RADIOPHARMACEUTICALS

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Additional Notes	**This note for guidance concerns the application to radiopharmaceuticals of Directive 65/65/EEC and of parts 2, 3 and 4 of the Annex to Directive 75/318/EEC as amended, with a view to the granting of a marketing authorisation for a radiopharmaceutical.**

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1. INTRODUCTION

Applications for marketing authorisation in respect of radiopharmaceuticals should be accompanied, as in the case of all medicinal products, by the particulars and documents referred to in Directives 65/65/EEC and 75/319/EEC, as amended, and in the Annex of Directive 75/318/EEC as amended. The provisions of Directive 89/343/EEC also apply. The relevant provisions of the European Pharmacopoeia should be observed. Due account must be taken of the other relevant CPMP guidelines.

Most radiopharmaceuticals are used for the purpose of medical diagnosis. They are usually given only once, or sometimes on a few occasions, and contain only small amounts of the active substances with a radionuclide attached to them to allow scintigraphic imaging or measurement of biodistribution. Such radiopharmaceuticals do not often show any measurable pharmacodynamic effect. Radiation is a general property of all radiopharmaceuticals, which when administered give the patient an inevitable radiation dose. In the case of therapeutic radiopharmaceuticals, the radiation effect is the wanted property. Evaluation of the safety and efficacy of radiopharmaceuticals should include radiopharmaceutical and radiation hygiene aspects and radiation dosimetry in addition to general parameters.

Radiopharmaceuticals have changing composition with time, associated with the radioactive decay. The physical half-life of the radionuclide is often so short that, in these cases, the final preparation has to be done immediately before administration to the patient; this leads to the use of semi-manufactured products such as radionuclide generators, precursors and kits. Evaluation of the safety and efficacy of radiopharmaceuticals is also concerned with the specifications of generators, kits and other semi-manufactured products. Specifications may also require special attention in cases where samples from the patient are labelled with a radioactive substance before readministration (precursor radiopharmaceuticals). When radiopharmaceuticals go directly from the generator to the patient (e.g. ultra short-lived radioactive gases), the consistency of the production process has a particularly great importance.

This note for guidance covers the following products:

– ready-for-use radiopharmaceuticals;

– non-radioactive components (kits) for combination with a radioactive component (usually the eluate from a radionuclide generator);

– radionuclide generators;

– precursors used for radiolabelling other substances prior to administration (e.g. samples from patients).

2. PHYSICO-CHEMICAL, BIOLOGICAL OR MICROBIOLOGICAL TESTS OF MEDICINAL PRODUCTS

2.1 Qualitative and quantitative particulars of the constituents and development pharmaceutics

For the radionuclides, details must be given of their source, i.e. whether fission or target material is used.

Radioactivity should be expressed in Bequerels at a given date, and hour in appropriate cases (other units may be added). If a calibration time is stated, the time zone used should be stated (e.g. GMT/CET).

Where practicable, the proportion (specific activity, carrier free or carrier added) of inactive isotopes in the carrier should be stated.

For radiopharmaceutical kits, any added compound (e.g. stannous salt for reduction of pertechnetate ions in the eluate from a technetium ^{99m}Tc generator) and manipulation essential for radiolabelling should be stated.

Where applicable, evidence to confirm the efficacy and specificity of the radiolabelling of the labelling medium (e.g. ^{99m}Tc) should be supplied. A discussion of the necessary specification (e.g. purity, pH) of radiolabelling medium should be stated for kits.

After radiolabelling, the compatibility of the product with the containers and closures should be considered and validated where appropriate.

2.2 Description of method of preparation

Because of the complexity of the production of radiopharmaceuticals, it is important that methods for obtaining and maintaining sterility during manufacture (preparation and assembly) are adequately described. Information should be given on validation of those processes.

a) Radiopharmaceutical kits: the instructions for final preparation should include:

- minimum and maximum for both volume and amount of radioactivity to be added;
- any special quality requirement for the radiolabelling medium;
- the standing time and any other manipulation necessary during final preparation (detailed and justified);
- details supporting recommendations on quality control procedures such as checking radiochemical purity of the prepared radiopharmaceutical prior to administration;
- as relevant, data on stability of particles (e.g. of colloidal size) after reconstitution and justification for the quantity of added materials.

These aspects should be discussed and documented adequately in the Development Pharmaceutics part of the dossier.

b) Generators

The recommendations for use of the generators should be discussed and documented.

c) Precursors

The recommendations for use of the precursors should be discussed and documented.

2.3 Control of starting materials

For the purposes of this section "starting materials" shall mean all the constituents of the medicinal product, if necessary, all the constituents of its containers and closures and where applicable, all constituents of the radionuclide source and any other materials used in the final process prior to administration. A full description is required of the separation of radionuclides and the control of radionuclide purity, as well as specific activity (with respect to impurities and degradation products). Specifications of components of the container (including the name of the approved producers) should be given. Specifications of any radiation shielding of the finished products should also be given.

For some radiopharmaceuticals, it is difficult to distinguish between control of starting materials and control of the finished product. For such products, all the information should preferably be placed in the section "Control tests on the finished product".

2.4 Control tests on the finished product

For products intended for intrathecal injection, regardless of volume, an appropriate endotoxin test is required unless its omission can be fully and adequately justified.

For terminally-sterilised products, process parameter release* (sometimes called parametric release) could well be justified. In the case of an aseptically-assembled product a sterility test is required.

For some radiopharmaceuticals it may not be possible to obtain the results of certain tests, e.g. sterility test, pyrogenicity tests, before the product is released. However, these tests should be done as a monitor for the manufacturing process.

Potential and actual impurities should be considered not only for any direct effect on the patient but also for their possible influence on the radiochemical purity or biodistribution of the product.

2.5 Stability tests

For all radiopharmaceuticals, the shelf life of the product as supplied by the manufacturer should be specified and justified, as should a shelf life after reconstitution where applicable, taking into account radiochemical and radionuclide degradation products.

For radiopharmaceutical kits, the shelf life of the prepared product should be defined; in this case, data should be submitted which detail the minimum and maximum levels of radioactivity (and maximum and minimum volumes) and other relevant factors that are recommended for use in the preparation of the product to be administered to the patient.

For radiopharmaceuticals prepared in multiple-dose vials, the stability following removal of successive doses should be discussed.

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* For the purpose of this guideline, process parameter release is defined as "the decision to release a batch of product for sale or supply based on an assessment of measured and recorded information relating to the validation, maintenance, operation and control of a process."

3. Toxicological and Pharmacological Tests

It is appreciated that toxicity may be associated with a radiation dose. This toxicity is a consequence of the use of radiopharmaceuticals in diagnosis and the wanted property of radiopharmaceuticals used in therapy. The evaluation of safety and efficacy of radiopharmaceuticals should, therefore, address both general parameters of the medicinal product and radiation dosimetry aspects.

Toxicity studies should be designed to examine the chemical rather than the radiation aspects of toxicity.

Knowledge of the toxicology of the ligand per se is of value. However, if the radiolabel is likely to produce chemical changes in the ligand, it would be preferable to carry out the toxicity studies on material in which radioactive decay has proceeded for long enough as to expose the test animals to breakdown products as well as to the parent complex.

For other radiopharmaceuticals, consideration should be given to ascertaining the toxicity of the parent molecule, either by reacting the ligand with a non-radioactive isotope of the element in question, or, if appropriate, by allowing decay of the product to occur so that there is no significant residual radioactivity.

Whatever the strategy and method chosen, it should be justified.

Distribution and elimination studies should be performed with the labelled compound.

For no-carrier-added radioactive elements and simple salts thereof, if the toxicity of the element or simple salt is known and can be submitted in the application, no additional toxicity studies would normally be required.

The contents in many final preparations (e.g. kit preparations) may be so small that is may be justified to use a bulk preparation for toxicity testing but the stability of the bulk material over the period of testing should be validated. The duration of animal toxicology testing will be determined by the anticipated duration of clinical use. In cases where the pharmacokinetic properties of the radiopharmaceutical (e.g. retention in certain organs) may lead to long term exposure, the observation period of the toxicity study may have to be extended.

Radiation dose should be evaluated with respect to target organs and physiological functions.

For radiopharmaceuticals, studies should be designed to assess:

a) the in vivo stability of the radionuclide complex;

b) the animal biodistribution of the radionuclide;

c) the potential chemical toxicity;

d) the radiation exposure of tissues resulting from administration of the radiopharmaceutical.

3.1 Single dose/repeated dose toxicity

These tests should be carried out according to the principles applicable to other medicinal products. The length of the studies should relate to the period of clinical use of the radiopharmaceutical, e.g. for a single (day of) treatment to patients, the toxicity dosing period would be two weeks, but observation for adverse effects may need to continue beyond this time.

3.2 Examination of reproductive function and foetal toxicity

Although radiopharmaceuticals are not normally recommended for potentially pregnant women, studies on reproduction may be required in certain cases, especially if the radiopharmaceutical is intended for repeated use in women of child-bearing potential. Otherwise the study on reproductive function may justifiably be limited to ascertaining the effect on fertility.

3.3 Mutagenic potential

Mutagenicity testing may be limited to screening for gene and chromosome mutations and should be performed to allow characterisation of the mutagenic potential of the non-radioactive equivalent of the product.

3.4 Carcinogenic potential

An evaluation of any carcinogenic potential of the substances involved must be presented. If no carcinogenicity tests are performed, this must be clearly indicated in the "Summary of product characteristics".

3.5 Pharmacodynamics

Measurable pharmacodynamic effect is not normally expected to be seen for radiopharmaceuticals. The likelihood of their absence may be deduced from toxicity testing, but in reassurance information should be supplied that no pharmacological effect is seen in major organ systems.

3.6 Pharmacokinetics

Information should be provided as to the distribution and elimination of the radiolabelled substances. If relevant, information should be provided on absorption and biotransformation. Important pharmacokinetic parameters should be investigated in the animal species used in the toxicological studies.

The animal pharmacokinetic studies should always provide data to allow estimation of tissue and whole-body radiation doses, which can be extrapolated to man.

4. CLINICAL DOCUMENTATION

Diagnostic radiopharmaceuticals differ in many ways from therapeutic radiopharmaceuticals. Consequently clinical documentation on diagnostic radiopharmaceuticals will be different from that relating to therapeutic radiopharmaceuticals.

Radiopharmaceuticals for diagnostic use are part of a diagnostic system where other factors such as instrumentation, time schedule, etc. also play an important role which should be discussed. The same criteria as for non-radioactive therapeutic medicinal products apply to therapeutic radiopharmaceuticals.

4.1 Clinical pharmacology

Whenever possible, initial pharmacodynamic and pharmacokinetic studies with radiopharmaceuticals should be performed in suitable patients, rather than in healthy volunteers.

Pharmacodynamics:

It is expected that many radiopharmaceuticals will not have any pharmacological action.

During early studies, the subjects should be monitored for a sufficient period to ascertain any change in major organ function. Any adverse events should be reported, giving nature and frequency.

Pharmacokinetics:

Pharmacokinetic studies should always provide the data necessary for the calculation of radiation doses.

The results should be presented in a form which allows evaluation of the proposed radiation dose and discussion of the in vivo stability of any radionuclide/carrier complex.

4.2 Clinical trials

The main purpose of clinical trials with new radiopharmaceuticals is to prove their safety in use and their value as diagnostic or therapeutic agents. Comparison with existing agents or with other relevant medicinal products and procedures should be the method of choice to prove efficacy. In particular, radiopharmaceuticals for diagnostic use may need to be compared with alternative techniques.

Diagnostic/therapeutic efficacy:

Each indication should be the subject of at least one separate trial.

Adverse reactions:

A summary should be given on the investigations performed to ascertain the nature, severity and frequency of any adverse reactions.

Interactions:

Signs of interactions should be carefully observed during clinical trials and consideration given to medicinal products likely to be used concurrently.

Dosage:

The clinical trials should provide a reliable basis for the dosing recommendations.

5. RADIATION DOSIMETRY

Information on pharmacokinetics should be sufficient for radiation dosimetry calculations. Data from animal studies (extrapolated to estimated radiation doses in man) should be confirmed as relevant or superseded by data obtained from patients. Radiation dose estimates should consider the impact of age and clinical condition, particularly impairment of hepatic or renal function.

It is recommended that calculations of absorbed dose to organs should be carried out in accordance with the Medical Internal Radiation Dosimetry (MIRD) schedules. The model used for calculations of the cumulated activity (time integral of the activity) in source organs should be explained; the origin of data used, such as animal studies or measurements in humans, should be stated. Physical parameters, such as absorbed dose to target organs per unit of cumulated activity in source organs, should be taken from MIRD tables.

The effective dose-equivalent should be calculated using the current weighting factors established by the International Commission on Radiological Protection (ICRP). These weighting factors are not applicable to children, pregnant women or elderly patients and modifications should be given for radiopharmaceuticals intended for use in such patients.

If other methods of calculation of the absorbed dose in organs are used, details should be given with reference to the original reports.

The absorbed dose in the organ receiving the highest exposure and in all organs included in the calculation of the effective dose-equivalent should be stated. The unit must be milligrays per unit of activity administered: mGy/MBq.

The estimation of the radiation dose must be summarised in terms of the effective dose-equivalent using the weighting factors given by ICRP. The unit must be millisieverts per unit of activity: mSv/MBq.

6. LABELLING AND PACKAGING

6.1 Labelling

The label on the container should state:

– the name of the product and the name of the radionuclide;

– any product identification code;

– the name of the manufacturer;

– an identification number (batch number);

– for liquid preparations, the total radioactivity in the container, or the radioactive concentration per millilitre, at a stated date and, if necessary, hour, and the volume of liquid in container;

– for solid preparations, such as freeze-dried preparations, the total radioactivity at a stated date and, if necessary, hour;

– for capsules, the radioactivity of each capsule at a stated date and, if necessary, hour and the number of capsules in the container;

– where relevant, the international symbol for radioactivity.

In addition, the label on the package should state:

– qualitative and quantitative composition;

– the route of administration;

– the expiry date;

– any special storage conditions.

Information on batch coding should be provided to the authorities.

6.2 Packaging

The suitability of packaging material for the product and for the labelling procedure to be carried out should be described. It may be necessary to describe special radiation shielding.

6.3 Package leaflets

Package leaflets play a particularly important role for semi-manufactured products such as preparation kits and should include:

- the name of the product and a description of its use;
- a list of the contents of the kit;
- the name and the address of the manufacturer of the kit;
- identification and quality requirements concerning the radiolabelling materials that can be used to prepare the radiopharmaceutical;
- directions for preparing the radiopharmaceutical including range of activity and volume and a statement of the storage requirements for the prepared radiopharmaceutical;
- a statement of the useful life of the prepared radiopharmaceutical;
- indications and contra-indications in respect of the prepared radiopharmaceutical;
- warnings and precautions in respect of the components and the prepared radiopharmaceutical including radiation safety aspects;
- where applicable, the pharmacology and toxicology of the prepared radiopharmaceutical including route of elimination and effective half-life;
- the radiation dose to the patient from the prepared radiopharmaceutical;
- precautions to be taken by the user and the patient during the preparation and administration of the product and special precautions for the disposal of the container and its unused contents;
- a statement of recommended use for the prepared radiopharmaceutical and the recommended dosage;
- a statement of the route of administration of the prepared radiopharmaceutical;
- and, if it is appropriate for particular kits (i.e. those subject to variability beyond the recommended limits) the leaflet should contain the methods and specifications needed to check radiochemical purity.