

# Radiopharmacy Introduction

This Chapter is an amended version of the Good Radiopharmacy Practice Position Paper (GRPP), prepared as a policy document by the SIG Radiopharmacy and Nuclear Medicine of the Netherlands Association of Hospital Pharmacists (NVZA).

## Introduction

In practice, Healthcare Inspectorate (IGZ) inspections in hospitals identify issues during the preparation and reconstitution and/ or aseptic handling (RAH) of radiopharmaceuticals in relation to the interpretation and application of the Dutch Good Manufacturing Practice for hospitals (GMP-z) guidelines.

This Chapter aims to provide an unambiguous framework to ensure that there is no doubt about the guidelines and circumstances that apply to every situation.

## Principles, legislation and regulations

In the Netherlands, around 65 hospitals have a Nuclear Medicine Department. More than 50% of these Departments are currently supplied by one of the three radiopharmacies of GE Healthcare. In the other hospitals, the radiopharmaceuticals are prepared by the Radiopharmacy, as well known as the "hot lab". As this generally concerns centers with a major Nuclear Medicine Department, it can be said that the largest volume of radiopharmaceuticals is produced in the hospitals themselves. Radionuclides and radiopharmaceuticals are also purchased ready-made and are prepared for administration by the hot lab.

Radiopharmaceuticals are ordinary pharmacy preparations, but differ from other prepared medicines due to their small-scale preparation (always prepared shortly before for administration (PFA)) on a patients name, sometimes preceded by a labelling step with a radionuclide generated in-house or not), their short shelf-life (due to radioactive decay) and the low pharmacological doses that are generally used. The radiation dose for the patient is generally low, as most radiopharmaceuticals are used for diagnostic purposes. Adverse reactions are extremely rare. Administration only takes place in the hospital and often just once or a few times in the life of a patient.

Stock preparation, as for other pharmacy preparations, does not occur and resupplying (particularly by the commercial radiopharmacies, occasionally by hospital radiopharmacies) is only performed on a named patients base (and is always on the basis of a prescription).

The production of radionuclides as a raw material for radiopharmaceuticals can be vulnerable, as demonstrated by the recent global molybdenum crisis. Several production sites are required to guarantee the required continuity of care. The distance criterion plays a role for nuclides with an extremely short life. In-house production/preparation is often the only option.

The following legislation and regulations govern the preparation and the RAH of radiopharmaceuticals:

Dutch Nuclear Energy Act

Dutch Medicines Act

GMP, including the relevant Annexes (particularly Annexes 1, 3 and 13)

Dutch GMP for hospital radiopharmacies, incl. Z1, Z2, Z3 and Z4

European Pharmacopoeia. A relevant general Chapter will be published shortly: 5.19

Extemporaneous preparation of radiopharmaceutical preparations.

A number of publications have addressed the interpretation of the above-mentioned legislation and regulations in daily practice.

The most important pharmaceutical quality assurance standards are included in the Quality Guidelines of the Netherlands Association of Nuclear Medicine (NVNG) and the cGRPP guidance from EANM. A usable interpretation of Annex 3 of the GMP appeared in the GPP guide (PE 010-4) of the PIC/S in 2014.

The Nuclear Medicine Procedure Guidelines provide general radiopharmaceutical recommendations and information about the preparation method and quality controls that should be applied to every radiopharmaceutical.

If preparations, including radiopharmaceuticals, are used for clinical trials of medicinal products, additional rules apply and a manufacturer's license and an IMPD are also required. In 2005 the GMP-z Committee issued a position paper on this subject. This argues that Annex 13 of the GMP can be applied to preparations for clinical trials, but where that refers back to the GMP, the GMP-z should be applied. It is important to determine whether a radiopharmaceutical for a clinical trial is an Investigational Medicinal Product (IMP) or Non Investigational Medicinal Product (NIMP). Examples of NIMPs are radiopharmaceuticals that are used standardly to determine end points. In 2014, the European Parliament adopted the Clinical Trial Regulation which will replace the existing Clinical Trial Directive in the near future. From that time onwards a manufacturer's license and GMP are no longer required to prepare radiopharmaceuticals for diagnostic use in clinical trials. However, the guidelines replacing GMP must be assessed by the national competent authorities. The GMP-z remains the basic standard for preparing medicinal products in hospitals in the Netherlands and this standard will continue to apply to radiopharmaceuticals. In 2013 the GMP-z version of Annex 3 was drafted and approved by the Healthcare Inspectorate (IGZ).

If a preparation is supplied to another dispensary (inter-institutional supply) the Circular for large-scale preparation applies. If the preparation process is described in the GMP, the GMP applies. If not, the professional standard (GMP-z) applies.

The Health and Safety at Work (ARBO) guidelines also apply. Due to risks of radiation for the preparer, the Dutch Nuclear Energy Act (KEW) prevails and requirements are imposed on the design and pressure hierarchy of a hot lab.

This Chapter does not deal with other aspects of radiation hygiene in a hot lab.

### **Interpretation and details of legislation and regulations**

The following sets out the various situations that could occur in respect of the preparation and RAH of radiopharmaceuticals in a hot lab in a hospital and notes which

interpretation of GMP(-z) applies. Some instructions for implementation are also given. The main starting point is that the GMP-z is decisive for preparation/RAH for own patients. Additional requirements are imposed on preparations for clinical trial and in the framework of supplying to other radiopharmacies. For example, the GMP applies if the relevant process is described in the GMP. The following scenario assumes preparation/PFA for own patients in first instance.

Generally speaking, the process of preparation and/or preparing radiopharmaceuticals for administration consists of the following steps:

Obtaining a radionuclide by eluting a generator, through own production with a cyclotron (seldom the case in a hospital dispensary) or by purchasing;

Obtaining a pharmaceutical to be labelled by buying a kit or by own preparation;

Obtaining a radiopharmaceutical by labelling the pharmaceutical with the radionuclide or by purchasing;

RAH of a prepared or purchased radiopharmaceutical (alternative: purchase radiopharmaceutical in a ready-to-use vial).

The above-mentioned steps can be used individually, but also in combination.

The supplier's assessment is important when the raw materials or radiopharmaceuticals are purchased. Particularly when purchasing non-registered generators, kits and ready-to-use radiopharmaceuticals it is essential to pay attention to assessing the quality level and the quality assurance of the manufacturer. When purchasing non-registered radiopharmaceuticals or pharmaceuticals the reasons and added value in relation to registered commercial alternatives must be substantiated and reported to the Healthcare Inspectorate (IGZ).

According to GMP-z Z3 simple aseptic actions can be performed under limited, increased or maximum product protection. As there are generally no separate rooms available for these different regimes, the above assumes a GMP class-A work space with GMP class D as the standard background space. In certain situations, preparation in a safety cabinet will suffice without imposing requirements on the background. If blood cell labelling is performed, this must be separated in the room (at least in a different safety cabinet) or in time from other preparations in connection with the risk of cross-contamination or exchange.

To determine the circumstances and measures required for the activities, a risk evaluation on the basis of ICH Q9 may prove useful. Examples:

Elution and RAH of an extremely short-lived radiopharmaceutical such as rubidium-82-chloride can take place near the camera, just prior to administering to the patient.

Eluting a generator may take place in a GMP Class-C room, provided the subsequent preparation, filtration and PFA take place in a GMP Class-A room.

Certain actions, for example centrifugation and/or heating, may be performed outside the safety cabinet, provided a closed system is used.

When the shelf-life of radiopharmaceuticals is determined, the radioactive decay and the stability are generally decisive. If this is not the case, the microbiological shelf-life comes into play. This may be derived from the 'GMP-ziekenhuisfarmacie'.

## Literature

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