- life, decaing to Tellurium-123, that is stable.

This irradiation step usually takes place from 1 p.m. to 6 p.m., having an average time of 5 hours. This time determination depends on the production demands, being able to vary from a minimum of two hours and a maximum of eight hours. After the end of the irradiation, the operator turns off the entire

system and it must remain on hold for the next six hours. However, due to obstacles involving the impossibility of having night shifts in the IEN, the ideal decay time of 6 hours ends up being extrapolated to 13 hours after the end of the irradiation, which inevitably affects the final product result due to the additional radioactive decay. Either way, the valves are closed and nothing can be done wrapping this system until the beginning of the next day's work that starts at seven o'clock in the morning.

On the other hand, during this time of waiting, this same professional, who is usually a technician in chemistry, prepares the synthesis process of the molecule that takes place in a proper hot cell, supplying them with all the necessary inputs, which are: sodium hydroxide, purified water, sterile vials for storage of iodine, seals, labels and lead shielding. In addition, is necessary to check if the hot cell exhaustion is working and the ion exchange columns, which works as an iodine trap, are in good conditions.

Chemical Processing with the KIPROS Production System

Obtained ^{123}I, it starts the second stage of the production process that is performed with KIPROS system. The first step is to remove this radioisotope from the target chamber, which is full of xenon gas mixed with iodine produced. This gas is cryogenically pumped out of target and transferred to a proper container to be used in a future production. In this cryogenic process, the gas migrates from the target chamber to its storage location opening a proper valve which connects it with a vasel that is kept frozen and in a vacuum condition. During this process, there are no losses of iodine, as it is adsorbed at the surface of the walls of the target chamber.

The extraction of ^{123}I occurs through the injection of purified water inside the target chamber, which is heated in order to remove the iodine. This small volume (approximately 60 ml) is then pumped through ducts to the processing hot cell. During this process, this ^{123}I passes through ion exchange columns that keep it retained inside it, and allows the passage of any other impurity, such as tellurium, sending them directly to the tailings tank. Thus, the step of extraction of this retained ^{123}I in the column is made by passing a solution of sodium hydroxide, with its own PH characteristics. After production volume is extracted, it must to be fractionated and sent to clinics and hospitals, when the final product to be supplied is sodium iodide (NaI). All these procedures are done inside the proper hot cell.

In cases where Metaiodobenzylguanidine (MIBG) is being produced, there is still the labeling step of this molecule, which is made after the extraction of ^{123}I into the hot cell, where the radioactive material is taken into a furnace. For this procedure, the MIBG molecule must be inserted into the hot cell during the standby step, after irradiation process.

As soon as the technician receives the material in the processing cell, he informs the pharmacist who works on the issuance of service order tags and calls what was the total activity produced so that he can do all the necessary calculations in order to know if, with the activity produced, it will be possible to attend all hospitals. If this is not possible, it is necessary to decide which hospitals will be treated based on several variables, such as the quantity requested, the distance to be

traveled to the hospital location, among others.

He uses a spreadsheet where the activity that the hospital requested and how much was produced is verified so that the aliquot to be withdrawn from this total production can be calculated, considering the time of decay until the delivery of the demand. In this way, it is possible to inform the operator the quantity to be withdrawn (in mCi), always greater than what was requested, so that, when delivered on the required date, the product has the activity requested.

Once this professional who works in the hot cell receives the information from the pharmacist how much to extract, he performs the fractionation and removes that aliquot from the total produced, placing it inside the bottle which is sealed and taken to the labeling stage. In addition to this aliquot to be sent, another one is separated for the quality control, but in this case in much reduced quantities, to carry out all the necessary quality control procedures.

Thus, the step of extracting the ^{123}I and labeling the molecule in the warm cell takes About 30 minutes, whereas for the MIBG, the duration can reach 1 hour and 40 minutes. In parallel, while the product is fractionated and packaged, the pharmacist already starts the shipping process with the emission of the labels to avoid any problem with aliquot exchange and thus already identify the radiopharmaceutical as soon as it is received, and then be delivered to the shipment. Consequently, two lead castles are received, one is sealed to be delivered to the shipment and then sent to the hospital, and the other one opened to be delivered to quality control, which will verify if the purity of the material is suitable for shipment.

Quality Control

Quality control includes tests for product identity, radionuclide purity, radiochemical purity and biological purity. The purity of the radionuclide is measured with a high- purity germanium detector, while the radiochemical purity is determined by the thin layer chromatographic method. The biological purity is verified with the Limulus test.

In this way, the team receives the open (unsealed) lead castle with its aliquot, which is fractionated on the spot by its professionals for the four necessary quality controls (physical, chemical, biological and microbiological) and passes one of these aliquots to the operator of the hyper pure germanium detector, usually a physicist, which controls the radionuclide purity. Meanwhile, the pharmacist does the radiochemical, biological and microbiological purity with the other three aliquots. For MIBG, these tests also permit to know the percentage of iodide in the labeled Metaiodobenzylguanidine.

In order for the delivery of the material occur, all purity tests must approve the aliquot, except for the microbiological control since it takes considerably longer to be completed, beyond the half-life of the ^{123}I. These quality control steps take around 40 minutes.

While the radionuclide and radiochemical purity steps are in procedure, the team responsible for the shipment, together with a radioprotection professional, awaits the approval of the quality control team to seal the pack, issue the invoices and release the vehicles for the transport. This radiation protection professional carries out measurements to check the dose level and the transport conditions of the vehicle.

After receiving the lead castle, the technician responsible for the expedition packs it into a specific transport bucket with dry ice, in order to be sealed after the approval of the quality control team, which will be examining its aliquot. In this way, with the approval of the quality control, the person responsible for the shipment seals the transportation bucket, places a final label on the container so that it can be properly identified and issues its invoice. Two other labels are issued for documentation purposes.

The expedition has an average duration of 30 minutes, of which the first 15 minutes run parallel to the quality control, and after the samples are approved, the other 15 minutes occur.

That said, it is possible to arrive at the following times which give the duration of the entire production, as shown in (Table 2).

Table (2): Cadence of production with the cyclotron CV-2

SODIUM IODIDE		MIBG	
Production Process	**Length**	**Production Process**	**Length**
Preparations for Irradiation	30 min	Preparations for Irradiation	30 min
Irradiation	2 h	Irradiation	5 h
Decay after Irradiation	13 h	Decay after Irradiation	13 h
Processing	30 min	Processing	1 h e 40 min
Quality Control	40 min	Quality Control	40 min
Expedition[a]	15 min	Expedition[a]	15 min
TOTAL:	16 h e 55 min	TOTAL:	21 h e 05 min

An ideal production scenario proposed for the MIBG, for example, which currently has a considerably higher demand for NaI, would have the irradiation starting at 7:00 p.m. and ending at 0:00 p.m. Thus, the radioactive decay time after irradiation would be only 6 hours, considering the beginning of the processing at 6 o'clock in the morning, and the use of the total activity produced would be greater, once it was lost of 7 hours with the decay after irradiation.

Development of an Iodine-123 Production Routine for the New Radiopharmaceuticals Production Facility

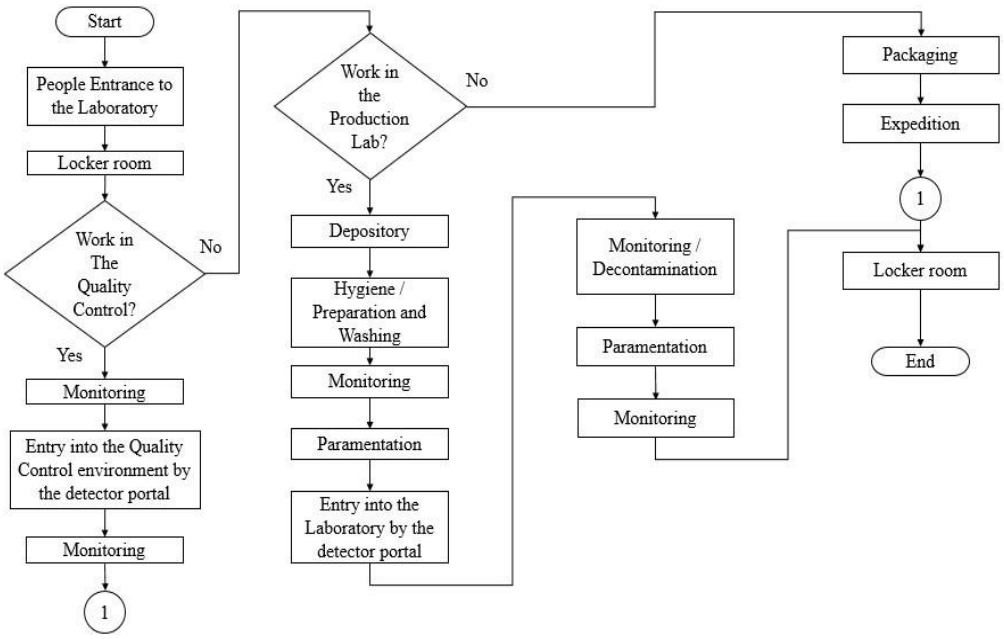
Production Plant Access

The new facility has four access routes, three of which are exclusive for entry and exit of people, and one for entry and exit of inputs and by-products of production.

The inflow of people is given by the entrance hall, where the main access, used for both employees and for possible technical visits, is located. After entering the plant, everyone goes down the hallway to the bathrooms, where employees wear their own clothes according to their duties before heading to their work areas.

(Figure 8) shows the transition between each of the plant areas according to the functions of each employee linked to the production steps.

Figure (8): Flow diagram of areas transitions according to each activity.



Outside the main entrance and exit, there are two other emergency exits: one located next to the main entrance and another on the side of the facility, near the shipping area where the flow of materials is greater. However, these doors should never be used to enter the controlled area as they are interlocked and equipped with audible (or visual) alarms that alert the staff if any of the doors are open for a long period of time.

It is also important to highlight the access to two areas of the plant that are given only outside: the waste room (nº 9) and the gas central (nº 5). These rooms do not have doors to the interior of the installation, only windows that allow the visualization of its interior through the glass. In addition, one of the laboratories is positioned at the rear of the plant and, therefore, its technical area (nº 31) behind the processing cells has external access for maintenance, in addition to internal access for possible interventions during operation.

Quality Control Analysis

For occupationally exposed individuals (OEI) who work in quality control, in order to guarantee the aspects of radiological protection in the controlled area, it must be accessible only through a detector portal before starting their work routine, thus by the monitoring room.

The controlled area includes areas that need to be controlled to ensure good manufacturing practices and radiation protection. Therefore, the controlled area is designed and constructed to provide radiation protection and compliance with GMP. The area covers the radiation protection zones as well as all production areas that are used to work with open radioactive sources. Both requirements are achieved through administrative controls such as controlled access, segregation of workspaces, and written protocols such as standard operating procedures (SOP), as well as engineering controls such as interlocking doors,

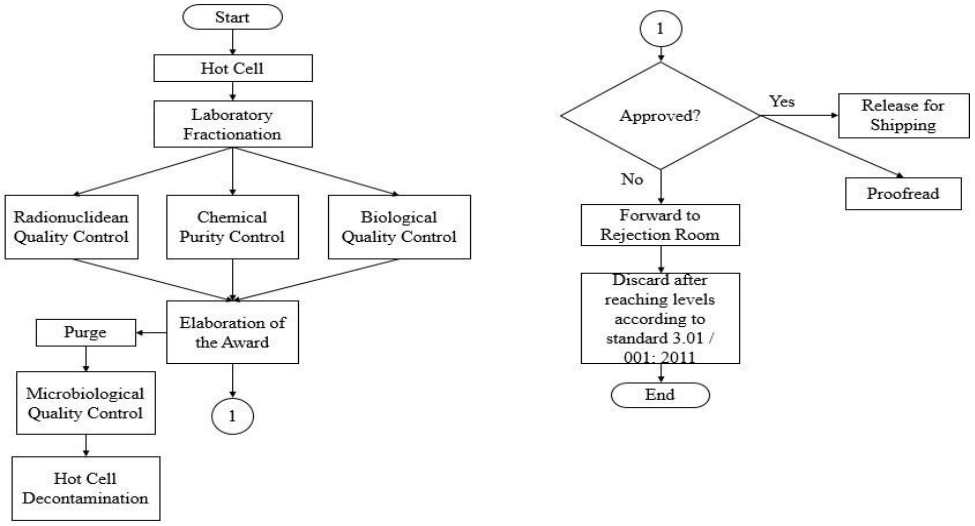
appropriate pressure gradients, an appropriate number of air exchanges, and pass-through.

All aspects that have been mentioned serve the purpose of ensuring not only the efficiency of the plant but also the safety of the worker. Therefore, following a 2000 hours /year model, all installation procedures and systems should ensure that the OEI does not receive a dose rate greater than 3 μSv / h within a controlled area.

The first environment after the monitoring is the physicochemical control, where the hyper pure germanium detector is used to perform the radionuclide purity test with high pressure liquid and gas chromatographs. In the area related to biological and microbiological control, smear and culture development of microorganisms are carried out.

Just as the quality control is done today, it will be done in the future with the radiopharmaceutical, which can be either sodium iodide, as MIBG, leaving the hot cell with an aliquot for the quality control and the other for packaging and, subsequently, shipment. The flowchart in (Figure 9) illustrates the entire procedure adopted by quality control until release for shipment.

Figure (9): Flowchart of quality control procedures.



Production Analysis and Shipping

In the layout presented, nine rooms make up the production block (considering quality control as one of the final stages of production): two production laboratories (nº 23), two proofread rooms (nº 14), a weighing room (nº 24), a physical-chemical quality control (nº 25), a biological quality control (nº 20), a microbiological quality control (nº 22) and the cleanse room (nº 19). The installation is designed to ensure the orderly handling of materials and equipment to avoid confusion and contamination of equipment and products, whether due to personal or environmental conditions.

In this way, the changing rooms (nº 27), which are part of the monitoring and decontamination rooms (nº 26), should be equipped with lab coats, boots, and at the monitoring site where access to the production laboratories should have a step-over bench separating the cleaned area from

the potentially contaminated area. Nevertheless, through the plant it is possible to identify that the rooms will have two wash basins and two showers for decontamination purposes. Due to the small number of operators working in the controlled area of a radioisotope production facility, a portal detector to enter the area is sufficient.

The input of raw material, as already mentioned, is given by the lateral receiving and conferencing access, being checked and sent to the quarantine (nº 16) where it is identified and registered in the stock to be transferred and stored in the component storage room (nº 15). It is important to note that when the input is the guanidine molecule for MIBG labeling, it should be stored cold in the store, unlike most other inputs that are stored at room temperature.

As production input is required, it is taken to the hygiene room (nº 13) for the purpose of being properly cleaned and transported through the pass-through to the production laboratory (nº 23). While in the preparation and washing step (nº 18), the bottles and seals used in the processing cells are placed in autoclaves to be sterilized and then transferred to the production laboratory by supplying the hot cell. In cases where MIBG is to be produced, before filling the cell with the guanidine to be synthesized with iodine contained in 25 g vials, it must be weighed since the amount used in each production is 5 g, and is separated shortly before the synthesis to not degrade.

The hot cells located inside the production laboratory environment named in (Table 1) by technical area (nº 31) have a naval partition separating it from the laboratory so that the doors giving access to the main aisle can be fully opened, taking into account the purpose of using the space for monitoring or maintenance.

After fractionation of the final product in the hot cell, already in the lead castle, the material is transferred to the conditioning room (nº 12) through the pass-through, where all the preparation of this product is carried out for transportation, when that if you get quality control approval, it is sent to the shipment.

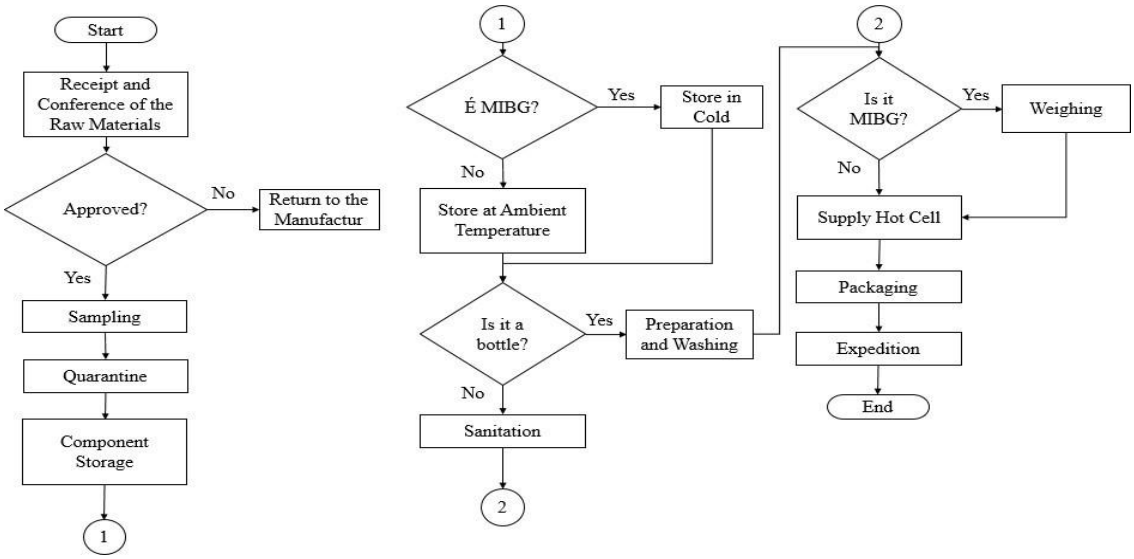
After the product has passed the packaging with the labeled protective containers, the expedition (nº 17) inserts it in properly labeled and protected transport containers, verifies transport documents in relation to the contents of the packaging and products with the radioprotection professional for dispatch of the radiopharmaceutical.

In (Figure 10), it is possible to observe the flow of this whole process, beginning in the receipt of the production inputs until the expedition.

In this new plant with the Cyclone 30XP, the acceleration of the beams will be by negative ions which makes the operating principle considerably different, especially in the extraction, since the ion source adds electrons instead of ionizing, and the present deflection process in CV-28 it does not exist in this new cyclotron, so the beams behave as negative protons being a negative hydrogen (one atom with one proton and two electrons). Also, with the energy capacity of 30 MeV, it will be possible to fully cover the section of shock, in order to reach the optimal state of production, increasing the productive capacity between 4 and 8 times. Consequently, it will be possible to produce the same total activity that the CV-28 produces for delivery to hospitals at 12 hours after processing, at around 100 mCi (3.7GBq), but reducing the average irradiation time of

The target 5 to 2 hours for the production of MIBG

Figure (10): Flowchart of production inputs until they become finished products.



In this way, it is possible to propose a new routine of production with the Cyclone 30XP, in which, considering an ideal scenario, it would be possible to have 2 irradiations in the same day. Instead of irradiation occurring between 1:00 p.m. and 6:00 p.m., as it does today, it would start at 8:00 a.m. and end at 10:00 a.m. After irradiation, there would be 6 hours wait for the decay time to start the extraction and all subsequent steps, concluding with the expedition at around 6:35 p.m. In the sodium iodide production scenario, the irradiation would begin at 9:00 a.m. and end at 9:48 a.m. While the extraction would begin at 3:48 p.m., with the completion of all steps until the expedition at around 5:13 p.m. The second irradiation is suggested to occur in the period of 10 p.m. to midnight for MIBG, and from 11:12 p.m. to midnight for sodium iodide, when it would be expected until 6 a.m. to proceed with all subsequent steps in the production chain, finishing with the expedition around 8:35 a.m., and 7:25 a.m. respectively.

Table (3): Production rate with cyclotron 30XP

SODIUM IODIDE		MIBG	
Production Process	**Length**	**Production Process**	**Length**
Preparations for Irradiation	30 min	Preparations for Irradiation	30 min
Irradiation	48 min	Irradiation	2 h
Decay after Irradiation	6 h	Decay after Irradiation	6 h
Processing	30 min	Processing	1 h e 40 min
Quality Control	40 min	Quality Control	40 min
Expedition[a]	15 min	Expedition[a]	15 min
TOTAL:	8 h e 43 min	TOTAL:	11 h e 05 min

a: considering only the time that is not done in parallel with other stages of the process.

Results

In this chapter, the results obtained through the comparative analysis of current and future production with the new radiopharmaceutical installation and the Cyclone 30XP accelerator in the IEN will be analyzed.

By observing how the production of ^{123}I is produced in the current IEN radiopharmaceutical division, one can define its main directly connected supplies that supply the hot cells, which are: the iodine storage bottle, next to its stopper and sealing, lead castle that helps contain radiation doses while the radiopharmaceutical is not being used, sterilized water, sodium hydroxide, ion exchange columns, the guanidine used in the labeling of the MIBG and the label for identification of the bottle.

Thus, we observed the transfer of the material from the target chamber to the hot cell, the procedures performed in the cell, the procedures performed by the quality control and the end of the entire production cycle with the packages, documentation of transportation and shipping. Through these steps, a quantitative analysis of the ideal number of employees to work in each sector was carried out to meet the requirements of GMP, data: four professionals for irradiation, three others in chemical processing with the KIPROS system of operation (the hot cell operator being the same as the target in the irradiation step), and three professionals in quality control, totaling nine employees.

Once all the steps were defined, it was possible to present the plant of the new installation, highlighting its areas and routes of entry and exit, in addition to the flow of materials and quality control, to then make a comparison between execution times and total activity produced. Gains from increased production can be achieved due to the greater range of energy and current, since the higher the current the target supports, the shorter the time required for irradiation, thus achieving a production rate in 2 hours similar to that of the IEN answers today with 5 hours of irradiation. It should be noted that considering the nominal maximum current of the Cyclone 30XP, this reduction of the irradiation time could be much higher. But for target safety and radiation protection issues, a current limited to about 30μA was considered in the target.

In a direct way, it is possible to compare the current production with the Cyclone 30XP in two ways: considering that the current routine is maintained in the future, and considering the ideal scenario with two irradiations per day.

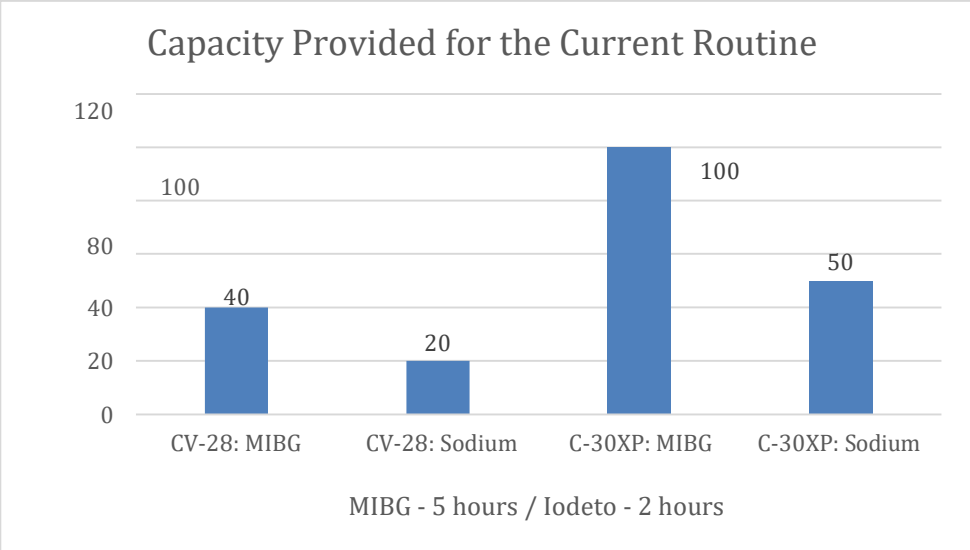
For the case in which the current routine is maintained, it is estimated that the current daily production of IEN is about 400 mCi (14.8 GBq), at the end of the irradiation, for the production of iodine-123 with 5 hours of beam. Processing of both MIBG and NaI occurs 13 hours later, at which point this activity has already fallen to about 202 mCi (7.5 GBq) of iodine-123. For NaI labeling, there is almost no loss, which makes it possible to deliver to hospitals approximately 57 mCi (2.1 GBq) 24 hours after processing.

In the case of MIBG processing, the synthesis efficiency entails a loss of about 30% of the activity. Therefore, the MIBG activity provided to hospitals 24 hours after processing is approximately 40 mCi (1.5 GBq). As the demand for NaI is currently significantly lower than the demand for MIBG, its irradiations have a time of two hours and the activity supplied is about 20 to 25 mCi (740 to 925 MBq). Thus, with data already reported in Table 2 and Table 3, it is possible to observe a superficial increase of production in 2.5 times using Cyclone 30XP, considering the same period of irradiation, as shown in (Figure 11).

A fact still relevant to be highlighted is that the time required for this radiopharmaceutical to reach the end customer must be taken into account, so that this activity, with an average time of 24 hours for delivery in the current scenario, from the end of the production and 37 hours after irradiation, becomes the equivalent of 25% of

its total when ready for use in the patient, further limiting the supply of demand for the product.

Figure (11): Comparative analysis of the current production routine between CV-28 and Cyclone 30XP (C-30XP).



All of these factors are taken into account at the moment of fractionation and distribution to the clinics and hospitals, so that all have the required activity at the time of the exams.

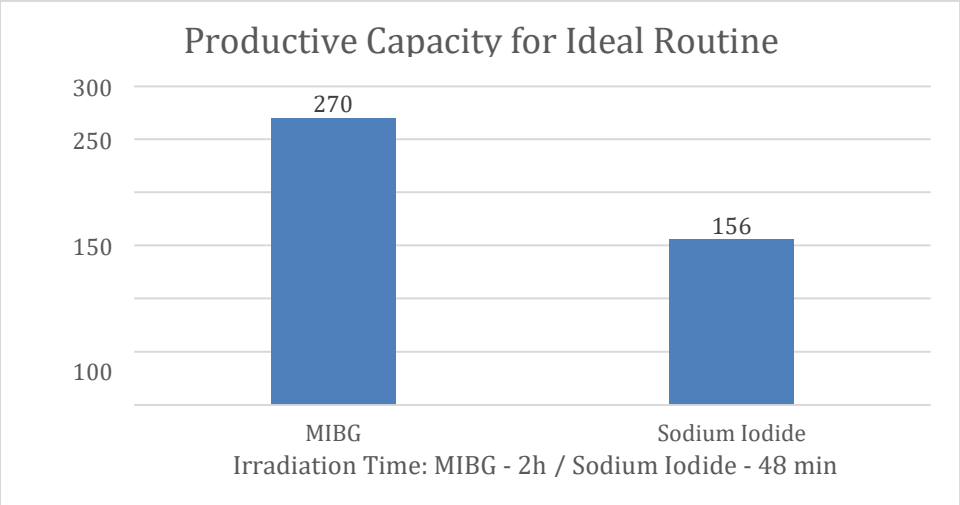
In the scenario where the ideal production routine is reproduced, only possible with the Cyclone 30XP due to its intrinsic characteristics, IEN will have the possibility of further expanding its production capacity due to the fact that there is no unnecessary loss due to long waiting time after the irradiation. So that, at the end of the 6 hours waiting for the radioactive decay, the procedure of packaging, quality control and dispatch of the material begins.

(Figure 12) presents the ideal production capacity considering the gains with the performance of 30XP associated to the reduction of the decay time, which allows a 575% increase in the MIBG production capacity by the IEN for a single irradiation of two hours. Because of this greater efficiency of the cyclotron, it is possible to deliver the MIBG (which takes more time to be made) on the same day it is produced, and can also plan a new irradiation for the night period. Considering that the half-life of ^{123}I is 13.2 hours, and the mean total time from irradiation to shipment, which would be 8 hours and 35 minutes in the case of MIBG, this radiopharmaceutical has a high probability of being delivered even before completing a half-life.

In this case we would have the possibility of doubling this production, making a total of 540 mCi of MIBG and 780 mCi of NaI of supply capacity per day. Of course, this maximum delivery capacity would only be possible if hospitals and clinics were able to use it on the same day, which is not possible for hospitals outside the

metropolitan area of Rio de Janeiro because of transportation.

Figure (12): Production capacity of the Cyclone 30XP with the proposed ideal routine.



In addition to the optimization of production with the new cyclotron, it is necessary to consider the reduction in the costs involved with electric power supply, which will be considerably smaller because it is a newer technology and consumes less energy than the CV-28 built in the 1970s. One of the reasons for choosing the nighttime irradiation schedule is the benefit of the electric tariffs that are lower in this period of 10 p.m. and midnight.

Conclusion

In this paper, it was proposed an analysis of the production of ^{123}I in IEN, which currently provides for Brazil the MIBG radiopharmaceutical and sodium iodide, in order to map their processes and steps bringing absolutely strategic information about its supply chain and enabling not only greater internal efficiency, but also expanding the possibilities of the decision-making process, which includes an expansion project with a new radioisotope and radiopharmaceutical production facility, and a new cyclotron.

After this, the plant of the new facility to be integrated with the existing installations of the radiopharmaceutical division of the IEN was presented, detailing its areas and flows of inputs, materials and people. In this way, some of the basic elements of a Standard Operational Procedure (SOP) can be obtained, which is to keep the process in operation by means of standardization and minimization of deviations in the execution of activities, seeking to ensure that the actions taken to guarantee quality standards are standardized and implemented as planned.

Thus, an ideal production routine was proposed for both facilities with a comparative evaluation between the efficiency and production time of the CV-28 and the Cyclone 30XP, thus demonstrating an increase in the average daily MIBG production capacity for 270 mCi (10 GBq) to be delivered to the final customer, while in the current scenario it is delivered around 40 mCi (1.5 GBq). In addition, with Cyclone 30XP it is possible to perform two irradiations in an ideal scenario, so that the final increase in daily production can be up to thirteen times

that of today, delivering a total of 540 mCi (20 GBq) and propitiating an increase that can reach four times the national scope that the institute has in the present day.

Therefore, it is concluded that the implementation of this new project in the IEN will allow its commercial expansion and reduce the disparity that is in the present when the productive capacity of the country does not sustain its demand. In addition, it will expand its portfolio of radioisotopes, thus expanding the country's research capacity, contributing to various types of examinations in the field of nuclear medicine and achieving an increase in the Institute's profit generation, more prestige, and expanding its market share.

In order to clarify, it is important to highlight that during the execution of this work, the plant of the new facility was updated, which resulted in some modifications in the design of its areas, but there was no change that could modify the study performed and neither compromise the faithfulness of this work.

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