RADIOPHARMACEUTICAL PRODUCTION FOR PET: QUALITY ASSURANCE PRACTICE, EXPERIENCES AND ISSUES


MRC Cyclotron Unit
Hammersmith Hospital
Ducane Road
London W12 OHS, U.K.

INTRODUCTION

Pharmaceutical quality assurance is an overall concept embracing the establishment of certain criteria before production begins, the control of certain factors during production and the evaluation of certain results after production (Bryant, 1989). It is recognised that the provision of radiopharmaceuticals labelled with carbon-11 ($t_{1/2} = 20.4$ min, $\beta^+ = 99.8\%$), nitrogen-13 ($t_{1/2} = 9.96$ min, $\beta^+ = 100\%$), oxygen-15 ($t_{1/2} = 2.03$ min, $\beta^+ = 99.9\%$) or fluorine-18 ($t_{1/2} = 109.8$ min, $\beta^+ = 96.9\%$) for positron emission tomography (PET) poses special problems of quality assurance (Vera Ruiz et al., 1990). First, the short half-lives of these radionuclides exclude lengthy techniques from routine analysis. Secondly, because many PET radioligands must be produced along with only small amounts of carrier and are often derived from potent drugs, traces of structurally-related contaminants can easily detract from radiopharmaceutical quality. Thirdly, rapid labelling procedures sometimes exploit reagents which themselves are potential sources of toxins. Therefore, our approach to quality assurance, in PET radiopharmaceutical production, depends on using a well-defined protocol that delivers high quality product from materials of assured grade, supported routinely by rapid quality control procedures that measure or test parameters important to efficacy and safety. This combination, in our view, is integral to ensuring 'good manufacturing practice' (Sharp, 1983).

This chapter reviews techniques that are useful to assure PET radiopharmaceutical quality, together with some observations on our experience of implementing a quality assurance programme at the MRC Cyclotron Unit. Some of the issues that arise when adopting our approach to quality assurance are also discussed.
To assure the quality of PET radiopharmaceuticals, powerful direct and indirect techniques are applicable to investigate and measure the following important quality criteria:

- Radionuclidic purity
- Radiochemical purity
- Chemical purity
- Specific activity
- Shelf life
- Sterility, Apyrogenicity, pH and Isotonicity

Each of these parameters requires definition and further discussion on methods of assurance, as follows.

**Radionuclidic Purity**

The radionuclidic purity of a radiopharmaceutical may be defined as *the fraction of total radioactivity that is present as the specified radionuclide*. Radionuclidic purity is required to avoid unnecessary radiation dose to the subject of the study and to limit errors on PET measurements *in vivo*. Generally, radionuclidic impurities arise from undesired nuclear reactions induced in target materials and by recoil reactions, especially in window foils (see Clark & Buckingham, 1975, p. 32). Consequently, radionuclidic purity is best controlled by careful selection of production parameters, such as the nuclear reaction, the beam energy, the beam current, the purity of the target substance, the isotopic composition of the target substance, the types of material composing the target body and its window, and, where applicable, the choice of sweep gas.

The most useful methods for producing important radioactive gases, for 'on-line' clinical use, generate only low levels of non-isotopic short-lived radionuclidic impurities under controlled conditions (Table 1). Radio-GLC (analytical gas chromatography, equipped with detectors for mass and radioactivity), coupled to half-life analysis of separated peaks, is a useful means of determining contamination by positron-emitting radionuclides, and simultaneously gives information on radiochemical purity (*vide infra*) (Clark & Buckingham, 1975, p. 54). Careful and continuous control of the production method is an important aspect of routine quality assurance. *Routine* quality control is best achieved using radio-GLC as an integral part of production (Clark & Buckingham, 1975, p 50-53; Meyer, 1982; Clark *et al.*, 1987; Strijckmans *et al.*, 1989). Thereby, radiochemical purity, chemical purity and specific activity (*vide infra*) can be measured simultaneously and 'on line' to the patient.