5. PRODUCTION OF RADIONUCLIDES

A radiopharmaceutical preparation contains its radionuclide:

as an element in atomic or molecular form, e.g. [^{133}Xe], [^{15}O] O_2;

as an ion, e.g. [^{131}I] iodide, [^{99m}Tc] pertechnetate; and

included in or attached to organic molecules by chelation, e.g. [^{111}In] oxine or by covalent bonding, e.g. 2-[^{18}F] fluoro-2-deoxy-D-glucose.

Radionuclides can be produced in the following ways:

in reactions of neutrons (target irradiation in nuclear reactors);

in reactions of charged particles (target irradiation using accelerators, in particular cyclotrons); and

by separation from radionuclide generators.

The probability of nuclear reaction occurrence depends on the nature and energy of the incident particles (protons, neutrons, deuterons, etc.) and on the nature of the nucleus that is irradiated by them. The rate of production (yield) of a given radionuclide resulting from the irradiation depends in addition on the isotopic composition of the target material and its chemical purity, and in the case of neutrons on their flux, and in the case of charged particles on beam current.

In addition to the desired nuclear reaction, simultaneous transformations usually occur. Probability of their occurrence is given by the same factors as mentioned in the previous paragraph. Such simultaneous transformations may give rise to radionuclidic impurities.

5.1 Neutron irradiation

Irradiation of stable radionuclides in nuclear reactors usually results in proton-deficient nuclei, i.e. electron emitters that are formed in (n, γ) reactions (so-called radioactive capture). The product is isotopic with the target nucleus and it may thus contain a considerable amount of carrier.

A number of nuclides with high atomic number are fissionable by neutrons. Nuclear fission, denoted as (n, f) reaction, results in a large number of radionuclides of various masses and half-lives. The most frequently used fission is that of Uranium-235. Iodine-131, molybdenum-99 and xenon-133 can be produced by irradiation of Uranium-235 in nuclear reactors and by their separation from more than 200 radionuclides formed in that process.

5.2 Charged particle irradiation

Irradiation of stable radionuclides with charged particles usually results in neutron deficient nuclei that decay either by electron capture or by positron emission.

They are formed in particular in (p, xn) reactions (where x is the number of emitted neutrons). The product is not isotopic with the target nucleus and its specific radioactivity might be close to that of a carrier-free preparation. Cyclotrons are now commonly used for production of radioisotopes for PET radiopharmaceuticals where the use of high-power electron linac machine is an emerging alternative technology for isotope production

5.3 Radionuclide generators

Radionuclide generator systems use a parent radionuclide which decays to a daughter radionuclide with a shorter half-life.

By separating the daughter radionuclide from the parent radionuclide by a chemical or physical process, it is possible to use the daughter radionuclide at a considerable distance from the production site of the generator despite its short half-life.

5.4 Target materials

The isotopic composition and purity of the target material determines the relative percentages of the principal radionuclide and radionuclidic impurities. The use of isotopically enriched target material, in which the abundance of the required target nuclide has been artificially increased, can improve the production yield and the purity of the desired radionuclide.

The chemical form, the purity, the physical state and the chemical additives, as well as the bombardment conditions and the direct physical and chemical environment, will determine the chemical state and chemical purity of the radionuclides which are produced.

In the production of radionuclides, and particularly of short-lived radionuclides, it may not be possible to determine any of these quality criteria before further processing and manufacture of radiopharmaceutical preparations. Therefore, each batch of target material must be tested in test production runs before its use in routine radionuclide production and manufacture of the radiopharmaceutical preparations to ensure that, under specified conditions, the target yields the radionuclide in the desired quantity and quality specified.

The target material is contained in a holder in gaseous, liquid or solid state, in order to be irradiated by a beam of particles. For neutron bombardment, the target material is commonly contained in quartz ampoules or high purity aluminum or titanium containers. It is necessary to ascertain that no interaction can occur between the container and its contents under the irradiation conditions (temperature, pressure, time).

For charged particle bombardment, the holder for target material is usually built of aluminum or another appropriate metal, with a low cross section for the irradiating particles and also having a good thermal conductivity to remove the heat generated. The target will have inlet and outlet ports, a surrounding cooling system and usually a thin metal foil target window. The nature and thickness of the target window have a particular influence on the yield of the nuclear reaction and may also affect the radionuclidic purity.

The production procedure shall clearly describe the target material; construction of the holder for target material; loading of target material into the irradiation system; method of irradiation (bombardment); separation of the desired radionuclide and evaluates all effects on the efficiency of the production in terms of quality and quantity of the produced radionuclide.

The chemical state of the isolated radionuclide may play a major role in all further processing.