ANNEX 3

MANUFACTURE OF RADIOPHARMACEUTICALS

Principle

The manufacturing and handling of radiopharmaceuticals is potentially hazardous. The level of risk depends in particular upon the types of radiation emitted and the half-lives of the radioactive isotopes. Particular attention must be paid to the prevention of cross-contamination, to the retention of radionuclide contaminants, and to waste disposal. Special consideration may be necessary with reference to the small batch sizes made frequently for many radiopharmaceuticals. Due to their short half-life, some radiopharmaceuticals are released before completion of certain Quality Control tests. In this case, the continuous assessment of the effectiveness of the Quality Assurance system becomes very important.

Note

Manufacture must comply with the requirements of EURATOM Directives laying down the basic standards for the health protection of the general public and workers against the dangers of ionising radiation, as well as complying with other relevant national requirements.

Personnel

1. All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are manufactured should receive additional training specific to this class of products. In particular, they should be given detailed information and appropriate training on radiation protection.

Premises and equipment

2. Radioactive products should be stored, processed, packaged and controlled in dedicated and self-contained facilities. The equipment used for manufacturing operations should be reserved exclusively for radiopharmaceuticals.

3. In order to contain the radioactive particles, it may be necessary for the air pressure to be lower where products are exposed than in surrounding areas. However, it is still necessary to protect the product from environmental contamination.

4. For sterile products the working zone where products or containers may be exposed should comply with the environmental requirements described in the Supplement on Sterile Products. This may be achieved by the provision within the work station of a laminar flow of HEPA-filtered air and by fitting air-locks to entry ports. Total containment work stations may provide these requirements. They should be in an environment conforming to at least grade D.

5. Air extracted from areas where radioactive products are handled should not be re circulated; air outlets should be designed to avoid possible environmental contamination by radioactive particles and gases.

   There should be a system to prevent air entering the clean area through extract ducts e.g. when the extract fan is not operating.

Production

6. Production of different radioactive products in the same work stations and at the same time should be avoided in order to minimise the risk of cross-contamination or mix-up.

7. Process validation, in-process controls and monitoring of process parameters and environment, assume particular importance in cases where it is necessary to take the decision to release or reject a batch or a product before all tests are completed.

Quality control

8. When products have to be dispatched before all tests are completed, this does not obviate the need for a formal recorded decision to be taken by the Qualified Person on the conformity of the batch. In this case there should be a written procedure detailing all production and Quality Control data which should be considered before the batch is dispatched. A procedure should also describe the measures to be taken by the Qualified Person if unsatisfactory test results are obtained after dispatch.

9. Unless otherwise specified in the marketing authorisation, reference samples of every batch should be retained.

Distribution and recalls

10. Detailed distribution records should be maintained and there should be procedures which describe the measures to be taken for stopping the use of defective radiopharmaceuticals. Recall operations should be shown to be operable within a very short time.