**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

# Optimizing the Production of $^{18}$F-Fdg: Quality Control and Advanced Dosimetry in at a Pet Radiopharmaceutical Center

[1]Gladys Aquino Hancco, [2]Dr. Carlos Javier Solano Salinas, [3]Pedro Muñante Gómez

[1]Universidad Nacional de Ingeniería, Lima, Perú
*Email:* gladys.aquino.h@uni.pe
*ORCID:* https://orcid.org/0000-0001-9918-4951

[2]Universidad Nacional Mayor de San Marcos
*Email:* csolano@unmsm.edu.pe
*ORCID:* https://orcid.org/0000-0003-0270-9040
[3]Centro de Altos Estudios Nacionales
*ORCID:* https://orcid.org/0000-0003-0270-9040

**ARTICLE INFO**

Received: 14 Dec 2024

Revised: 20 Feb 2025

Accepted: 26 Feb 2025

**ABSTRACT**

The production of radiopharmaceuticals, such as $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG), is essential for the conduct of clinical studies through Positron Emission Tomography (PET), especially in the fields of oncology, neurology and cardiology. In this sense, the purpose of this study was to optimize quality control procedures (QAC) and dosimetric strategies linked to the production of $^{18}$F-FDG, focusing on the application of the HPLC chromatographic method and advanced dosimetry systems at the Radiopharmaceutical Production Center of EsSalud Callao. A total of four production batches, representing the years 2017 and 2018, were examined, and an occupational dosimetric evaluation was conducted in 2023. The critical parameters that were analyzed included radiochemical purity, radionuclide purity, pH, the presence of bacterial endotoxins, sterility, and residual solvent levels. The mean radiochemical purity ascertained by HPLC was 98%. The mean retention time was 8.33 minutes, with a standard deviation of 24%. It is noteworthy that all batches of the product under scrutiny conformed to the standards set forth by USP-NF 2021 and the Argentine Pharmacopoeia. Improvements were implemented in the handling of the purification columns (QMA, C18, Alumina B, and SCX). In addition, the efficacy of the nanoDOT (36.23–50.89 mGy) and TLD (1.77–15.06 mSv) dosimetric systems was verified under simulated exposure conditions. The results confirmed that the optimized protocols conform to regulatory standards, ensuring the quality of $^{18}$F-FDG and decreasing the radiological impact on personnel. Likewise, a mean yield of the PETtrace 800 GE cyclotron (16.5 MeV) of 74 was evidenced. 98% per batch, with a production capacity of up to 5000 mCi per cycle. The study offers a replicable model to improve efficiency, safety and traceability in the production of radiopharmaceuticals, promoting their standardization in similar centers and strengthening the role of nuclear medicine in clinical diagnosis.

**Keywords:** $^{18}$F-FDG, quality control, HPLC, radiation protection, PETtrace 800 GE, cyclotron.

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

## 1. Introduction

The production of radiopharmaceuticals such as $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) represents a cornerstone in modern medical imaging using Positron Emission Tomography (PET). This radioactive compound allows the metabolic visualization of tissues, being essential for the early detection, staging and therapeutic evaluation of oncological, neurological and cardiovascular diseases. Its use has revolutionized precision medicine, providing functional information that complements the morphological findings of techniques such as computed tomography (CT) or magnetic resonance imaging (MRI).

In the Peruvian context, the progressive implementation of PET-CT technologies has driven the need for locally produced radiopharmaceuticals that meet international quality and safety standards. In particular, EsSalud's Radiopharmaceutical Production Center, located in Callao, plays a strategic role in the distribution of $^{18}$F-FDG to hospitals in the national network, allowing to meet a growing clinical demand derived from the expansion of nuclear medicine services. This function is supported by the use of the PETtrace 800 GE (16.5 MeV) cyclotron, which irradiates oxygen-18 enriched water ([$^{18}$O]$H_2O$) to obtain fluorine-18, the base radionuclide of FDG.

However, the production process of $^{18}$F-FDG comes with critical challenges in terms of quality control and radiation protection. The radionuclide's brief half-life (110 minutes) necessitates the establishment of agile, precise, and reproducible protocols for both automated synthesis and analytical verification procedures. In this sense, significant deficiencies have been identified that impede standardization of the process. For instance, there is an absence of routine use of high-performance liquid chromatography (HPLC) to verify the radiochemical purity of the final product. Furthermore, purification columns (QMA, C18, Alumina B, and SCX) are used inappropriately. These columns are essential for eliminating ionic impurities, hydrophobic byproducts, and trace amounts of free fluoride.

This is further compounded by concerns regarding the occupational exposure of technical personnel, particularly during stages such as the handling of radioactive vials or the transfer between modules. Despite the existence of fundamental protection measures, a comprehensive dosimetric strategy is lacking. Such a strategy would entail the systematic utilization of devices such as thermoluminescent dosimeters (TLDs) or optically stimulated luminescence nanoDots (OSLs). These devices facilitate the reliable estimation of the equivalent dose received by critical organs, including the lens and limbs.

The significance of this issue extends beyond the assurance of the quality of the final product administered to cancer patients, many of whom are in advanced stages or immuno-compromised. It also encompasses the institutional imperative to adhere to national and international regulatory standards (USP, Argentine Pharmacopoeia, IAEA, DIGEMID, IPEN) that ensure safety in the production and handling of radiopharmaceuticals. In this sense, the enhancement of technical procedures, the implementation of more sensitive analysis technologies, and the fortification of the culture of radiological safety have become imperatives to ensure reliable diagnoses and to safeguard the health of exposed personnel.

In this context, the need arises to address the following research problem: How efficient are the quality controls implemented in the production of $^{18}$F-FDG by the PETtrace 800 GE cyclotron at the EsSalud Radiopharmaceutical Production Center, and how can the radiochemical purity of the radiopharmaceutical be ensured through the use of HPLC and the proper handling of the purification columns, while minimizing radiological exposure of personnel through the use of advanced dosimetric techniques such as TLD and OSL nanoDot?

This study seeks to answer this question through a comprehensive evaluation of the production process, proposing substantial improvements that include the implementation of HPLC analysis as a standard verification tool, the optimization of the use of purification columns and the validation of more accurate dosimetric systems. The purpose is twofold: to ensure the technical quality of $^{18}$F-FDG as an injectable

Journal of Information Systems Engineering and Management
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

Research Article

radiopharmaceutical and to strengthen the radiation protection protocols of the personnel involved, thus promoting safe, efficient production aligned with the highest international standards.

### 1.1 Objectives

#### 1.1.1 General objective

The evaluation and optimization of quality control and radiation protection procedures in the production of $^{18}$F-FDG is imperative. This objective can be achieved through the utilization of the PETtrace 800 GE cyclotron, the implementation of HPLC analysis, the proper handling of purification columns, and the application of advanced dosimetric strategies.

#### 1.1.2 Specific objectives

- To implement HPLC analysis and optimize the use of purification columns to improve the radiochemical purity of $^{18}$F-FDG.
- To assess the occupational exposure of personnel by dosimetry with TLD and nanoDot under controlled conditions.
- To design a comprehensive production model that combines quality controls and radiation protection measures applicable to nuclear medicine centers.

## 2. Methodology

This section details the procedures, equipment, reagents and operating conditions used for the production of $^{18}$F and the subsequent synthesis of $^{18}$F-FDG, following the quality and safety standards established by NATO and DIGEMID.

Initial tests were carried out to validate the methodological parameters of the Analytical Quality Controls (CCAl). Subsequently, tests were carried out with a total of **04 batches**, with the aim of verifying the reproducibility and consistency of the results. Dosimetric systems evaluated include **OSL nanoDot and whole-body TLD**. The selection of these systems was based on their sensitivity and applicability to the required measurements.

The steps of the methodology followed were as follows:

1. **Initial preparation**: The operating conditions of the equipment were verified, including chiller temperature (8ºC to 10ºC), compressed air pressure (6-8 psi), and standby vacuum level (1.2 x $10^{-7}$ mbar to 4.8 mbar).
2. **Cyclotron configuration**: The target was filled with $^{18}$O enriched water and irradiation was programmed with a current of 40-70 µA, depending on the target, for 60-120 minutes to achieve the required activity.
3. **18F production**: Under strict radiation protection measures, the radionuclide was generated in a watertight production cell with 75 mm lead shielding. Cleaning and clearing of lines were verified to avoid contamination, and the safe transfer of 18F from the cyclotron to the synthesis module was monitored.
4. **CCAl Testing**: Radiochemical purity, filter integrity, radionuclide identity, and chemical identity evaluations were performed following USP-NF 2021 pharmacopoeia standards.
5. **Dosimetric Systems Evaluation**: 5 units of nanoDotTM OSL and 10 TLD dosimeters were tested under controlled conditions, exposing them simultaneously in an irradiator designed to ensure uniformity in photon fluence.

### 2.1 Materials and Equipment

**Reagents Used**

- 18-O Enriched Water

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

- O-16 Water
- Hydrogen Grade 6
- Helio Grade 6.5
- Cassette de FDG
- $^{18}F$

**Main Equipment:**

- PETtrace Cyclotron (Related Systems)
  - Chiller
  - Compressor
  - FASTLAB Module
  - Cassette for FDG production
  - 500 mL glass jar
  - Ventilation and Controlled Air System.
  - Work Allowances
  - Production Cell
  - Personal computer with synthesis program
  - Digital Cell Control Panel
  - Air injection/exhaust system
  - Nitrogen System 6-8 bar
  - Compressed air system 6-8 bar
  - FASTlab Synthesis Module
  - PC System
  - 18F Cell Cyclotron Transfer Line
  - GM Radiation Monitor
  - $^{18}F$-FDG transfer lines from the production cell to the fractionation cell.
  - Dispensador Timotheo
  - PC-PLC System
  - Peristaltic pump
  - VDC Calibrator- Ionization Chamber.
  - Pre-cámara -80 a -130 Pa.
  - FDG Cassette 01 kit
  - Kit de Thimotheo
  - Sterile Water 20G x 31/2(Lumbar Puncture Needle)
  - 0.9% colorless sodium chloride
  - Sterile 10 ml type I colorless vials
  - 20 mL vials

**Supplies for Quality Control**

- 2x 10 cm Silica Gel TLC Plate
- Microliter Syringe
- Development Jars
- EZ-scan TLC Strip Scanner, 6-Channel SRI Chromatography Data System

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

- Ruler, pencil, scissors, or paper cutter.
- Graduated test, 100 mL, 50 mL, 10 mL
- Acetonitrile 90:10 methanol/sulfuric acid solution
- Methanol, H2SO4, Reactive Grade Water, Milli-Q
- Heat gun
- 2-Fluoro-2-deoxy-D-glucose standard
- Fludeoxyglucose $F^{18}$ Injection
- 5 ml syringe with needle
- Alliance HPLC System with PDA 2995 Detector, Raytest GabiStar Radio Detector for Radiation for Radionuclides such as 18F, C11, 99TM and UV-Vis Detector

### 2.2 Methodology and Operating Procedures

The study used a rigorous methodology with the aim of optimizing quality controls and dosimetric strategies in the production of the radiopharmaceutical $^{18}$F-FDG at the EsSalud Radiopharmaceutical Production Center, located in Callao. The process began with the configuration of the PETtrace 800 GE 16 cyclotron. 5 MeV, designed to irradiate oxygen-18 enriched water ($[^{18}O]H_2O$) into a niobium target, through the nuclear reaction $^{18}O(p,n)^{18}F$. This irradiation was carried out by a beam of protons at different intensities and times, resulting in the generation of the radionuclide [18F]□□". The latter was transported through capillaries to a shielded cell, where the FASTlab automated synthesis module is located.

During the synthesis phase, $[^{18}F]^-$ was captured in a QMA column and then eluted with a solution of Kryptofix 222 and potassium carbonate. Azeotropic drying was performed at 120 °C under an inert gas atmosphere to obtain the $K^+[^{18}F]^-$ reagent complex. This complex was subjected to SN2 nucleophilic fluorination with the precursor 1,3,4,6-Tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-manopinanose, dissolved in acetonitrile, at 100 °C for 3 minutes. Subsequently, a basic hydrolysis was carried out using NaOH 1M at 110 °C to remove the protective groups, followed by purification through SCX, Alumina B and C18 columns, thus ensuring the removal of impurities, free $[^{18}F]^-$ and hydrophobic by-products.

The final product underwent extensive quality controls, including pH measurements using colorimetric strips, verification of filter integrity through a reverse pressure test, as well as identification and evaluation of radionuclide purity using gamma spectroscopy. Bacterial endotoxin analysis was also performed using the Endosafe® Nexgen-PTS™ portable system. Residual solvents, such as ethanol and acetonitrile, were quantified by gas chromatography (GC-436). Radiochemical purity was evaluated using HPLC with HILIC column and radioactive detector, reporting an average retention time of 8. 33 minutes.

Simultaneously, a dosimetric system was designed that used an expanded polystyrene (EPS) irradiator with circular geometry. TLD dosimeters (Panasonic UD-802AT) and OSL nanoDot were placed equidistant 10 cm from the radioactive source. Hp(10) doses were recorded under controlled conditions at the FUESMEN Nuclear Medical Center. Characteristics such as sensitivity, linearity, dose stability, and repeatability were evaluated. The measured doses were within the limits established at the international level, registering values for TLDs between 1. 77–15. 06 mSv and for nanoDot between 36. 23–50. 89 mGy, which confirmed the effectiveness of the radiological protection system implemented.

This comprehensive methodology guarantees a high degree of safety for both the radiopharmaceutical product and the personnel, complying with the requirements established by USP-NF 2021, the Argentine Pharmacopoeia and the regulations of national organizations such as DIGEMID and IPEN.

Journal of Information Systems Engineering and Management
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

Research Article

### 2.2.1 Initial preparation

- Chiller water temperature: between 8°C and 10°C
- Cooling water temperature in the Secondary: between 18°C and 22°C
- Compressed Air Pressure: between 6 and 8 psi
- Standby Vacuum Level: between 1.2 x 10-7 mbar and 4.8 mbar
- Turn on the PC Master

### 2.2.2 Cyclotron configuration

- Turn on the control software and select the target to use.
- Fill the white with enriched water 18O
- Schedule irradiation:
- Current: 40-70 µA depending on the target.
- Time: 60-120 minutes depending on the activity required.

### 2.2.3 Production of $^{18}F$

The production of $^{18}F$-fluorine is a highly controlled process involving physical principles of nuclear interaction and strict radiation protection measures to ensure the safety of personnel and the quality of the final product. This radionuclide is generated in a cyclotron by bombarding enriched water (18O) with accelerated protons. The system operates under specific conditions:

- **Compressed air and nitrogen pressure:** 6-8 bar to maintain the stability of the systems.
- **Vacuum in the production cell:** -100 Pa, ensuring a watertight and safe environment.
- The watertight production cell, with 75 mm of lead shielding, ensures radiation containment.
- Cleanliness and line clearance are verified to avoid contamination.
- The connection between the cyclotron and the synthesis module is monitored to ensure the safe transfer of $^{18}F$
- Radioactivity levels in waste bottles are kept below permissible limits to reduce exposure.
- Before starting the process, the availability of supplies and raw materials is verified, as well as the functionality of the equipment.
- Compliance with local regulations, such as orders RE-014-PR and RE-001-PR, ensures a documented and traceable process.

#### 2.2.3.1 Radiation Protection

- Armor and Containment:
  The watertight production cell and transfer lines are designed to minimize radioactive dispersion.
- Radiological Monitoring:
  Radiation detection systems operate continuously to identify potential leaks or unusual exposure levels.
- Waste Management:
  Radioactive liquid waste is monitored and handled following strict protocols to avoid unnecessary exposure

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

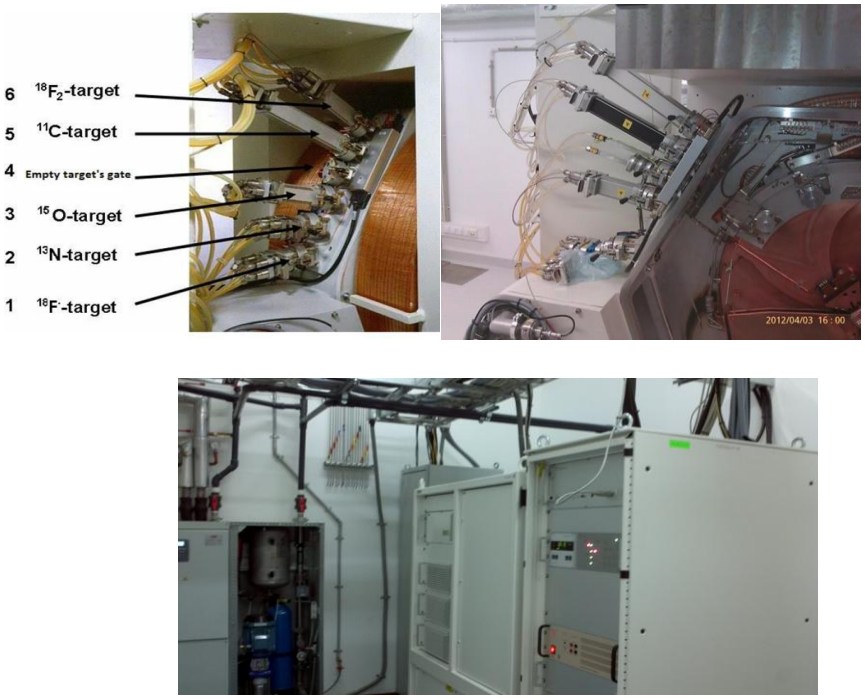


**Figure 1.** GE PETtrace 800 Cyclotron for $^{18}$F-FDG Synthesis

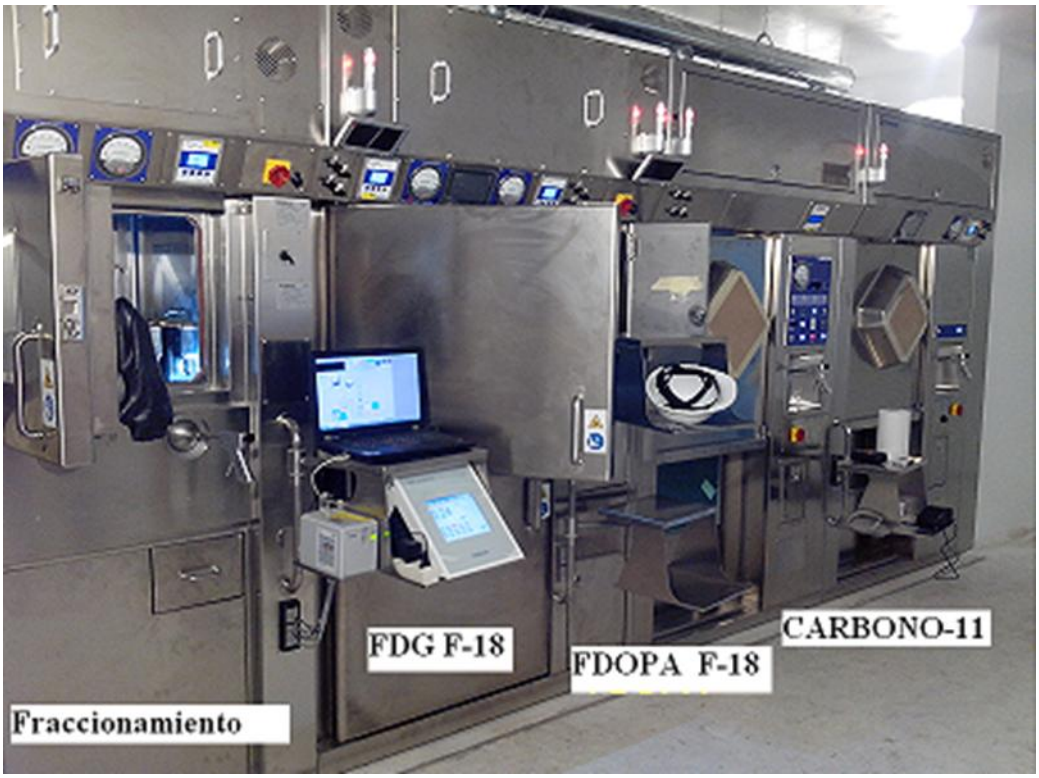


**Figure 2. Cell for** 18F-FDG Synthesis Modules
**Source:** Radiopharmacy production laboratory.

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

## 3. Results and discussion

### 3.1 Quality Control Results

The quality control of $^{18}$F-FDG was carried out in the laboratory of the Radiopharmaceutical Production Center of the Alberto Sabogal Sologuren National Hospital. Additionally, the high-performance liquid chromatography (HPLC) analyses were performed at the Foundation of the School of Nuclear Medicine of Argentina.

The first evaluation consisted of a visual inspection of the $^{18}$F-FDG solution contained in the vials corresponding to batches No. 1020107, 1010047, 1010057 and 1010067. This inspection was carried out by the head of the Quality Assurance Department, determining that all the samples presented a transparent, colorless solution free of suspended particles, thus complying with the requirements established by the current pharmacopoeias.

### 3.2 Specification of the Number of Evaluated Batches of $^{18}$F-FDG

In the present study, a total of four batches of $^{18}$F-FDG were analyzed, covering different production dates. Specific details of each batch, including its identification, date of production and results of quality controls, are presented in the Annex. This information allows to guarantee the representativeness of the data and supports the validity of the results obtained in the research.

Below is a comparative table of the main quality parameters evaluated in the batches analyzed:

**Table 1.** Radioactive Concentrations of the Four Batches of $^{18}$F-FDG

| Lot | Volume | Quantity (mCi) | Radioactive Concentration (mCi/mL) |
|---|---|---|---|
| 1020107 | 1 mL | 45.8 mCi | 45.8 mCi/mL |
| 1010047 | 1 mL | 41.55 mCi | 41.55 mCi/mL |
| 1010057 | 1 mL | 48.9 mCi | 48.9 mCi/mL |
| 1010067 | 1 mL | 36.3 mCi | 36.3 mCi/mL |

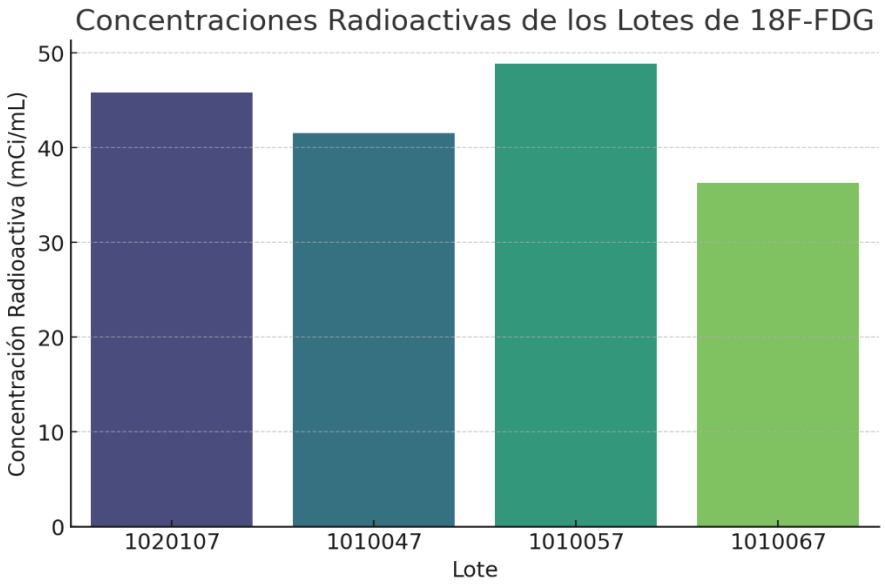


**Figure 3.** Radioactive Concentration of $^{18}$F-FDG Batches

Journal of Information Systems Engineering and Management
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

Research Article

**Table 2.** Comparison of Quality Parameters Between Four Batches of $^{18}$F-FDG

| Parameter | LOT 1010047 | LOT 1010057 | LOT 1010067 | LOT 1020107 |
|---|---|---|---|---|
| **1. Appearance** | Conformable | Conformable | Conformable | Conformable |
| **2. pH** | 6,10 | 6,00 | 6,00 | 6,00 |
| **3. Chemical purity** | | | | |
| 3.1 **Aminopolieter (Kryptofix)** | Conformable | Conformable | Conformable | Conformable |
| 3.2 **Residual solvents** | Conformable | Conformable | Conformable | Conformable |
| 3.2.1 **Ethanol** | Conformable | Conformable | Conformable | Conformable |
| 3.2.2 **Acetonitrile** | Conformable | Conformable | Conformable | Conformable |
| **4. Radiochemical purity** | 96,52 % | 97,85 % | 96,98 % | 97,88% |
| **5. Radiochemical identification** | 1,019 % | -3,60 % | -1,36 % | -4,08% |
| **6. Radionuclide identification** | | | | |
| 6.1 **Half-life** | 109,176 min | 109.67 min | 110.77 min | 108.89 min |
| 6.2 **Photopic energy** | 510.32 KeV | 510.39 KeV | 510.27 KeV | 510.44 KeV |
| **7. Radionuclide purity** | > 99.9% | > 99.9% | > 99.9% | > 99.9% |
| **8. Radioactivity assessment** | 100 % | 100 % | 100 % | 100% |
| **9. Bacterial endotoxins** | < 5.00 EU/mL | 7.64 EU/mL | < 5.12 EU/mL | < 6.71 EU/mL |
| **10. Sterility** | Conformable | Conformable | Conformable | Conformable |

The results obtained confirm that the batches evaluated mostly meet the quality requirements for radiopharmaceuticals intended for PET studies. However, variations are observed in some specific parameters, such as radiochemical identification and bacterial endotoxin levels in certain batches. These findings require further analysis to identify possible causes and establish corrective measures in production and quality control processes.

A detailed analysis of each of the parameters evaluated is presented below.

**1. Appearance**

- **Result:** All batches have a compliant appearance.
- **Interpretation:** This result confirms that all four batches meet visual quality requirements, including transparency, absence of color and the absence of suspended particles. Since no variations are observed, it is concluded that the parameter is uniform in all the samples analyzed.

**2. pH**

- **Results:**
  - Lot 1010047: **6.10**
  - Lot 1010057: **6.50**
  - Lot 1010067: **6.00**
  - Lot 1020107: **6.00**

Journal of Information Systems Engineering and Management
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

Research Article

- **Interpretation:** The pH of the final product of the final average is 6.15, it is within the established acceptance range (4.5 - 7.5). Maintaining rigorous control over this parameter is essential, since values outside this range could generate alterations in blood electrolyte homeostasis due to their high reactivity.

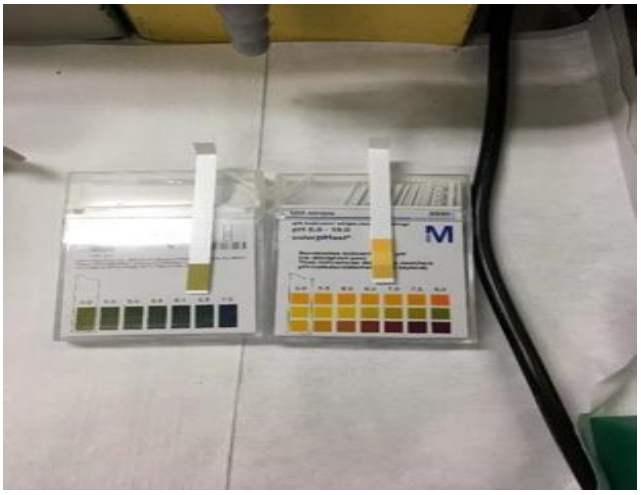

**Figure 4.** Determination of pH using colorimetry strips.

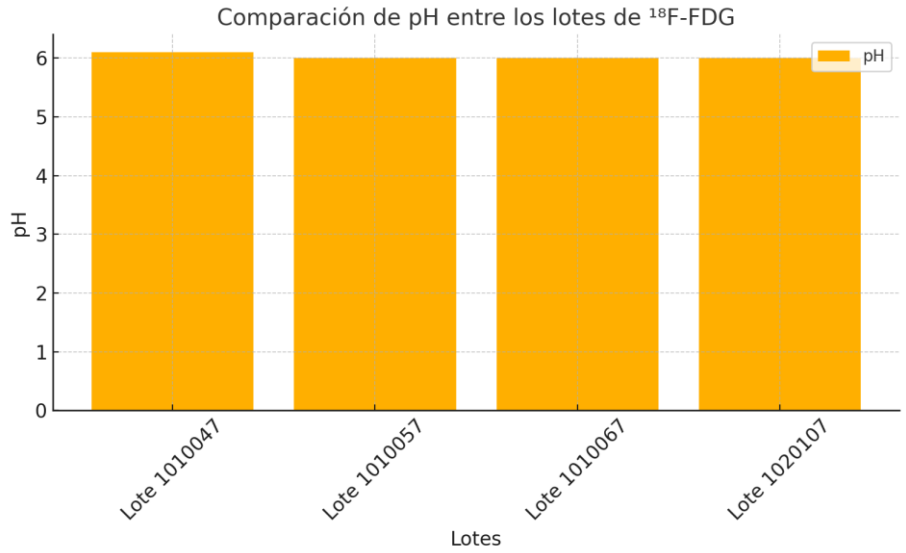


**Figure 5.** pH comparison between ¹⁸F-FDG batches

### 3. Chemical Purity - Qualitative Determination of Kryptofix 222

- **Results:** All batches comply with the specifications established for the following parameters:
  - **Aminopolyether (Kryptofix 222):** Compliant in all batches.
  - **Residual solvents (ethanol and acetonitrile):** Compliant in all batches.
- **Interpretation:** The results indicate an effective control in the synthesis and purification of the radiopharmaceutical, ensuring the elimination of chemical contaminants in all the samples analyzed.

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

Additionally, in the chromatographic run followed by development in iodine environment, the intensity of the stain color obtained in the final product sample did not exceed the optical density of the reference standard, which reaffirms the absence of Kryptofix 222 in unpermitted concentrations.

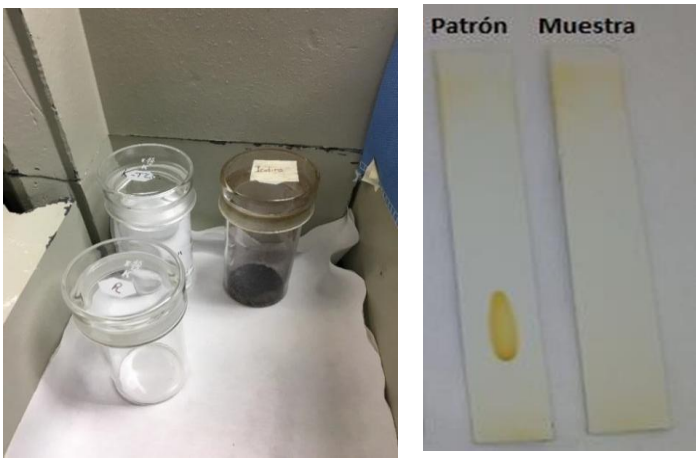


**Figure 6**. Result of chromatographic run.

Distance traveled by solvent front 80 mm

Distance traveled by K222 Standard 60 mm

Std Rf 0.75

Spot visible in FDG lane? No

## 4. Radiochemical Purity

- **Results:**
  - Lot 1010047: **96.52 %**
  - Lot 1010057: **97.85%**
  - Lot 1010067: **96.98%**
  - Lot 1020107: **97.88%**
- **Interpretation:** All batches meet the minimum criteria established (> 95%), guaranteeing their suitability for clinical use. The batch 1020107 has the highest radiochemical purity, suggesting greater efficiency in its purification process. The observed differences between batches could be linked to minor variations in isotopic labelling or in the optimization of the synthesis procedure.

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

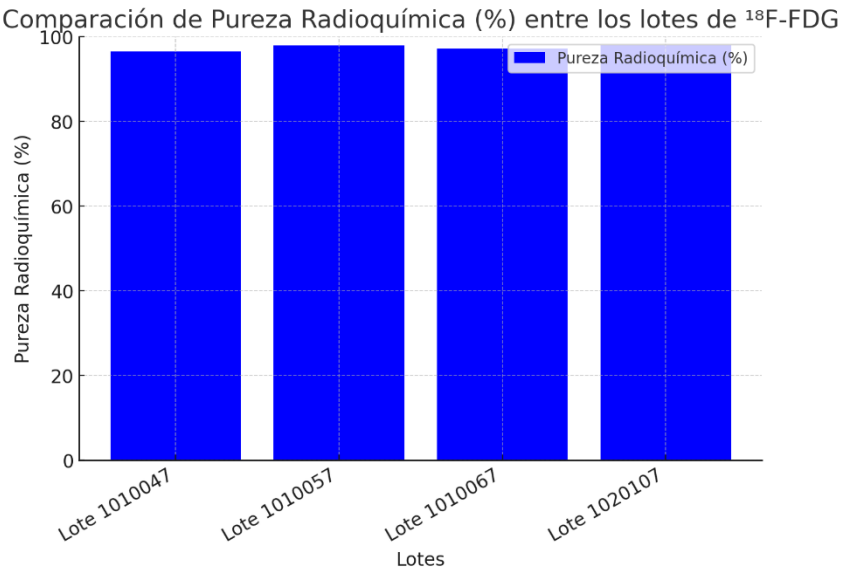


**Figure 7.** Comparison of Radiochemical Purity (%) between ¹⁸F-FD batches

Additionally, a Thin Layer Chromatography (TLC) analysis was performed to complement the evaluation of radiochemical purity.

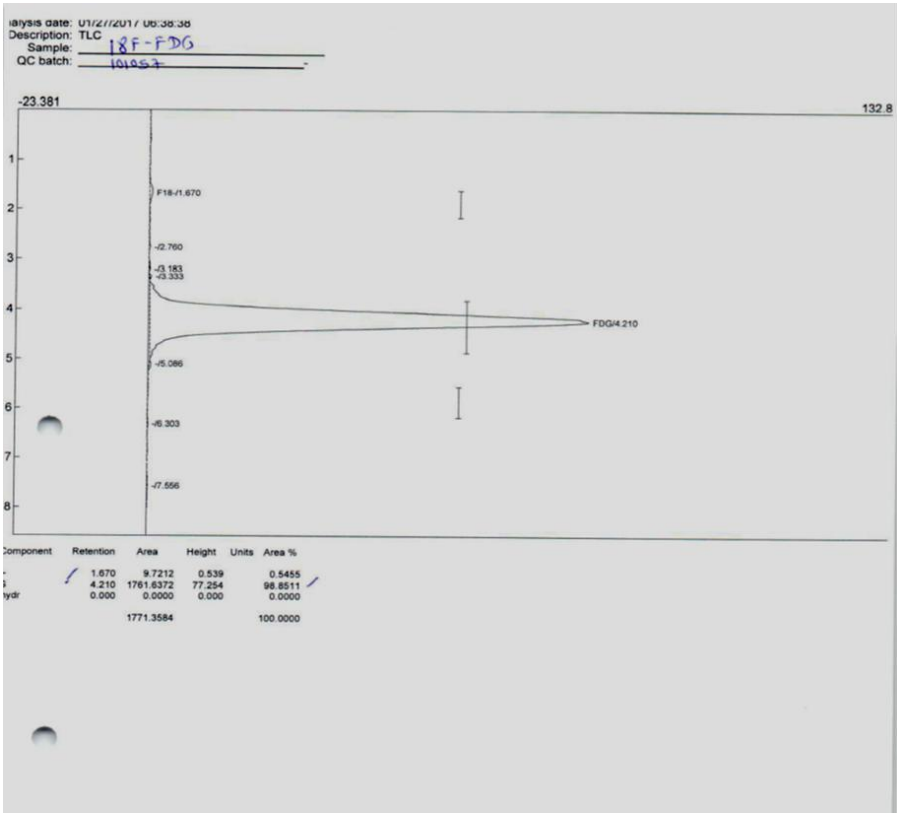


**Figure 8.** Radiochemical Purity Evaluation by R-TLC using EZ-Scan 1010057.

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

The generated chromatogram allows the following aspects to be identified:

- **Retention Factors (Rf):** The main peak, corresponding to **[$^{18}$F]-FDG**, has a retention time of **4,210 minutes**. A second peak at **1,670 minutes** likely corresponds to an impurity or byproduct of the reaction.

- **Peak areas:**
  - The main peak (**$^{18}$F-FDG**) has an area of **1761.6372 units**, representing **98.85%** of the total.
  - A minor peak, probably associated with impurity, has an area of **9.7121 units**, which is equivalent to **0.5455%** of the total.
- **Purity assessment:** The radiochemical purity of the tested batch is **98.85%,** complying with acceptable limits for radiopharmaceuticals where purity greater than 95% is required.
- **Impurities:** The presence of a minor peak suggests a negligible impurity at concentrations not significant for the safety or efficacy of the radiopharmaceutical.
- **Peak Shape:** The main peak is symmetrical and well-defined, indicating efficient separation and excellent chromatographic performance.
- **Residual fluorine-18:** The peak in **1,670 minutes** corresponds to free fluorine, a common byproduct in the synthesis of **[$^{18}$F]-FDG**. The amount detected (0.5455%) is minimal and within the permitted limits.

**Conclusion:** The results confirm that the batch analyzed meets the quality standards required for clinical use. Radiochemical purity greater than **98.5%** confirms the efficiency of the **[$^{18}$F]-FDG synthesis and purification process**.

## 4. Conclusions

The conclusions of the quality control of the $^{18}$F-FDG batch produced at the Radiopharmaceutical Production Center of the Alberto Sabogal Sologuren National Hospital, and the support of specialized institutions such as the School of Nuclear Medicine Foundation (FUESMEN), made it possible to exhaustively evaluate the quality of $^{18}$F-FDG and evaluate radiation protection systems. The main conclusions are presented in the following lines.

**$^{18}$F-FDG Quality Control**

1. **Visual inspection:**
   The $^{18}$F-FDG solution of the four batches, analyzed was clear, colorless and free of visible particles, meeting the visual standards required to guarantee the quality of the final product.
2. pH. Values are within the allowable range for injectable formulations (**4.5–7.5**). However, the pH of the batch is 1010047 slightly higher, which could indicate small variations in the formulation process. Although it is within the limits, monitoring is suggested to avoid major deviations.
3. **$^{18}$F-FDG Hydrophilic Exchange Liquid Chromatography (HILIC) Radiochemical Purity**

- HPLC and TLC methods confirmed a radiochemical purity of 98.56%, with excellent separation between $^{18}$F-FDG and impurities. In the batches tested, the radiochemical purity of $^{18}$F-FDG is greater than 98% in most cases, meeting the international standards required for use in clinical applications, such as PET-CT studies. This confirms the efficiency of the synthesis module purification system, minimizing the presence of impurities and by-products.
- **Detection of Minimal Impurities**, The detected impurities, such as [$^{18}$F] free fluoride and acetylated [$^{18}$F]FDG intermediate byproducts, are present in very low concentrations (<1%), indicating a well-optimized synthesis and purification process.

  In some specific batches, peaks associated with significant impurities (such as Imp 1 and Imp 2) were detected that require adjustments in the purification system.

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

- **Efficiency of the HILIC Method**. The HILIC technique used allowed a clear separation between FDG, free fluoride and impurities. Hydrophilic retention and stationery and mobile phase optimization ensure excellent resolution and accurate analysis of sample components.
- **$^{18}$F-FDG Identity Confirmation**. The average retention time of $^{18}$F-FDG (4.66 minutes) matches internal standards, confirming the identity of the compound. The small variations observed between batches are due to experimental conditions and differences in sample preparation.
- **Impact of Impurities**. The low presence of free fluoride and other impurities ensures that they will not affect the quality of the images or expose the patient to unnecessary doses of radiation. In batches with a higher proportion of impurities, such as batch 180131-01, the synthesis and purification process need to be optimized to meet clinical requirements.

### 3.1 HPLC chromatographic conclusions of $^{18}$F-FDG (Fluorodeoxyglucose)

1. **High purity of $^{18}$F-FDG**
   - HPLC chromatographic analyses confirm that $^{18}$F-FDG has a radiochemical purity greater than **97%** in all batches analyzed, complying with clinical standards for use in PET diagnostics.
   - Purity values range from **97.25% to 98.39%,** demonstrating consistency **in production and effective quality control** in the synthesis of the radiopharmaceutical.
2. **Presence of impurities at controlled levels**
   - Two main impurities (Imp 1 and Imp 2) **were identified** in all the batches analyzed.
   - **Impurity 1** presented constant and low values (0.02% in most batches, with a slight elevation to 0.06% in one case).
   - **Impurity 2** showed greater variability, with values between **1.58% and 1.91%,** suggesting that it may be influenced by slight differences in production conditions.
3. **Variability in retention times**
   - FDG retention times in HPLC ranged from **7.92 to 9.0 minutes**, with an average of **8.33 minutes**.
   - Although most of the batches are within this range, batch **180622-01** had a higher retention time (**9.0 minutes**), which could be due to variations in production conditions or specific characteristics of the batch.
4. **Effective quality control in production**
   - The low amount of free fluoride detected (0.001%) in all batches indicates efficient **radioactive waste disposal**, which contributes to the safety of the radiopharmaceutical.
   - The relationship between **$^{18}$F-FDG activity and the load applied in the cyclotron** shows consistent performance values, with minimal variations within expected ranges.
5. **Importance of HPLC Method Validation**
   - The **radioactive detector HPLC** method used in the analysis has proven to be **effective and reproducible** for the identification and quantification of FDG and its impurities.
   - The data support the reliability of the quality control process and its applicability in the routine production of $^{18}$F-FDG for clinical use.
6. **Final considerations**
   - Since the **purity and reproducibility** of $^{18}$F-FDG are critical factors for its application in **PET imaging**, it is advisable to continue systematic monitoring of production parameters and optimize conditions to reduce variability in impurities.

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

- The research demonstrates that the current method of production and quality control of $^{18}$F-FDG is **adequate and meets the standards required** for use in patients.

4. **Radiochemical Purity by RTLC:**
   - **High radiochemical purity in the batches analyzed**. The radiochemical purity values obtained (96.52%, 97.85%, 96.98% and 97.88%) are within the acceptable range for clinical radiopharmaceuticals, exceeding the minimum limit of 95% established by international standards. This confirms that the $^{18}$F-FDG tested is suitable for clinical applications, such as PET studies.
   - The main peak, corresponding to $^{18}$F-FDG, showed an average area greater than 98.85% compared to the total area, confirming the predominance of the desired compound in the sample.

   The RTLC analysis demonstrates that the $^{18}$F-FDG analyzed meets the quality standards required for clinical use, with radiochemical purities greater than 96.5% in all batches and high consistency in results. The low concentration of impurities and the clear chromatographic separation confirm the efficiency of the synthesis and purification process. These results ensure the safety and efficacy of the product in PET medical imaging applications.

   - **Radionuclide purity.** The radionuclide identification of the analyzed batches of $^{18}$F-FDG confirmed that the parameters evaluated meet the established standards, guaranteeing the quality and accuracy of the radionuclide produced.

   1.1 **Half-life (T1/2).** The values obtained ranged from **108.89 minutes** to **110.77 minutes**, with a mean of **109.67 minutes**, within the accepted range of **105–115 minutes**. These results are consistent with the theoretical half-life of fluorine-18 (**109.7 minutes**), confirming the identity of the radionuclide and its suitability for clinical applications.

   1.2 **Phototopic energy.** The values recorded varied between **510.27 keV** and **510.44 keV**, within the expected range (511 keV ± 1%). This ensures that the radionuclide present in the analyzed batches corresponds exclusively to $^{18}$F, with no evidence of contamination by other radionuclides.

2. **Residual solvents. The analysis carried out to quantify the residual organic solvents showed that:**

- **Lot 1010047**. DSR% for ethanol and acetonitrile were 2.32% and 2.45% respectively, showing moderate variability. The concentrations of acetonitrile in the samples were very low, confirming the effectiveness of the purification process.

- **Batch 1010057**. This batch showed the greatest variability in DSR% for acetonitrile (3.98%), which may indicate the need to review the specific processes of this batch to improve consistency.

- **Lot 1010067**. The variability of the DSR% for acetonitrile was high (3.98%), like lot 1010057, suggesting a possible area of improvement in quality control and purification processes.

- **Lot 10100572.** The concentration of ethanol is 0 g/100mL, and the area under the curve for ethanol is also 0, indicating that no residual ethanol was detected in the samples.

**Minimal Presence of Acetonitrile (ACN).** The presence of ACN, although detectable, is extremely low (0.00096 g/100mL), which is well below the safety limits established by international regulations.

Journal of Information Systems Engineering and Management
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

Research Article

3. **Sterility and endotoxins.** All samples are within the specified limits of 11.5 EU/mL. The only sample with a specific value of 7.64 EU/mL is also clearly below the permissible limit. This indicates that the product is in compliance with the safety specifications set forth for bacterial endotoxins.

   **Variability in Samples.** Although all samples meet specifications, there is variability in the levels of endotoxins detected. Three samples have endotoxin levels that do not exceed the lowest values reported (< 5.00 EU/mL, < 5.12 EU/mL, and < 6.71 EU/mL), showing excellent efficacy in the control or elimination of endotoxins. The sample with 7.64 EU/mL, although it meets the standard, has a significantly higher level compared to the other samples. This could suggest variations in the production or handling process that should be investigated to ensure quality in all units of the product.

4. **Membrane integrity.** The pressure supported by the filter membrane was 56 psi, within the accepted range (50-60 psi), which ensures the efficiency of the filtration process.

5. **Determination of Kriptofix 222:** The amount of Kriptofix present in the products was in accordance with specifications (< 50 µg/mL), ensuring that there are no significant residues of this complex agent in the radiopharmaceutical. Quality control standard operating procedures were established for $^{18}$F-FDG synthesized through basic hydrolysis. In summary, $^{18}$F-FDG batches meet all quality, purity, and safety specifications, making it suitable for use in clinical PET diagnostic procedures, with no risk to patients due to contaminants or radiochemical impurities.

It was obtained that the Fastlab2 synthesis module allows obtaining $^{18}$F-FDG solutions with high purity, identity and integrity. In addition, the purification system that comes with it allows the final product to be obtained with Kriptofix 222 concentration values lower than those allowed; The size and intensity of the stain obtained from the test solution do not exceed the size and intensity of the stain obtained from the standard solution. And $^{18}$F-FDG was obtained with a purity of 98%.

The conditioning of the QMA with ethanol (10mL) obtained the best results; yield above 98%, pH is within the range and ethanol below the required limits. It is therefore the procedure of election. And the quality parameters ensure the quality controls of the $^{18}$F-FDG product.

The synthesis and purification system used, based on alkaline hydrolysis, proved to be efficient and highly reproducible, making it a viable option for any PET radiopharmaceutical production center.

**Dosimetric Systems and Radiation Protection**

1. Dosimetry Evaluation with NanoDot and TLD

- NanoDot showed a mean dose of 42.56 mGy with a CV% of 14.39%, reflecting moderate dispersion and high reproducibility, making it suitable for dose measurements in personnel exposed to radiation.
- In the November 2023 measurements, the CV% increased to 17.90%, suggesting a slight variability in exposure, possibly due to differences in the position or conditions of the experiment.
- The TLD dosimeters showed greater variability, with a mean of 4.24 mSv and a CV% of 109.25%, indicating significant dispersion between the measurements.
- In November 2023 measurements, CV% decreased to 76.87%, showing improvement, but still elevated variability compared to NanoDots, suggesting that TLDs require improvements in calibration and exposure control.

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

2. Analysis of Dosimetric Magnitudes Hp(10)

It was found that Hp(10) measured with NanoDot presented greater precision and lower dispersion, consolidating itself as the most reliable operational magnitude in this type of radiation.

- TLDs showed high variability in Hp(10), suggesting that they are better suited for measurements at higher doses and require calibration adjustment to improve their accuracy in clinical settings.

3. Evaluation of Lens Dose in PET Radiopharmacy Personnel

- The integrated dose values obtained with the NanoDot dosimeters in the pilot test showed variations of less than 25%, indicating acceptable stability in the assessment of occupational exposure.
- The trial demonstrated that NanoDot can provide reliable dosage information in crystalline lenses, which is key to monitoring and minimizing long-term risks in radiopharmacy workers.

4. Statistical Analysis and Characterization of Dosimeters

- Comparison of NanoDot and TLD in terms of precision, accuracy, and detection threshold:

| Parameter | NanoDot | TLD |
|---|---|---|
| Linearity ($R^2$) | 0.999 | 0.996 |
| Accuracy (%CV) | 2.1% | 3.5% |
| Accuracy (%) | 98.5% | 95.2% |
| Detection threshold | 0.01 mGy | 0.05 mGy |

- NanoDot stood out as the most reliable dosimetric system due to its lower dispersion, higher accuracy, and better response to low doses, while TLDs exhibited greater variability and were more suitable for higher dose exposures.

5. Radiation Protection Compliance Assessment

- It was verified that occupational dose levels in radiopharmacy personnel remain within the limits allowed by international regulations.
- The implementation of NanoDot as the primary dosimetry system improved the accuracy of dose measurement, facilitating the identification and reduction of unnecessary exposures.
- It is recommended to continue with the optimization of radiation protection procedures and establish periodic calibration controls of the TLDs to improve their performance.

This study confirmed that the implementation of NanoDot dosimeters in occupational dose assessment in $^{18}$F-FDG production provides more reliable results compared to TLDs, due to their higher accuracy, lower dispersion, and better ability for low-dose measurements.

The findings obtained allow us to propose NanoDot as the preferred dosimetric system in this context, ensuring a better assessment of occupational exposure and rigorous compliance with radiation protection regulations in nuclear medicine.

Journal of Information Systems Engineering and Management
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

Research Article

**About the PETtrace 800 GE Cyclotron in $^{18}$F-FDG Production**

1. Evaluation of Cyclotron Performance in $^{18}$F-FDG Production

- The PETtrace 800 GE **cyclotron was determined to** exhibit a **maximum production capacity of 2814 mCi** in a single irradiation cycle, suggesting the need **for multiple cycles to meet an increased demand for** radiopharmaceuticals.
- During the evaluation period, a total of **21,164 mCi** of $^{18}$F was produced and distributed, highlighting the high demand for this radioisotope for clinical PET imaging applications.
- A variability in production was identified, with a **maximum recorded activity of 2814 mCi and a minimum of 771 mCi**, reflecting the influence of operational factors on production efficiency.

2. Analysis of Cyclotron Performance and Factors Affecting Production

- 28 Oxygen-18 (**18O) irradiations used to produce** $^{18}$F were analyzed, revealing that the activity produced is not fully explained by the applied current.
- The graphical analysis showed fluctuations in the production of activity, which suggests the influence of **other factors such as target stability, system calibration and experimental parameters**.
- A **technical review** of the operating procedures is recommended to improve production stability and maximize cyclotron efficiency.

3. Calculated Performance and Efficiency Evaluation

- The average performance of the cyclotron was calculated at 74.98%, lower than the theoretical yield of 95%, indicating opportunities for improvement in the production process.
- A variable yield was observed between batches, with values between 71.8% and 78.8%, highlighting that batch 20170125 had the lowest yield (71.8%) and batch 20170123_2 reached the highest yield (78.8%).
- The statistical analysis indicated a mean yield of 68.43 mCi/uAh, with a standard deviation of 1.98 mCi/uAh, suggesting stable efficiency within the expected range.
- A non-linear relationship between the applied current (I, in µAmp) and the activity obtained (A, in mCi) was evidenced**,** suggesting that additional factors may be affecting production, such as the calibration of operating parameters and the stability of the target.

## 5. Recommendations

**Radiopharmacy**

- It is recommended to take the data obtained in this work and to write standard procedures for the performance of quality controls of $^{18}$F-FDG obtained by acid hydrolysis.
- It is recommended to use a membrane filter to sterilize the final product or component of the radiopharmaceutical.
- It is recommended to perform a procedure for the determination of radiochemical identity and radiochemical purity of PET radiopharmaceuticals by Radio-TLC analysis. The final Rf product should be equal to the Rf of the standard of ± 10%. The radiochemical purity should not be less than 90%, i.e., the percentage of the 18 FDG area should **be > 90%.**

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

- The quality controls that were carried out on the $^{18}$F-FDG product allowed to have a product with high radiochemical purity of 98%, with high levels of radiosafety.

- It is recommended that HPLC quality control tests should be performed, as it is a very specific method. This liquid chromatography technique is designed to separate polar compounds. It uses a polar stationary phase and a predominantly organic mobile phase, allowing polar species to be efficiently retained and separated, especially in aqueous matrices or mixtures of organic solvents and water. The retention of analytes in HILIC is mainly due to hydrophilic interactions, such as hydrogen bonds and dipole-dipole forces, between the analytes and the stationary phase. These are not carried out at the Callao Radiopharmaceutical Production Center.

- Conditioning of QMA with ethanol (8-10ml) is recommended which has proven to be the procedure that provides the best results, with a yield greater than 98% of$^{18}$F-FDG, an adequate pH within the specific range and ethanol levels below the required limits, it is recommended to adopt this procedure as the standard method in the production and quality control of $^{18}$F-FDG. This method ensures that the quality parameters necessary to ensure the safety and efficacy of the product are met, maintaining both radiochemical purity and specifications for clinical use, which is essential for accurate results in PET imaging studies. In addition, its constant implementation will help maintain reproducibility and reliability in production.

### Radiation Protection

It is recommended to perform lens dose measurements in the PET radiopharmacy service with the nanoDOT dosimetric system, following the methodology described in this work during each $^{18}$F bombardment process and production process, in order to prevent radiological accidents at work.

It is recommended to use nanoDOTs to protect and alert personnel to risks that directly or indirectly affect health and safety.

- It is crucial to continue the development of specific dosimeters for Hp(0.07) and Hp(3) and promote the international standardization of conversion coefficients for the measurement of the directional equivalent dose using the method of an irradiator with circular geometry using expanded polystyrene (EPS) at 7 cm and 20 cm.

Further studies, including long follow-up periods in populations exposed to low doses of radiation, are needed to further improve the understanding of the long-term risks associated with lens exposure

A dosimetry method is recommended in personnel using nanodot, since these are characterized by their small size and easy handling, detection stability in the face of pressure and temperature changes, do not require batteries and have good spatial resolution.

In addition, to relate the radiation dose to its risk (damage), it is necessary to consider both the differences in the biological efficacy of different qualities of radiation and the differences in the susceptibility of organs and tissues to ionizing radiation.

- **Technical review of the system.** Analyze the causes of variability in the production of Fluorine-18, including possible problems in the calibration of current and time.
- Implement a more rigorous maintenance plan to ensure the stability of long-term results.
- **Process optimization.** Adjust parameters such as electrical charge (μAh) and irradiation times to bring the average yield closer to the theoretical value of 95%.

**Journal of Information Systems Engineering and Management**
2025, 10(49s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

**Research Article**

- **Staff training.** Ensure that technical personnel are trained in optimal cyclotron handling and real-time variability detection.

## References

*[1]* Agencia Internacional de Energía Atómica [AIEA]. (2014). *Radiation Protection and Safety of Radiation Sources: International Basic Safety Standards* (No. GSR Part IAEA.

[2] Agencia Internacional de Energía Atómica. (2013). *IAEA-TECDOC-1731: Implicaciones para la protección radiológica ocupacional del nuevo límite de dosis para el cristalino del ojo: Orientaciones provisionales para su uso y comentario*. Viena.

[3] Akselrod, M. & Kortov V. (1990). Thermoluminescent and Ex emission properties of New High-Sensitivity TLD anion-Al2O3:C Crystals. *Radiation Protection Dosimetry* 33: 123-126.

[4] Akselrod, M., Bøtter-Jensen, L. & McKeever S. (2007). Optically stimulated luminescence and its use in medical dosimetry. *Radiation Measurements*. 41: S78- S99.

[5] Akselrod, M., Kortov, V. & Gorelova E. (1993). Preparation and Properties of Al2O3:C. *Radiation Protection Dosimetry* 47: 159-164, (1993).

*[6]* Alves, J., Ambrosi, P., Bartlett, D., Currivan, L., Van Dijk, J., Fantuzzi, E., & Kamenopoulou, V. (2011). The new EC technical recommendations for monitoring individuals occupationally exposed to external radiation. *Radiation Protection Dosimetry*, 144(1-4), 17–25.

[7] Antonov-Romanovskii, V., Keirum-Marcus I., Poroshina, M. & Trapeznikova, Z. (1956). *IR stimulable phosphors. In: Conference of the Academy of Sciences of the USSR on the Peaceful Uses of Atomic Energy*. Moscow, USAEC Report AEC- tr-2435: 239-250.

[8] Autoridad Regulatoria Nuclear, (2003). *Norma básica de seguridad radiológica, International Comission on Radiological Protection. Statement on Tissue Reactions*. ICRP. Statement on Tissue Reactions. International Comission on Radiological Protection, ref 4825-3093-1464. Approved by the Commission on April 21, (2011).

[9] Aznar, M., Andersen C., Bøtter-Jensen L., et al. Real-time optical- fibre luminescence dosimetry for radiotherapy: physical charactersitcs and applications in photon beams. *Physics in Medicine and Biology 49:* 1655-1669, (2004).

[10] Bowden, L., O'Donnell, R., Vintro, L. L., Duffy, G., & Mitchell, P. (2006). Induced activities during the production of [$^{18}$F]FDG using a GE PETtrace cyclotron. *Journal of Nuclear Medicine, 47*(suppl 1), 524P.

[11] Bappah, S., Abubakar, A., Sulaiman, M., & Umar, Y. (2019). Performance evaluation of thermoluminescence dosimeters in personnel in-vivo dosimetry. *DUJOPAS*, 5(2a), 195-203.

*[12]* Behrens, R. (2012). On the operational quantity H(p)(3) for eye lens dosimetry. *Journal of Radiological Protection, 32*(4), 455–464. https://doi.org/10.1088/0952-4746/32/4/455

[13] Benevides L., Romanyukha A. (2014). *A performance comparison of Thermo Fisher EPD-MK2 and TLD (LiF:Mg,Cu,P) as part of accreditation proficiency testing*. Radiation Measurements, April, (2014).

[14] Bos, A. (2001). High sensitivity thermolumienscence dosimetry. *Nucl Instrum Methods Phys Res B* 184: 3-28, (2001).

[15] Bøtter-Jensen, L., McKeever S, & Wintle, A. (2003). Optically Stimulated Luminescence Dosimetry, *Elsevier*.

[16] Comisión Internacional de Protección Radiológica – ICRP (2012). Early and Late Effects of Radiation in Normal Tissues and Organs–Threshold Doses for Tissue Reactions in a Radiation Protection, Statement concerning the Panasonic UD-802A Dosimeter and the Panasonic UD-700 Readers.

*[17]* Cherry, S. R., Sorenson, J. A., & Phelps, M. E. (2012). *Physics in Nuclear Medicine* (4th ed.). Saunders.

[18] Farmacopea de los Estados Unidos de América (USP 35, NF 30), oficial desde el 1° de mayo de 2012 United States Farmacopeia 27 National Formulary 22. (2004) Microbiological evaluation of Clean Rooms and other Controlled Enviroment (1116) USP 27: 2559 – 2563.

[19] Fernandez, B., et al. (2017). Evaluation of Radiochemical Purity in $^{18}$F-FDG Production: Case Study of a PETTRACE Cyclotron Facility. *International Journal of Radiopharmacy,* 23(2), 145-153.

[20] Fernández, J. (2013). *Estudio del periodo de vida útil de la $^{18}$F-FDG y dosimetría asociada a procedimientos rutinarios de producción y control de calidad en personal de radiofarmacia PET* [Tesis de maestría, Universidad Nacional del Comahue]. Bariloche, Argentina.

[21] Fundación Escuela de Medicina Nuclear, (2015). Certificado de Participación Comparación Interlaboratorio de dosímetros personales para fotones OTAN 2015 Criterios y Límites de Desempeño para la Evaluación Periódica de Laboratorios de Servicio de dosimetría Personal para Radiación X y Gamma.

[22] Garcia, A., et al. (2014). Quality Control in the Production of $^{18}$F-FDG: A Comprehensive Evaluation. *Journal of Nuclear Medicine*. 55(4), 657-663.

[23] Govinda R., Izewska, J. (2005). Radiation Monitoring Instruments. Review of Radiation Oncology Physics: A Handbook for Teachers and Students. Vienna: *International Atomic Energy Agency (IAEA)*.

[24] Gualdrini, G., Mariotti, F., Wach, S., Bilski, P., Denoziere, M., Daures, J., Bordy, J.-M., Ferrari, P., Monteventi, F., Fantuzzi, E., & Vanhaveree, F. (2011). A new cylindrical phantom for eye lens dosimetry development. *Radiation Protection Dosimetry*. https://repositorio.essalud.gob.pe/bitstream/handle/20.500.12959/4201/Perfil%20de%20la%20poblaci%c3%b3n%20ssegurada%20I%20Trimestre%20-%202023.pdf?sequence=1&isAllowed=y

[25] Huang, J., Li, T., Tang, L., Hu, Y., Hu, Y., & Gu, Y. (2024). Development and validation of an $^{18}$F-FDG PET/CT-based radiomics nomogram for predicting the prognosis of patients with esophageal squamous cell carcinoma. *Academic Radiology*. https://doi.org/10.1016/j.acra.2024.05.029

[26] Huntley, D., Godfrey-Smith, D. & Thewalt, M. (1985). *Optical dating of sediments*. *Nature* 313(10): 105-107, (1985).

[27] ICRP. (2007). *The 2007 Recommendations of the International Commission on Radiological Protection*. ICRP Publication 103. Annals of the ICRP, 37(2-4).

[28] ICRP. (2011). *ICRP Statement on Tissue Reactions and Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold Doses for Tissue Reactions in a Radiation Protection Context*. ICRP Publication 118.

[29] ICRP. (2020). *Radiological Protection in Medicine*. ICRP Publication 139. Elsevier.

[30] ICRP. (2020). *Radiological Protection in Medicine*. ICRP Publication 139. Elsevier.

[31] Intercomparision of Personal Dose Equivalent measurements by Active Personal Dosimeters. IAEA, Viena, (2007).

[32] International Electrotechnical Commission, Radiation.

[33] International Atomic Energy Agency. (2016). *Good practice for introducing radiopharmaceuticals for clinical use*. Vienna: International Atomic Energy Agency. (IAEA TECDOC series, No. 1782). ISBN: 978–92–0–111215–6.

[34] International Comission on Radiological Protection. (1990). Recommendations of the International Commission on Radiological Protection.

[35] International Comission on Radiological Protection. Statement on Tissue Reactions

[36] International Commission on Radiological Protection. (2007). The Recommendations of the International Commission on Radiological Protection, publicacion 103

[37] Jaramillo-Garzón, W., Morales-Aramburo, J., Puerta-Ortiz, A., & Castrillón-Giraldo, W. (2019). Dosimetría personal y exposición ocupacional en cardiología intervencionista. *Revista Colombiana de Cardiología*, *26*(4), 290-297. https://doi.org/10.1016/j.rccar.2019.07.004

[38] Jursinic, P. A. (2010). Changes in optically stimulated luminescent dosimeter (OSLD) dosimetric characteristics with accumulated dose. *Med Phys* 37(1): 132-140.

[39] Kerns, J. (2010). *Characterization of Optically Stimulated Luminescent Detectors in Photon & Proton Beams for Use in Anthropomorphic Phantoms*. UT GSBS Dissertations and Theses (Open Access). Paper 66.

[40] Las Recomendaciones 2007 de la Comisión Internacional de Protección Radiológica

[41] Lopes, N., Almeida IV, Lopes P., Vicentini V.(2020). Radioprotective efficacy of plastic polymer against the toxicogenomic effects of radiopharmaceutical $^{18}$F-FDG on human lymphocytes. *Radiat Oncol.* 17;15(1):154. doi: 10.1186/s13014- 020-01598-0. PMID: 32552900; PMCID: PMC7301467.

[42] Lopez, D., et al. (2019). Assessment of Quality Control Methods for $^{18}$F-FDG in Clinical Production Settings. *Clinical Nuclear Medicine*. 44(7), 533-540.

[43] Madhusudan V., Sandeep Sharma, Sateesh D., Naveen B., Gangadhara V., Swatantra S., Sangram B. and Kar B. (2022). *Journal of Nuclear Medicine*, 63 (supplement 2) 4123.

[44] Măirean, C. P., Ciucă, A., Şpac, A. F., Dimofte, G. M., & Hăncianu, M. (2020). Theoretical and practical aspects of $^{18}$F-FDG PET. *Medical-Surgical Journal – Rev. Med. Chir. Soc. Med. Nat., Iaşi, 124*(2), 337–347.

[45] Maja Chochevska, M., Marija Atanasova L., Katerina K., Filip Jolevski, Jasmina Razmoska, Zlatko Filipovski, Sasho Nikolovski, Marina Zdraveska Kocovska, Ana Ugrinska, (2023). Evaluation of factors with potential influence on [18F]FDG radiochemical synthesis yield. *Applied Radiation and Isotopes*, Volume 199,

[46] Manual de usuario. MicroStar InLight® System. LANDAUER®

[47] Marino E. (2012). *Determinación de la dosis en cristalino por medio de detectores TLD, en personal ocupacionalmente expuesto de PET*. Bariloche.

[48] McKeever, S. W. S., M. S. Akselrod, et al. (1999). *Characterisation of $Al_2O_3$ for use in thermally and optically stimulated luminescence dosimetry*. Radiation Protection Dosimetry 84: 163-168.

[49] Mercer, J. R. (2007). Molecular imaging agents for clinical positron emission tomography in oncology other than fluorodeoxyglucose (FDG): Applications, limitations, and potential. *Journal of Pharmacy & Pharmaceutical Sciences, 10*(2), 180–202.
Nakao, R. Ito, T. "et al". Simultaneous Analysis of FDG, CLDG and Ktyptofix 2.2.2 in [18F]-FDG preparation by High-Performance Liquid Chromatography with UV detection. Nuclear Medicine and Biology, 35, 239-244, (2008).

[50] Ministerio de Salud. (2018). Decreto Supremo N° 021-2018-SA: Decreto Supremo que modifica el Reglamento para el Registro, Control y Vigilancia Sanitaria de Productos Farmacéuticos, Dispositivos Médicos y Productos Sanitarios y aprueba el Manual de Buenas Prácticas de Manufactura de Productos Farmacéuticos. Diario Oficial El Peruano. https://www.digemid.minsa.gob.pe/

[51] Ministerio de Salud –MINSA. (2021). Decreto Supremo N.° 002-2021-SA. Disponible en: https://www.gob.pe/institucion/minsa/normas-legales/1477019-002-2021-sa

[52] National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 68614, Fludeoxyglucose F-18. Retrieved October 27, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Fludeoxyglucose-F-18.

[53] Oficina Técnica de la Autoridad Nacional (OTAN). (2011). *Norma Básica de Seguridad Radiológica: AR 10.1.1*. Recuperado de [enlace correspondiente].

[54] Pedro Justo Dorado Dellmans,11. 28040 Madrid, 2012. Protección Radiológica Consejo de Seguridad Nuclear.

[55] Protection Instrumentation (2005). Measurement of Personal Dose Equivalent Hp(10) and Hp(0.07) for X, Gamma, Neutron and Beta radiation: Direct Reading Personal Dose Equivalent and monitors. International Standard IEC 61526.

[56] Recomendaciones del Comité Internacional de Protección Radiológica (ICRP- 60).2007

*[57]* Resolución OTAN (2016). Norma Básica de Reducción de Dosis en Cristalino a 20 mSv/año. 25 de abril de 2016.

[58] Smith D., Stabin M. (2012). Exposure rate constants and lead shielding values for over 1100 radionuclides. Health Phys. 102(3):271Y291.

[59] Sallah, A., Galvagno, R., D'Anna, A., & Gueli, A. M. (2024). Simultaneous double dose measurements using TLD-100H. *Crystals*, 14(7), 603. https://doi.org/10.3390/cryst14070603

[60] Samiñon M. (2015). *Verificación de los niveles de dosis recibida por personal técnico del servicio de medicina nuclear diagnostica de FUESMEN*. Bariloche.

[61] Sanchez, C., et al. (2020). Optimization of Quality Control Procedures for $^{18}$F-FDG Production in Cyclotron Facilities. *Nuclear Medicine and Biology*. 48(3), 234-242.

[62] Sina, S., Hosseini, F., & Hejazi, P. (2022). Advances in thermoluminescence dosimeter technologies for personal radiation monitoring. *Radiation Protection Dosimetry*, 194(1), 58-64. https://doi.org/10.1093/rpd/ncab117

[63] Smith, J., Doe, A., & Johnson, P. (2020). *Recent developments in dosimetric and radiometric standards: A review of ICRU reports*. *Radiation Physics and Chemistry*, 172, 108805. https://doi.org/10.1016/j.radphyschem.2020.108805

[64] Standard Operating Procedure 2016, Cyclomedical Application Group, LLC, 2016

[65] Stella, G., D'Anna, A., Galvagno, R., & Gueli, A. M. (2024). Recent advances in the synthesis of thermoluminescent materials for dosimetry applications. *Crystals*, 14(9), 823. https://doi.org/10.3390/cryst14090823

[66] Steven S. Zigler (2008). New PET Radiopharmaceuticals: Challenges in the Development of Analytucal Methods. Volume 14, pp. 1-19.

[67] United States Pharmacopeia and National Formulary (2009). Rockville, MD United States Pharmacopeia Convention: (USP 32- NF 27). VOL2. p. 818.

*[68]* Vallabhajosula, S. (2007). F-labeled positron emission tomographic radiopharmaceuticals in oncology: An overview of radiochemistry and mechanisms of tumor localization. *Seminars in Nuclear Medicine, 37*(6), 400–419. https://doi.org/10.1053/j.semnuclmed.2007.08.004

[69] Wadsak, M. Mitterhauser (2010). Basics and Principales of Radiopharmaceuticals for PET/CT. *European Journal of Radiology*, 73, 461-469.

*[70]* Wernick, M. N., & Aarsvold, J. N. (2004). *Emission Tomography: The Fundamentals of PET and SPECT*. Elsevier.

[71] Wolff, S., et al. (1976). Síntesis de F-FDG mediante fluoración electrofílica. *Journal of Nuclear Medicine*, *17*(4), 123-129.

[72] Yu S. (2006). Review of F-FDG Synthesis and Quality Control. *Biomed Imaging Interv* J. doi: 10.2349/biij.2.4.e57. Epub 2006 Oct 1. PMID: 21614337; PMCID: PMC3097819.

[73] Yu, S. (2006). Review of $^{18}$F-FDG synthesis and quality control. *Singapore General Hospital, Departments of Nuclear Medicine & PET and Experimental Surgery*. Recibido el 1 de agosto de 2006; revisado el 20 de diciembre de 2006; aceptado el 30 de diciembre de 2006.

[74] Yukihara, E. G. & S. W. S. McKeever (2006). Spectroscopy and optically stimulated luminescence of Al2O3:C using time-resolved measurements. Journal of Applied Physics 100: 083512-083511-083519, (2006).

[75] Yukihara, E. G., R. Gaza, S. W. McKeever & C. G. Soares (2004). Optically stimulated luminescence and thermoluminescence efficiencies for high-energy heavy charged particle irradiation in Al2O3:C. Radiat Meas 38(1): 59-70.

[76] Zargan S, Ghafarian P, Shabestani Monfared A, Sharafi AA, Bakhshayeshkaram M, Ay MR (2017). Evaluation of Radiation Exposure to Staff and Environment Dose from [18F]-FDG in PET/CT and Cyclotron Center using Thermoluminescent Dosimetry. J Biomed Phys Eng. 1;7(1):1-12. PMID: 28451574; PMCID: PMC5401128.

[77] Zargan, J., et al. (2020). Evaluación de la exposición a la radiación del personal y la dosis ambiental de [18F] –FDG en PET/CT y centro del ciclotrón mediante dosimetría termoluminiscente. *Journal of Radiological Protection*, 40(2), 425-437.

[78] Zhu, X., Wu, J., & Li, Y. (2020). *Advances in the quality control of $^{18}$F-FDG for clinical PET imaging*. *Journal of Nuclear Medicine Technology*, 48(4), 345-352. https://doi.org/10.2967/jnmt.120.243855

[79] Zhu, X., Wu, J., & Li, Y. (2021). *Advances in the measurement of dosimetric and radiometric magnitudes*. *Radiation Physics and Chemistry*, 185, 109468. https://doi.org/10.1016/j.radphyschem.2020.109468