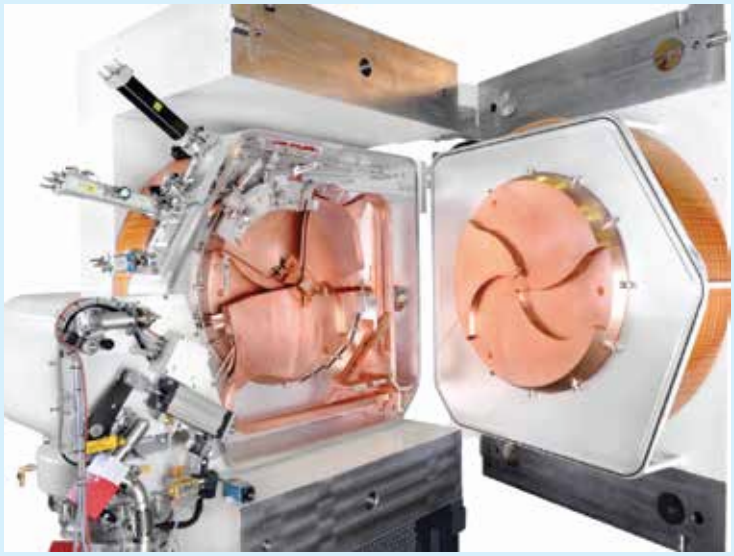
Association of Imaging Producers & Equipment Suppliers
European Industrial Association for Nuclear Medicine and Molecular Healthcare

Pictorial View of Nuclear Medicine
Cyclotrons for Medical Radionuclide Production

Production of radionuclides
There are four ways to produce radionuclides for medical applications: purification of fission products (uranium or thorium decay chain), irradiation of targets with neutron/gamma beam, extraction from decay products in generators, or irradiation of targets with proton, deuteron or alpha beam in an accelerator. Cyclotrons are circular accelerators that present the most convenient way to obtain on-site, short half-life radionuclides of high quality. However, radionuclides can only be produced under precise sets of parameters including particle energy, current, time, and adequate target material.

Basic principle of a cyclotron
In a cyclotron, charged particles are accelerated under high vacuum by an oscillating electric field and held in spiral trajectory by a static magnetic field. At the end of the trajectory the particle beam is deviated to hit a target and its energy is sufficient to allow transformation at the atomic level.

Technician operating a self-shielded cyclotron



Opened cyclotron showing the dees and the targets

Particles, energy and current
A cyclotron needs charged particles or ions to operate. These particles (protons, H+ or H-, deuterons or helium nuclei) are generated with an ion source and are accelerated. The useful particle energy ranges between 5 and 100 MeV but specific for each radionuclide, while the current, expressed in µA, is directly linked to the yield.

Cyclotron operation and safety
Operating a cyclotron is safe and does not generate large amounts of radioactive waste. In fact, as only short half-life radionuclides are produced, radioactive waste is also of short half-life. Safety is assured by thick shielding with concrete walls to prevent any radiation leak. The cyclotron is able to produce radiation only when electrical power is available and cyclotrons are operated usually with one single technician.

Which cyclotron for which radionuclide?
Smaller cyclotrons (energy below 12 MeV) are usually dedicated to the production of 13N (for 13N-ammonia) or 15O (for 15O water), sometimes 11C, all radionuclides with very short half lives. Fluorine-18 (18F) is usually produced with 10 to 20 MeV energy cyclotrons. This equipment is the most common tool used in PET manufacturing centers with the initial aim to produce 18F-FDG. These cyclotrons are also able to produce other radionuclides of interest for medical applications, such as 64Cu, 124I or 89Zr, provided they are equipped with the right targets.

For the production of 123I, 68Ge or 201Tl, higher energy (25 to 30 MeV) is required and very high energy cyclotrons (above 50 MeV) can be used to produce some specific radionuclides such as 82Sr or 117mSn.

Images courtesy of IBA SA, Siemens and GE Healthcare

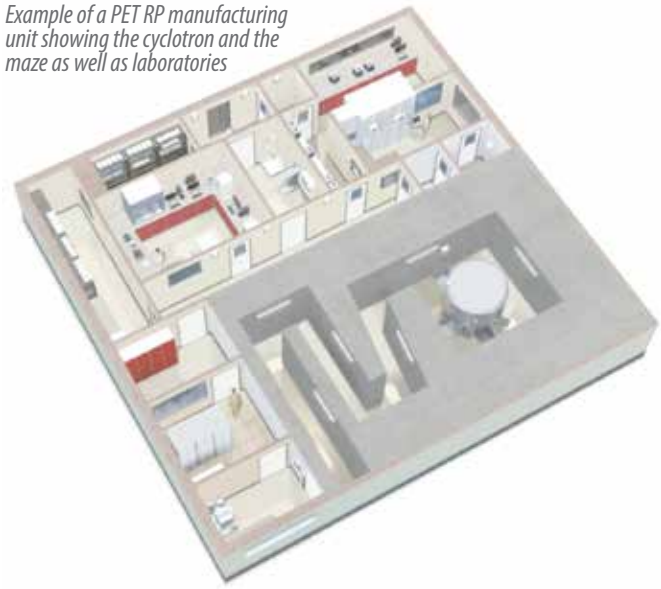
An initiative of the AIPES NewTechnologies Working Group

Pictorial View of Nuclear Medicine
From Cyclotron to Radiopharmaceutical

Production of radiopharmaceuticals in a cyclotron manufacturing center

Due to the short half-life of the radionuclides required by nuclear medicine (e.g. 109 min for 18F), manufacturing centers for radiopharmaceuticals are usually associated with the cyclotron facility and all the processes including target chemistry, purification, labelling, dispensing and quality analysis is performed at the same site. This whole manufacturing process has to be repeated every day and in some cases (very short half-life) several times a day.

Example of a PET RP manufacturing unit showing the cyclotron and the maze as well as laboratories



Targets and target processing

The beam generated by the cyclotron hits a target containing the material to be activated. This target, which can be solid, liquid, or gas, is selected for its potential in generating the purest radionuclide. Its container, combined with a powerful cooling system, must be inert and chemically resistant, as the beam also interacts with it, generating potential impurities. For example, the production of 18F needs a target of liquid 180-water, 123I is obtained from 124Xe gas while solid targets (deposits of metal) such as 112Cd-Cadmium are used to produce 111In. Many of these starting material isotopes are expensive because they are not naturally abundant and therefore need to be enriched artificially. At the end of irradiation, the radiochemist proceeds with the extraction of the target material and the chemical purification of the radionuclide.

On-site maintenance of a cyclotron by a technician

Radiopharmaceutical synthesis

The purified radionuclide is combined with a chemical entity (the vector precursor) in order to obtain a radiolabelled substance. This process is usually performed automatically in a synthesizer unit containing all reagents under sterile conditions. All these operations are performed behind shielded windows in leaded (so-called hot) cells. Finally the bulk material is dispensed in vials or syringes and stored in shielded containers ready for shipment. The whole manufacturing process must be performed under the strict respect of GMP rules.

Quality analysis and quality assurance

Samples of the final product are analyzed on-site for purity and content. Upon results, the doses are released for human use by the on-site radiopharmacist. Thus, strict procedures are in force in these radio-pharmaceutical facilities so as to ensure product safety according to GMP applicable to human sterile injectable drugs and to avoid any exposure or contamination to the workers and the general public.

Synthesis automate

FDG: Fludeoxyglucose
GMP: Good Manufacturing Practice
MeV: Mega-electron-volt
PET: Positron Emission Tomography
RP: Radiopharmaceutical
µA: microampere

Logistics

The location of the nuclear medicine department, the name of the patient, and the time of injection are known before the manufacturing process for a unit dose is started. Doses are adapted to the time of injection and weight of patient. The whole process takes into account the duration of the manufacturing and the time of transport. With short half-life labeled tracers (e.g. 18F-labelled compounds), the time of injection, and indirectly the time of delivery is specified at +/- 15 min.

Images courtesy of IBA SA, GE Healthcare and Siemens