IMPLEMENTATION OF A HOSPITAL RADIOPHARMACY IN A MOLECULAR IMAGING CENTER: CHALLENGES, OPPORTUNITIES, AND PERSPECTIVES

IMPLEMENTANDO UNA RADIOFARMACIA HOSPITALARIA EN UN CENTRO DE IMAGENOLOGÍA MOLECULAR: DESAFÍOS, OPORTUNIDADES Y PERSPECTIVAS

IMPLEMENTAÇÃO DE UMA RADIOFARMÁCIA HOSPITALAR EM UM CENTRO DE IMAGEM MOLECULAR: DESAFIOS, OPORTUNIDADES E PERSPECTIVAS

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ABSTRACT:

The Uruguayan Centre for Molecular Imaging (CUDIM) is a national initiative to cover molecular imaging needs on oncologic, neurologic and cardiovascular diseases, being this technology not available before its creation. Besides the aforementioned purposes, its objectives are also research of new clinical protocols, and development of new PET tracers, as well as education and training on this specialized area. A center with clinical and preclinical areas enables to achieve goals related to patient services, research and development.

To accomplish these objectives, equipment is required to perform radiopharmaceutical synthesis, characterization and quality control. Taking into account the patient safety and quality standards, radioprotection and pharmaceutical issues must be fulfilled.

68Ga-DOTA-TATE, 18F-2-fluoro-2-deoxyglucose and, 11C-methionine are produced on regular basis; 11C-choline, 18F-fluoride y 68Ga-gallgas have been added recently. PET studies are supported by the "Fondo Nacional de Recursos" (FNR) to all the Uruguayan population. Radiopharmaceutical indications have been protocoled for oncology and neurology diseases.

The design, implementation, start and development of a Radiopharmacy with clinical, research and development purposes need a multidisciplinary staff with a background on Pharmaceutical sciences and training on Radiochemistry/Radiopharmacy. CUDIM is an initiative to promote the molecular imaging development at national and regional level, having gathered all the efforts of those who feel identified with these goals.

Descriptors: Radiopharmaceutical, Hospital Radiopharmacy, Positron Emission Tomography (PET), Molecular Imaging.

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RESUMO:

O Centro Uruguaio de Imagem Molecular (CUDIM) é um empreendimento do país que visa atender às necessidades assistenciais de saúde na área da imagem molecular para doenças oncológicas, neurológicas e cardiovasculares, que até sua criação não contava com esta tecnología. Além dos fins de assistência, tem como objetivos a investigação de novos protocolos clínicos, o desenvolvimento de novos traçadores de PET, bem como a formação de recursos humanos nesta área. A existência de um centro que dispõe das áreas clínica e pre-clínica permite a combinação de objetivos de assistência, pesquisa e desenvolvimento.

Isto requer equipamentos que permitam a síntese de radiofármacos, caracterização e controle de qualidade. Do ponto de vista de segurança e qualidade voltadas para o paciente, deve-se verificar os requisitos de radioproteção e qualidade farmacêutica.

Até o momento, 68Ga-DOTA-TATE, 18F-2-flúor-2-desoxiglicose e 11C-metionina são produzidos, com a implementação recente de 11C-colina, 18F-flúor e 68Ga-gallgas. Outros radiofármacos estão em desenvolvimento. Os estudos de PET são financiados pelo Fundo Nacional de Recursos para toda a população do Uruguai. As indicações de radiofármacos têm sido protocoladas em Oncologia e Neurologia.

O projeto, a implementação, a prática e o desenvolvimento da área de Radiofarmácia para fins de saúde, pesquisa e desenvolvimento requerem uma equipe multidisciplinar de profissionais com formação em Farmácia e experiência em Radioquímica-Radiofarmácia. O CUDIM é uma tentativa de promover o desenvolvimento nacional e regional da imagem molecular, combinando esforços de todos aqueles que se identificam com esses objetivos.

Descritores: Radiofármacos, Radiofarmácia Hospitalar, Tomografia por emissão de pósitrons (PET), Imagem Molecular

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RESUMEN:

El Centro Uruguayo de Imagenología Molecular (CUDIM) constituye un emprendimiento del país para responder a las necesidades asistenciales en el área de imagenología molecular para enfermedades oncológicas, neurológicas y cardiovasculares, no contando hasta su creación con esta tecnología. Además de la finalidad asistencial, sus objetivos son la investigación de nuevos protocolos clínicos y el desarrollo de nuevos trazadores PET, así como la capacitación de recursos humanos especializados en esta área. La existencia en un centro que dispone de áreas clínicas y preclínicas permite aunar fines asistenciales, de investigación y desarrollo.

Para ello se requiere equipamiento que posibilite la síntesis de los radiofármacos, su caracterización y control de calidad. Desde el punto de vista de la calidad y seguridad orientada al paciente, se deben verificar los requisitos de radioprotección y calidad farmacéutica.

A la fecha son producidos 68Ga-DOTA-TATE, 18F-2-fluoro-2-desoxiglucosa y 11C-metionina; sumando recientemente 11C-colina, 18F-fluoruro y 68Ga-gallgas. Diferentes radiofármacos se encuentran en etapa de desarrollo. Los estudios PET son financiados por el Fondo Nacional de Recursos para toda la población de Uruguay. Las indicaciones de los radiofármacos han sido protocolizadas en oncología y neurología.

El diseño, implementación, puesta en marcha y desarrollo del área de Radiofarmacia con fines asistenciales, de investigación y desarrollo requiere un equipo multidisciplinario integrado por personal con formación en Ciencias Farmacéuticas y experiencia en Radioquímica-Radiofarmacia. El CUDIM constituye una apuesta para promover el desarrollo nacional y en la región de la imagenología molecular, aunando esfuerzos de todos aquellos que se sientan identificados con estos objetivos.

Descritores: Radiofármacos, Radiofarmacia Hospitalaria, Tomografía de Emisión de Positrones (PET), Imagenología Molecular

1. INTRODUCTION

Positron Emission Tomography (PET) is a diagnostic method through tomographic images that shows the tridimensional distribution of radiodrugs containing positron-emitting radionuclides in the body. It provides information at the molecular level about the functioning of different organs and tissues *in vivo* in a non-invasive manner. Usually, PET is coupled to Computed Tomography (CT), generating two images – an anatomical one (CT) and a functional one (PET) – which, when merged, provide a very precise panorama about the location of the patient's physiological alteration. PET has outstanding clinical applications in three major areas: Oncology, Cardiology and Neurology, currently being a relevant diagnostic methodology in such areas. Nowadays, the technique has mostly found applications in the Oncology clinical practice (97%).(1) In this pathology, the most important aspects to be assessed are initial and early diagnosis, tumor staging and determination of the malignancy degree (prognosis), treatment planning and monitoring and determination of disease recurrence (evolution), among others.

Unlike those employed in conventional Nuclear Medicine (SPECT), PET radiodrugs present different physical characteristics. Although there are many positron-emitting radionuclides, the most commonly used for PET include 18F, 11C, 13N and 15O. These radionuclides have a short semi-disintegration period, from 109 to 2 minutes, with logistics regarding distribution and administration to the patient representing an important challenge. In general, radiodrugs are administered as injectables with a single dose. These radiodrugs require handling and production conditions in consonance with the radiological safety and pharmaceutical quality criteria. It is essential to ensure that reproducible and clinically reliable results are obtained. All the operations must be carried out and supervised by duly trained and qualified personnel.(2) To such end, the Radiopharmacy has highly qualified personnel and an adequate infrastructure for the development, production, quality control and dispensing of PET radiodrugs. The radionuclides are produced in the cyclotron or obtained from a generator; and synthesis of the radiodrugs is performed in automated synthesis modules located in cells with adequate air quality. The production environment is located in a clean area. High-purity gases are required, both for the cyclotron supply and in the production and quality control environment.

This paper presents the preparation and quality control conditions of the 18F-FDG, 11C-Methionine and ^{68}Ga-DOTA-TATE radionuclides, in clinical use at CUDIM, as well as of other radiodrugs that will be employed in the near future.

2. BACKGROUND

The project of creating a center devoted to diagnosis by means of Positron Emission Tomography dates back to 2005, driven by Dr. Henry Engler with a group of professors from the Science, Medicine and Chemistry schools of the University of the Republic (*Universidad de la República*, UdelaR). The fundamental objectives from which the idea emerges are four, namely: (i) to provide assistance to the population in the form of diagnosis and monitoring of therapies linked to its specialty, (ii) to constitute itself as a Center for the training of professionals and scientists in the area, fostering the creation of graduate courses, (iii) to carry out research activities to develop new diagnostic markers, and (iv) to establish collaboration, coordination and academic exchange ties with similar scientific centers throughout the world.

In March 2006, the Uruguayan Cyclotron-PET University Commission (*Comisión Universitaria Ciclotrón-PET del Uruguay,* CUPU) is created, with the support of local (Rector's Office of the University of the Republic, Ministry of Public Health) and foreign (Uppsala University, International Atomic Energy Agency) authorities since its inception. Such Commission writes a report that is approved by the University's Central Executive Council(3) and constitutes itself as the project's conceptual framework. The Parliament approves the law to create the Uruguayan Center of Molecular Imaging in 2007.(4) The first stone is placed on November 24th, 2008, and the CUDIM is inaugurated on March 18th, 2020.

3. MATERIALS AND METHODOLOGIES

3.1 Infrastructure for the production of PET radionuclides and radiodrugs

CUDIM has a 16.5 MeV PETtrace (GE Healthcare) cyclotron, capable of producing the adequate radionuclides for the synthesis of the following PET radiodrugs: 18F (t ½ = 110 min), 11C (t ½ = 20 min), 15O (t ½ = 2 min) and 13N (t ½ = 9 min). The radiodrug production sector has 220 m2 of clean areas, with individual laboratories for the production of 18F, 68Ga and 11C radiodrugs. Synthesis of 68Ga-DOTA-TATE (68Ga-DOTA0-Tyr3-octreotate) is performed manually, although there is an automatic platform (GE FASTlab™ Gallea™) that will be commissioned in the near future. Synthesis of the 18F (18F-2-Fluoro-2-deoxyglucose and 18F-fluoride) or 11C (11C-Methionine and 11C-Choline) radiodrugs is performed in an automated manner using FASTlab™ or TRACERlab™ FX FN (in the case of 18F) and TRACERlab™ FX C Pro (in the case of 11C) synthesis modules. All the aforementioned modules are in shielded spaces (handling cells or Hot-cells) designed so as to ensure radiological protection to the operator and with adequate air quality (classes A or B) for the preparation of injectables (FIGURE 1).

Production of radionuclides and radiodrugs for use in patients implies having a series of electrical and air services, as well as high-purity gas and water systems. From the point of view of patient safety, the radiodrug production area must verify the radioprotection and pharmaceutical quality requirements.

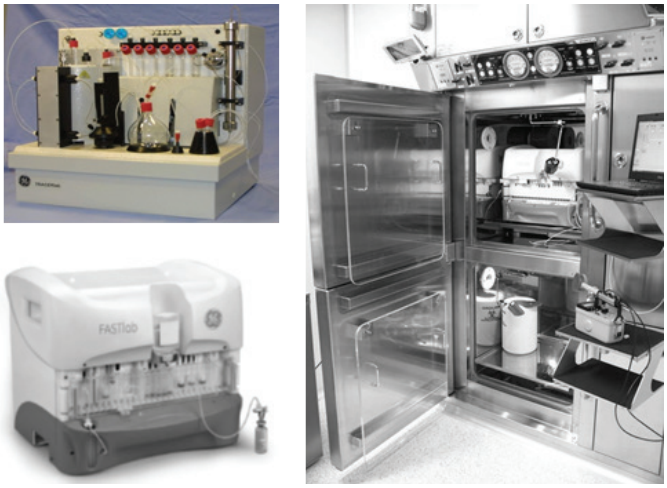

FIGURE 1: FASTlab™ FDG synthesis module (GE Healthcare) (upper left). TRACERlab™ FX_C Pro synthesis module (GE Healthcare) (lower left). COMECER BBS-2V Hot-cell with the FASTlab™ FDG module (right).

3.2 Infrastructure for Chemical-Pharmaceutical Development and Biomedical Development of PET radiodrugs

The Chemical-Pharmaceutical Development laboratories complete CUDIM's Chemistry area. They have state-of-the-art equipment for the analysis of new structures (UV-Vis spectrometers, IR, MS/MS coupled to HPLC and Multichannel Gamma Spectrometers, among others), as well as Hot-cells with modules for the synthesis of ^{11}C (TRACERlab™ FX C Pro) and ^{18}F (TRACERlab™ FX FN) radionuclides. The Biomedical Development sector has equipment for the study of radiodrugs in biological systems. Among them, the PET-SPECT-CT trimode chamber for small animals (GE Triumph™) and a Phosphor-imager (Typhoon™ FLA 7000) stand out, among others. It also has clean areas for sterilization, bacterial endotoxin and cell culture trials. It has a bioterium area, which will provide testing animals to be used in different methodologies for the biological evaluation of radiodrugs.

3.3 Methodologies employed for the synthesis and control of radiodrugs

3.3.1 ^{68}Ga-DOTA-TATE

The synthesis of ^{68}Ga ($t_{½}$ = 68 min) radiodrugs[5] is performed manually under shielded laminar flow. It consists in labeling DOTA-TATE with $^{68}Ga^{3+}$ obtained from a $^{68}Ge/^{68}Ga$ generator (Eckert & Ziegler IGG100-50M).[6-8] Such generator is eluted in a fractionated manner by means of a peristaltic pump with ultra-pure HCI. For the labeling of DOTA-TATE with ^{68}Ga, the activity peak of the fractionated elution (from 3.0 mL to 3.6 mL) is used, containing 90%-97% of the total eluted activity.

In the labeling process, the warm-up time and temperature (10 min at 100 °C in dry block) of the peptide solution and the solution for adjustment with pH 3.5-4.0 are established. The last step is to purify the labeling solution through an SPE cartridge (Sep-Pak C18 light) to mainly remove any amount of ^{68}Ge and $^{68}Ga(OH)_3$ that might be present. To such end, a special device that is actuated by means of syringes, valves and tubings is constructed, so as to separate the impurities in a vial, and the purified labeled material, formulated at pH 7.4, sterilized and containing 5% of EtOH, in another. This device allows performing remote purification, substantially improving the operator's radioprotection.

Quality control of the radiodrug is conducted according to European Pharmacopoeia 6.0.[9-10] The radiochemical purity of ^{68}Ga-DOTA-TATE is determined by means of HPLC using a C18 (4.6 mm x 150 mm) column and, as mobile phase: water with 0.1% trifluoroacetic acid and acetonitrile with 0.1% trifluoroacetic acid (gradient according to EP), Gamma and UV-Vis detection at 225 nm. In this system, the retention times are as follows: ^{68}Ga-DOTA-TATE rt = 5.0 min; $^{68}GaCl_3$ rt = 1.5 min. For determination of $^{68}Ga(OH)_3$-colloid, silica-gel TLC is used as stationary phase and, as mobile phase, Ammonium acetate 0.15 M: MeOH (1:1) (R_f (Colloid+$^{68}GaCl_3$) = 0, R_f (^{68}Ga-DOTA-TATE) = 1). Other physical-chemical trials that complete quality control of ^{68}Ga-DOTA-TATE are the following: determination of the EtOH percentage by means of GC, determination of radionuclide purity and identity (by means of Gamma spectrometry and determination of $t_{½}$ in ionization chamber), final pH measurement, and appearance of the solution. The microbiological trials include the sterilization and bacterial endotoxin tests (LAL test – Gel-Clot method) 24-48 hs post-preparation. The most probable radionuclide impurity (^{68}Ge) is determined along the elution profile by ^{68}Ga count in solid scintillation 48 h post-elution.

3.3.2 ^{18}F-2-Fluoro-2-deoxyglucose (^{18}F-FDG)

^{18}F-FDG is routinely synthesized by means of the FASTlab™ FDG module (GE Healthcare).[11-14] In this module, synthesis is performed by means of cassettes (disposable devices with all the necessary elements for the synthesis: reagent vials, tubings, reactors, pumping syringes, and purification cartridges). $^{18}F^-$ is produced at the cyclotron level by bombarding with $H_2{}^{18}O$ protons, according to the reaction (p,n). The activity of the $^{18}F^-$ that reaches the module is put into contact with the reagents contained in the cassette and, by means of a reaction with tetra-acetyl mannose triflate in acetonitrile:Kriptofix K222 (FIGURE 2a), tetra-acetylated ^{18}F-FDG is produced. This is hydrolyzed in an alkaline medium; the solution that contains it is neutralized, purified by extraction in solid phase, and transferred by means of a 0.22 µm filter to a sterilized vial. Fractionation of the dose is conducted under shielded laminar flow.

The physical-chemical quality control of ^{18}F-FDG is performed according to USP 30 NF 25,[15] and implies visual inspection, pH control, determination of residual solvents by GC (diethyleter, ethanol and acetonitrile), determination of radionuclide purity and identity (by Gamma spectrometry and determination of $t_{½}$ in ionization chamber), determination of chemical purity (absence of Kriptofix K.222, by TLC in silica, MeOH:NH_4OH 30% 9:1) and radiochemical purity (TLC, silica gel, MeCNgua 95:5, with the most expected impurity being $^{18}F^-$ with R_f = 0). The microbiological trials include the sterilization and bacterial endotoxin tests 24-48 hs post-preparation.

3.3.3 ^{11}C-Methionine

^{11}C-Methionine,[16-19] prepared in TRACERlab™ FX C Pro modules by means of reactions of ^{11}C-methylation with $^{11}CH_3I$ (FIGURE 2b), is synthesized to the starting point of $^{11}CO_2$ produced at the cyclotron level by proton bombarding of a $^{14}N_2 – O_2$ gas mixture. In the module, $^{11}CO_2$ is reduced to $^{11}CH_4$ by catalytic hydrogenation and transformed into $^{11}CH_3I$ by free-radical iodination. This latter reacts with the homocysteine thiolactone precursor on a tC18 cartridge, and the ^{11}C-Methionine that is formed is eluted from the cartridge with 5.5 mL NaH_2PO_4 0.05 M. The formulation is completed with 4.5 mL of NaCl 0.9% and the radiodrug is collected in a sterilized vial after going through a 0.22 µm filter.

The physical-chemical quality control of ^{11}C-Methionine is performed according to European Pharmacopoeia 5.0,[10] and consists in visual inspection, pH measurement, determination of radiochemical and chemical purity by HPLC (250 mm x 4.6 mm C18 column, mobile phase: KH_2PO_4 1.4 g/L, Gamma and UV-Vis detection at 225 nm), residual solvents by GC, radionuclide purity and identity (by Gamma spectrometry and determination of $t_{½}$ in ionization chamber), and enantiomeric purity by chiral TLC. The microbiological trials include the sterilization and bacterial endotoxin tests 24-48 hs post-preparation.

3.3.4 Administration of the radiodrugs and conduction of the PET/CT studies

The schedule corresponding to the patients' studies is sent the day before to the person in charge of the Production area, who calculates the radionuclide activity to be produced to supply the studies to be conducted during the day. Once the Quality Control area determines that the day's production lot meets all the specifications required by the corresponding Pharmacopoeia, the lot is released, in due conditions to be administered to the patients.

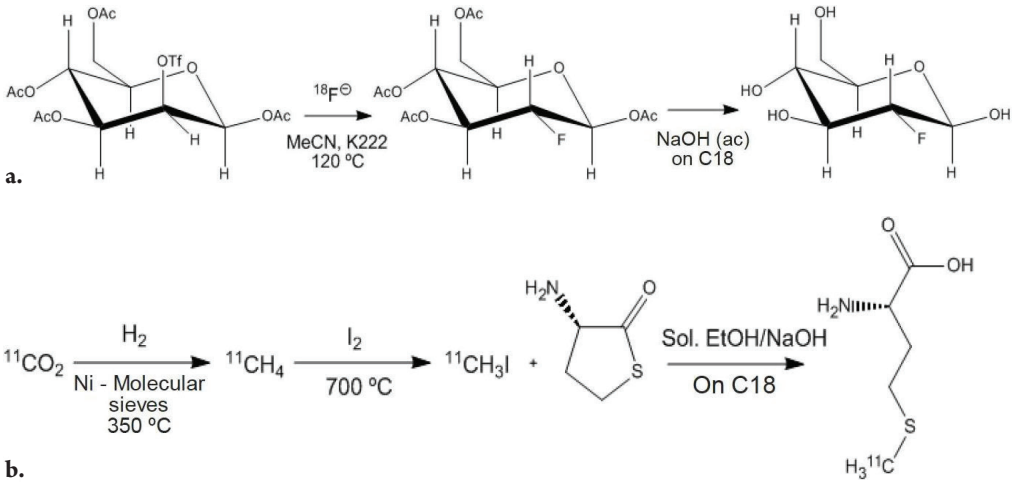

FIGURE 2 (a) Synthesis of ^{18}F-FDG; (b) Synthesis of ^{11}C-Methionine: (i) H_2 Ni/Molecular sieves, 350 °C; (ii) I_2, 700 °C.

The patient attends the Center with precise indications according to the study to be conducted (fasting of 6 hours or more depending on the radiodrug to be injected). Once the patient is in the center, the anthropometric parameters are determined (weight, height), as well as other metabolic parameters (glycaemia), if necessary. Once the radiodrug has been administered via the intravenous route, the patient is allowed to rest for a certain period of time so that the radiodrug is biodistributed. Once this time has elapsed, the study is fetched according to the pre-established protocols. The patient can then lead a normal life after the study.

To perform the tomographic studies, there are two PET-CT chambers: one of them is a GE Discovery™ 690 (64-channel CT and LYSO detectors PET) and the other is a GE Discovery™ STE (16-channel CT and BGO detectors PET).

4 RESULTS AND DISCUSSION

The Hospital Radiopharmacy has 220 m2 of clean areas and individual laboratories for the production of 18F, 11C and 68Ga radiodrugs (FIGURE 3). Radiological safety is monitored through a centralized radioprotection system, which has 15 measuring monitors distributed among the points of interest.

4.1 Production of radiodrugs

Synthesis of the ^{18}F-FDG, ^{11}C-Methionine and ^{68}Ga-DOTA-TATE radiodrugs is optimized, providing reproducible results and satisfactory yields to supply the patients' studies, and it complies with what is established by official pharmacopoeias in Uruguay (see Table 1).

4.2 Studies conducted in the patients

On June 15th, 2010, the first exam with the PET technology using ^{68}Ga-DOTA-TATE was performed in Uruguay, with collaboration of the Nuclear Research Center (Centro de Investigaciones Nucleares, CIN). Having commissioned the cyclotron in September 2010, the first patient was studied with ^{18}F-FDG on October 22nd of the same year. On April 15th, 2011, ^{11}C was used for the first time to make a diagnosis, employing the ^{11}C-Methionine radiodrug. ^{11}C-Choline was employed in patients for the first time on August 19th, 2011 (see Table 2).

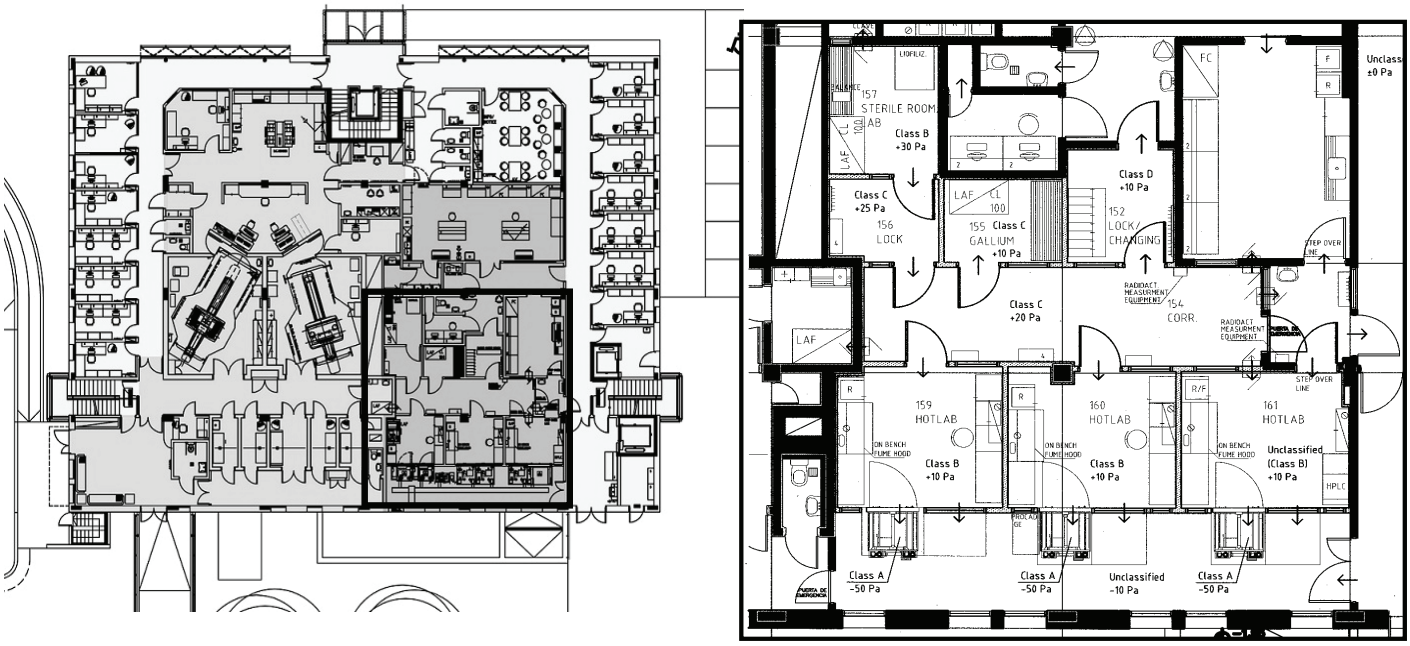

FIGURE 3: (a) Plan of CUDIM's ground floor showing the Clinical-Medical (light grey) and Radiopharmaceutical (dark grey) areas, (b) expansion of the area delimited in Figure (a) where the clean area for the production of radiodrugs is shown in a shaded tone.

TABLE 1 – Parameters of CUDIM's processes for the synthesis of radiodrugs.

Radiodrug	Yield (%) (without correction due to decay)	Radiochemical purity (%)	Synthesis time (min)
^{18}F-FDG	80±2 (n=92)	Above 98	22-25
^{68}Ga-DOTA-TATE (manual)	83±20 (n=93)	92-100	30-35
^{11}C-Methionine	26±8 (n=14)	Above 96	20-25

TABLE 2: Clinical use of the PET radiodrugs prepared at CUDIM and projection for 2011.

Radiodrug	1st use in diagnosis	Studies conducted until 08/19/2011*	Studies projected at the end of 2011	Applications
^{68}Ga-DOTA-TATE	06/15/2010	141	> 200	Neuroendocrine tumors, pheochromocytoma, thyroid cancer.
^{18}F-FDG	10/22/2010	1,101	> 1,800	Colorectal, Breast, Ovarian and Testicle Cancer, Hodgkin and non-Hodgkin Lymphoma, Melanoma, others
^{11}C-Methionine	04/15/2011	16	> 60	Gliomas, parathyroid cancer
^{11}C-Choline	08/19/2011	2	> 10	Prostate cancer
^{18}F-NaF	09/16/2011	2	> 5	Metastasis and other bone alterations
^{68}Ga-gallgas	09/07/2011	1	> 5	Studies of pulmonary ventilation
TOTAL TO THE PRESENT DAY		1,260	2,070	--

*Except for ^{18}F-NaF and ^{68}Ga-gallgas.

4.3 Chemical-Pharmaceutical Development and Biomedical Development

Three consecutive lots of the new radiodrug are prepared, verifying compliance with quality control (physical-chemical and microbiological). There is availability of ^{11}C-Choline, useful for the diagnosis of prostate cancer) and of ^{18}F-Fluoride, a tracer of alterations at the bone level, for the patients. In the near future, there are plans to continue developing methodologies for the synthesis and quality control of new ^{18}F and ^{11}C radiodrugs for new indications in Oncology and Neurology. An automated platform for the synthesis of ^{68}Ga-DOTA-TATE (FASTlab™ Gallea) is also being implemented. Acquisition of ^{15}O from the cyclotron and synthesis of $H_2{}^{15}O$ as a radiotracer of blood flow are in the planning stage, with important applications in Neurology and Cardiology. Commissioning of the bioterium and of the PET-SPECT-CT trimode chamber will soon indicate initiation of the activities of the Biomedical Development area. There is a collaboration agreement with Instituto Pasteur Montevideo and with the Clemente Estable Biological Research Institute. The first collaboration activities in research projects have been recently initiated.

4.4.Training

The Radiopharmacy has contributed to undergraduate training through Internships and Special Works of the Radiochemistry Chair at the Chemistry School and the CIN. Interns from Argentina (Fundación Centro de Diagnóstico Nuclear) and Brazil (Delfin Fármacos) have been received. This line of actions will be deepened in consonance with one of the center's goals, foreseeing conduction of a workshop with 42 participants from Latin America in October 2011: "Regional Workshop: Radiological Protection in PET/CT".

CONCLUSIONS

Implementation of the CUDIM has allowed introducing the studies based on molecular images from PET radiodrugs for the entire population of the country. The Hospital Radiopharmacy has contributed different diagnostic agents in a safe manner based on a suitable infrastructure and on personnel with expertise in the area. The Chemical-Pharmaceutical and Biomedical Development areas will allow having new agents and contributing in basic and applied research related to oncological, neurological and cardiovascular diseases.

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