Radiopharmaceutical Tracer – from first Step to first Patient

L. S. N. Soerensen, Copenhagen (DK)

PET imaging has become an increasingly widespread method in the diagnosis of cancer and some diseases of the brain. [18F]FDG is by far the most commonly used radiopharmaceutical; however it is not optimal for the diagnosis of all types of cancer. Therefore it is important to continuously develop and produce specialised radiopharmaceutical tracers, for diagnostic use. To get approval from the authorities to produce the radiopharmaceutical tracer for human use, a lot of thought, strategy and hard work have to be put into it. This includes qualification of production facilities and the equipment as well as validation of the analytical methods used for quality control of the product. Some products have a monograph in the European pharmacopeia if so, it can be followed. If a monograph for the compounds does not exist in the European pharmacopeia the analysis for the quality control has to be defined. Sometimes draft monographs are available and can be used as guidance.

To ensure the quality of the product and to safeguard the health of the patient, the radiopharmaceutical tracer has to be produced under regulations for good manufacturing practices (GMP). The objective of the regulations is to ensure that the quality of the product is such that it can safely be administered to the patient.

The keywords for GMP are documentation and control and they have to be implemented in planning the strategy for realising a new radiopharmaceutical tracer.

Working under GMP means following guidelines, all guidelines follows basic principles, such as:

- All manufacturing processes are clearly defined and controlled and critical processes are validated
- Procedures and instructions are written according to good document practices
- All personal are trained to carry out and document procedures correctly
- Records are made during manufacture to demonstrate that all steps were taken according to the defined procedures and instructions, and that quantity and quality was as expected. Any deviations are investigated and documented
- Records of manufacture that enable the history of the batch to be traced are retained in a comprehensible and accessible form
- Distribution of the product minimizes any risk to the product
- Available systems for recalling any batch from sale or supply exist
- Complaints are examined, quality defects are investigated and appropriate measures taken in respect to the defective product and to prevent recurrence

The GMP guidelines are only guidelines they are not prescriptive instructions on how to produce proper products. It is up to each manufacturer to set up its own process and quality programme.

Before initialising a clinical study the protocol for the preparation and validation of the process for producing the radiopharmaceutical have to be approved by the national authorities.

To complicate things further, we have to acknowledge that we are working with radioactivity and therefore have to consider the safety of the operator producing the radiopharmaceutical tracer.

This can be done by continuously taking measurements of the level of radiation received to the personnel involved in the production are exposed to. The consequence might be that work processes have to be changed to minimize the exposure.

In our PET centre we have recently implemented [18F] FET for human use. This process meant we had to put all of the theory mentioned above into practice. We started out by searching the literature to find information on production and quality control of this tracer. We also investigated whether a Ph.Eur.Monograph existed. For [18F] FET it turned out we only had a draft monograph to work with.

We considered on whether we had the facilities and the personnel to make [18F] FET and if

there were any known problems with the separations of the HPLC-peaks or unknown impurities.

Then we implemented the analysis methods described in the draft to see if it was possible to reproduce the results from the draft. The specifications for the analyses were finally determined. Then the analyses methods were validated and an experimental production was done.

A protocol was drawn up which described the process validation of [18F]FET and which specifications we had to comply with. The process validation consisted of three following productions, all of which had to stay within the defined specifications.

Based on the results obtained in the validation batches, the data were summarized in an application submitted to the authorities. In reviewing applications questions can arise and the authorities will send them back to us. Sometimes an elaboration will be sufficient but sometimes further testing will be needed. When the authorities are satisfied they will grant a permission to produce the radiopharmaceutical for use in humans.

References

1. EudraLex – Volume 4 Good manufacturing practice (GMP) Guidelines.