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Original

[^{18}F]FDG production facility at the Joint Research Centre Cyclotron (Ispra Site — Italy)

K. Abbas[1], F. Simonelli[1], N. Gibson[1], U. Holzwarth[1], A. Pecorale[2], F. Barberis Negra[2]

[1]European Commission, Joint Research Centre, Institute for Health and Consumer Protection, Ispra, Italy
[2]GE Healthcare, Milano, Italy

Abstract

The Joint Research Centre (JRC) MC40 Cyclotron is successfully used for routine [^{18}F]FDG production in compliance with the Marketing Authorization under a commercial partnership between JRC and General Electric Healthcare (GE HC). The commercial production has been operational since April 2004 without any significant interruption. This radiopharmaceutical site has been the first producing centre authorised in Italy. As regard to ^{18}F production, the cyclotron is running every night during about 6 hours. The [^{18}F]FDG radiopharmaceutical is distributed to hospitals and diagnostic centres in the north and central regions of Italy. The radiopharmaceutical is commercially recorded under the brand name SteriPET. This commercial activity does not interfere with other research projects that normally take place during daytime working hours.

Key words: Scanditronix MC40 cyclotron, $H_2{}^{18}O$ enriched water, proton irradiation, [^{18}F]FDG radiopharmaceutical

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Introduction

Nuclear Medicine has been a fundamental tool for many years for cancer treatment. In recent times, Positron Emission Tomography based on the cyclotron-produced radiotracer ^{18}F has significantly contributed to the development of medical imaging in oncology, and combined with CT scanning (PET-CT) has become one of the more widely used medical technologies. The Scanditronix MC40 cyclotron of the Joint Research Centre (JRC) of the European Commission (Ispra site) is one of a very limited number of such research facilities in the EU. Its characteristics allow the production of a wide range of radioisotopes and its seven beam-lines make possible the setting up of many different experiments. The facility is therefore very versatile in supporting research in many different areas. Currently the most important one is its contribution to the safety assessment of nanotechnologies by providing radiolabelled nanoparticles for uptake and biokinetics studies.

Correspondence to: Federica Simonelli
JRC–IHCP, Cyclotron TP 500, Via E. Fermi 2749,
I-21027 Ispra (VA), Italy
Tel: +39 0332 789285
Fax: +39 0332 785388
E-mail: federica.simonelli@jrc.ec.europa.eu

Background

The authorisations for the building and running of the MC40 Cyclotron in Ispra were obtained in 1980 and 1986, respectively. The facility is divided into bunkers for the Cyclotron itself and the irradiation halls with seven beam lines. In the surrounding area several hot laboratories and the control room are located.

The JRC-Cyclotron is a Scanditronix MC40 model, able to accelerate positive ions at variable energy. It can accelerate protons, deuterons, alphas (α) and Helium-3 particles. The relevant beam characteristics of the JRC-Cyclotron are reported in Table 1.

The activation of $H_2{}^{18}O$ enriched water yielding ^{18}F is carried out on beam line 4.

[^{18}F]FDG production facility

Concerning the [^{18}F]FDG commercial production, JRC is responsible for ^{18}F supply and for radioprotection support while GE HC is responsible for the [^{18}F]FDG synthesis, control and distribution to hospitals. The production site is located inside the controlled area of the cyclotron building. It consists of two laboratories: the production and the quality control and a shipment room (see Figure 1). The production laboratory comprises two automated synthesis modules and an automated dispensing unit, installed in three separate hot-cells.

The production of ^{18}F is carried out with a proton beam set to the energy of 19 MeV proton striking the target of $H_2{}^{18}O$ enriched water, using the nuclear reaction: $^{18}O(p,n)^{18}F$.

Table 1. Beam characteristics of the JRC-Cyclotron

Particles	Maximum energy [MeV]	Maximum extracted] intensity [μA]
p	40	60
α	40	30
$^{3}He^{2+}$	53	30
d	20	60

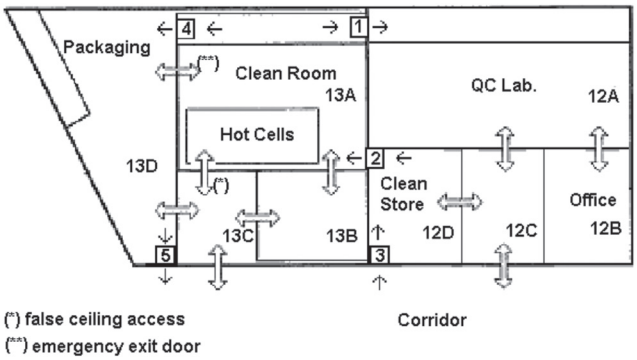

Figure 1. Radiopharmaceutical site layout

The target cavity is made of niobium. The target chamber is cooled with helium (front side) and water (rare side). The target capacity is around 4 ml ensuring a ^{18}F yield of 250 GBq per cyclotron run of 2 hours irradiation at 50 μA beam current.

At the end of bombardment (EOB), the activated $H_2{}^{18}O$ water is transferred by helium pressure to the synthesis module installed in one of the two hot-cells located in the production laboratory through a shielded pipeline, connecting the target chamber to the hot-cells. The production laboratory is classified as C grade; Class C (compatible with Class 10000, Class M5.5 or Class ISO 7) is needed for the implementation of Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) guidelines required for radiopharmaceutical productions. The whole site, comprising the production, the quality control and the shipment rooms, is under reduced pressure with respect to the corridor. The clean room (production room) is on upper pressure with respect to the remaining areas of the laboratory but still under reduced pressure with respect to the corridor.

The three hot-cells are connected to a dedicated ventilation system with absolute filters. The lead shielding of the hot-cells is around 8 cm thick and complies with the radioprotection regulations for the proceeding of single batches of ^{18}F up to 275 GBq. The synthesis modules and the dispensing unit located inside the three hot-cells are fully remote controlled by computers. The quality control of the produced [^{18}F]FDG is carried out according to the SteriPET Marketing Authorization.

[^{18}F]FDG synthesis and dispensing

The synthesis of [^{18}F]FDG is based on the nucleophilic substitution with ^{18}F, promoted by tetrabutylammonium (TBA) bicarbonate. The whole process for [^{18}F]FDG synthesis can be summarised as follows:

— collection of $^{18}F-$ in an anion-exchanger;
— reaction with acetylated triflate in acetonitrile under phase transfer catalysis (TBA);
— hydrolysation with HCl;
— purification by serial chromatography.

The synthesis module is a closed system. All openings to the environment are closed either by septa or by sterile filters. Before synthesis the module is rinsed with acetone and 70% ethanol and afterwards dried. The preparation duration of the synthesis module does not exceed 15 minutes. Between two syntheses, the apparatus is hermetically closed. The [^{18}F]FDG synthesis module ensures the recovery of the non-active ^{18}O water.

The production operator is guided during synthesis with short Standard Operation Procedures on the computer screen. A synthesis cycle is accomplished in about 35 minutes. After synthesis, the radiopharmaceutical is transferred to the dispensing unit by helium pressure. The yield of [^{18}F]FDG is around 75% (decay-corrected).

In the dispensing unit, a final sterilisation cycle is performed. Up to 17 vials of [^{18}F]FDG can be dispensed and sterilised in a single production run. The dispensing process is based on dispensing under laminar flow (ensuring Class A air quality) and sterilisation in the final vials with steam at 135°C during 3–4 minutes. The dispensing process lasts a maximum of 40 minutes, depending on the number of vials. After sterilisation, vials are remotely inserted in lead containers inside the hot-cell and then transferred through a pass through box into the shipment room. The software of the synthesis module, dispensing unit and quality control (QC) equipment is also designed according to GMP guidelines. All relevant parameters are recorded and stored and can be reviewed at any time.

[^{18}F]FDG quality controls

Quality control procedures on the product are carried out in the QC laboratory according to the SteriPET Marketing Authorization, where the specifications of the product as a radiopharmaceutical are presented. About 30 minutes are necessary to complete quality control analysis required for the release of the radiopharmaceutical. Radionuclide, chemical and radiochemical purity controls are carried out with gamma spectrometers, Radio-HPLC, HPLC and GC. Additionally, pH is controlled. The bacterial endotoxin test is part of the QC protocol. The [^{18}F]FDG can be released before completion of the biological analysis.

Status and outlook

As regards to the site production efficiency, the annual production plan foresees about 470 ^{18}F production run on 235 days, with a production average yield of 260 GBq of ^{18}F per run.

Due to the complexity of the cyclotron, three weeks of scheduled maintenance are carried out per year. This keeps the reliability of the cyclotron around 99% and allows to avoid interference between the scheduled ^{18}F commercial production and research use of the machine which requires frequent changes of energy and particle type.

Based on the experience with the radiopharmaceutical site at Ispra, GE HC set-up other 3 production facilities around Italy, in collaboration with national research centres or private companies.