

RADIOPHARMACEUTICALS BASED ON MONOCLONAL ANTIBODIES

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CONTENTS

1. INTRODUCTION
2. SOURCE MATERIALS
3. PRODUCTION FACILITIES
4. MANUFACTURING PROCEDURE FOR MONOCLONAL ANTIBODIES
5. MANUFACTURE OF MODIFIED AND DERIVATISED MONOCLONAL ANTIBODIES
6. RADIOPHARMACEUTICAL ASPECTS
7. PRE-CLINICAL SAFETY TESTS
8. CLINICAL DOCUMENTATION
9. RADIATION DOSIMETRY
10. LABELLING AND PACKAGING

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1 INTRODUCTION

Monoclonal antibodies may form the basis of radiopharmaceuticals for *in vivo* diagnosis or therapy. The antibody or antibody fragment is thus only one component of the medicinal product and in the evaluation of quality and safety of this group of products, the radiopharmaceutical and radiation protection aspects must be considered in addition to those of the antibody component. The same principle would apply to monoclonal antibodies used in conjunction with other agents e.g. toxins, though such products are not covered in this document. The monoclonal antibodies used as the basis of such products may be of murine origin, prepared in human cell lines or “humanised” using rDNA techniques. As regards monoclonal antibodies and radiopharmaceuticals, different notes for guidance have already been adopted by the CPMP: a note on “Production and quality control of monoclonal antibodies”, and a note on radiopharmaceuticals is published in this volume.

The notes for guidance are intended to be used by manufacturers submitting applications for marketing authorisation. They are *not* intended for non-commercial producers. The notes for guidance are advisory, not mandatory, and (as stated in the notes for guidance on murine monoclonal antibodies) “a flexible approach” should be adopted.

A special consideration with this class of products is that chemical modification of the antibody may be carried out. This may take the form of preparation of sub-fragments of antibody (e.g. Fab or F(ab')₂) and the antibody molecule (or a fragment of it) may also be modified by addition of a conjugating agent for the radionuclide. These modified forms require consideration with respect to quality, in addition to that for the monoclonal antibodies from which they were derived.

Consideration of radiolabelling procedures encompasses the quality control of the manufacturing steps and of the radiopharmaceutical aspects. In addition, the use of radionuclides of short half-life will require specifications or instructions for the antibody derivative/conjugate, the radionuclide (especially where specific purity requirements apply), and the preparation and quality control of the final product intended for administration to the patient, which typically, will be prepared by the user immediately prior to clinical use.

Frequently, the radionuclide and the monoclonal antibody components are marketed by different manufacturers who are responsible independently for the marketing authorisation and control of their product(s). The radionuclide (e.g. ¹¹¹In) may be authorised for use with a number of monoclonal antibodies (or indeed with any antibody). In each specific case the antibody manufacturer is responsible for providing the clinical and pharmaceutical data on the radiolabelled antibody.

2 SOURCE MATERIALS

The development and establishment of cell lines for the production of monoclonal antibodies in this field has often taken place in non-commercial institutions. The initial development may therefore not be as well documented as is generally required in the pharmaceutical

industry. In cases where the history of the myeloma cell line and parental cell line are limited by available data, more emphasis must be put on the characterisation at the seed lot stage and of the final product to ensure quality (e.g. freedom from adventitious agents).

However, every effort should be made to provide evidence of the origin and acceptability of the cell line. Non-commercial organisations collaborating with industry in the production of monoclonal antibodies that will form part of a marketed product should be strongly encouraged to improve their record-keeping so that full information on production of antigen, immunisation, establishment of cell lines, testing of antibodies, etc. can be provided.

3. PRODUCTION FACILITIES

Even though production may be on a smaller scale than is usual in the pharmaceutical industry, the appropriate good manufacturing practice should be followed for both the radionuclide and the antibody components. A strategy for avoiding cross-contamination of cell lines should be developed and specified if more than one antibody is produced within the same facility.

4. MANUFACTURING PROCEDURE FOR MONOCLONAL ANTIBODIES

Although the points to consider in the manufacture of the antibodies are in essence those outlined in the notes for guidance on murine and human monoclonal antibodies, special considerations apply in the case of antibodies intended for use with radiopharmaceuticals:

- for monoclonal antibodies prepared in only small amounts, it may not be essential to have both a master cell bank and a manufacturer's working cell bank;
- where production of only a small number of batches is envisaged, evidence should be provided of consistency of production of at least three production batches;
- where these batches are subdivided for further processing, evidence of consistency of this must be provided.

Purification of the antibody remains crucial and, in particular, virus contamination should be carefully attended to. Steps should be included that will inactivate or remove contaminating viruses that may be present. The purified bulk antibody should be tested for extraneous proteins and DNA. Reference should be made to the note for guidance on *Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses*.

5. MANUFACTURE OF MODIFIED AND DERIVATISED MONOCLONAL ANTIBODIES

Radiopharmaceuticals based on monoclonal antibodies utilise either an unmodified immunoglobulin or, more usually, a chemically modified form. Radiolabelling is either by direct attachment of a radionuclide or attachment via a conjugating agent.

Each relevant step in the production of chemically modified monoclonal antibodies requires validation and quality control covering source materials, limits for impurities arising from the production process, evidence for consistency of the process, etc.

Initial immunological studies may be carried out on the unmodified antibody but for the purposes of market authorisation the determination of definitive immunological properties should be performed at an appropriate stage. For example, characteristics such as class, subclass, and interaction with Fc receptors can best be determined with the monoclonal antibody in the unmodified form. In contrast, for regulatory purposes, any tests of toxicity, biological half-life, immunoreactivity and tissue cross-reactivity should be carried out on a form that is as close as possible to the product to be administered to the patient, e.g. for a chemically modified antibody on the derivatised form rather than the parent antibody. For the radiolabelled form, appropriate studies should be undertaken on the product intended for clinical use using “Cold” non-radioactive labelled material wherever possible. It should be noted that in the case of $^{99}\text{Tc}^{\text{m}}$, there is no equivalent non-radioactive isotope and often a small percentage of the modified antibodies actually carries the label.

In the instances in which the final product is a chemically modified or derivatised monoclonal antibody, criteria and specification limits for purity and potency should be applied to the derivatised form and include a test for immunoreactivity.

Material from an early batch that has been clinically evaluated should be retained as the manufacturer’s reference batch for purity and potency of subsequent batches. A secondary working standard may be established providing that equivalence with the primary reference is demonstrated.

6. RADIOPHARMACEUTICAL ASPECTS

6.1 Radionuclide

The radionuclide to be used for labelling the monoclonal antibody (whether derivatised or not) needs to be an authorised medicinal product indicated for use for that purpose (see Introduction). The radionuclide may be supplied as a component in the kit or separately.

Special purity measurements may apply and the radionuclide should have specifications for:

- a) identity: radionuclide characteristics;
- b) potency: radionuclide concentration.
- c) purity: radionuclide purity, radiochemical purity, specific activity, chemical composition, chemical impurities (e.g. metal ions, reducing substances);
- d) chemical stability, in vitro.

6.2 Radiolabelling method

Data on the radiolabelling method should be supplied by the antibody manufacturer.

- a) Where this is carried out by the manufacturer: The process should be validated. This includes quantitative relationships between the (derivatised) antibody and radionuclide, purification of the labelled product and removal of excess reagents, tests for radiochemical purity, quantity of radioactive material in the container, and stability data.

- b) Where this is carried out by the user: This is likely to be in the form of a radiopharmaceutical kit consisting of a (derivatised) monoclonal antibody, reagents and materials necessary for the radiolabelling procedure including any necessary purification of the product plus a package insert giving clear, precise instructions for the use of the kit, quality control, and potential hazards. Radiolabelling methods and quality requirements for the necessary reagents should form part of the product marketing authorisation application.

The radiolabelling procedure for kit preparations should be validated under relevant circumstances and the detailed specifications for the radiolabelling medium (e.g. $^{99}\text{Tc}^{\text{m}}$ or ^{111}In) should be discussed. Quantitative relationships between the antibody (in particular the immunoreactivity), the conjugating agent and the radionuclide should be presented.

- c) Specifications and quality control

Specifications to be fulfilled should be part of the application and could include the following:

- identity: product including protein, conjugating agent, radionuclide;
- potency: immunoreactivity, radionuclide concentration, protein concentration (specific activity);
- purity: radiochemical purity, aggregation, chemical impurities (conjugating material, reagents used in fragmentation of the antibody, labelling reagents, etc.), sterility, pyrogens;
- stability: in vitro/in vivo.

If it is considered necessary for the user to carry out appropriate quality control tests on the final radiolabelled product, the methods should be fully described and validated.

Samples of reference materials, antigens and special reagents should be made available upon request.

7. PRE-CLINICAL SAFETY TESTS

7.1 General

Due account should be taken of the note for guidance on Pre-clinical Biological Safety Testing on Medicinal Products derived from Biotechnology.

Radiolabelled monoclonal antibodies may be used for diagnosis and therapy. While the diagnostic use may cover many different types of diseases, the therapeutic use is currently limited to treatment of cancer as a means of getting a high radiation dose to the target organ. Testing requirements may therefore be different for the two uses. It is characteristic for the diagnostic use that smaller amounts of antibodies are needed.

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 substance parameters and radiation dosimetry aspects.

The usefulness of established toxicological investigations may be questioned in particular because of immunological incompatibility between the product and the animal species used. The strategy and method chosen should be justified.

The content of material in many final preparations (e.g. kits) may be so small that it may be justified to use a bulk preparation of the formulated product 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.

7.2 Single dose/repeated dose toxicity

These tests should, if possible, be carried out according to the same principles as for other radiopharmaceuticals. Some testing should be carried out, however the relevance of these tests may be discussed. Any conjugating material should be included in this discussion and testing may be necessary.

7.3 Examination of reproductive function; foetal toxicity; mutagenic potential; carcinogenic potential

Due account should be taken of the note for guidance on *Radiopharmaceuticals*.

7.4 Pharmacodynamics

Measurable pharmacodynamic effects are not normally expected to be seen from radiopharmaceuticals for diagnostic or therapeutic purposes. The likelihood of their absence may be deduced from toxicity testing and any observed effects should be reported.

7.5 Pharmacokinetics

Information should be provided as to the distribution and elimination of the radiolabelled substance(s). Where appropriate, information should be provided on absorption and biotransformation. The animal pharmacokinetic studies should always provide the necessary data for estimating tissue and whole body radiation doses which can be extrapolated to man. Studies in immunodeficient animals may be relevant.

8. CLINICAL DOCUMENTATION

8.1 General

There are two quite different types of radiopharmaceuticals; first radiopharmaceuticals which are used to effect a medical diagnosis and which are part of a diagnostic system where other factors such as instrumentation, time schedule etc., also play an important role which should be discussed; second, radiopharmaceuticals which are used for the treatment of diseases. Diagnostic radiopharmaceuticals differ in many ways from therapeutic radiopharmaceuticals and consequently clinical documentation has to be different. The same criteria as for non-radiolabelled therapeutic substances apply to therapeutic radiopharmaceuticals.

8.2 Clinical pharmacology

Whenever possible, initial pharmacodynamic and pharmacokinetic studies of the radiolabelled material 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. Emphasis should be paid to the formation of antibodies against the product (e.g. human anti-mouse antibodies: HAMA).

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. The effect of HAMA should be discussed.

8.3 Clinical trials

The main purpose of the clinical trials is to prove the safety of the new radiopharmaceutical and its value as a diagnostic or therapeutic agent.

Comparison with existing agents or with other relevant medicinal products and procedures should be the method of choice to prove efficacy. Particularly, radiopharmaceuticals for diagnostic use may have to be compared to alternative techniques. Controlled and non controlled studies should be separately summarised.

Diagnostic/therapeutic efficacy:

Where appropriate, each indication should be described separately and be the subject of at least one separate trial including data on specificity and sensitivity.

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.

9. RADIATION DOSIMETRY

Information on pharmacokinetics should be sufficient for radiation dosimetry calculations. Such data should preferably have been obtained in patients as appropriate animal models may not exist. Radiation dose estimates should consider the impact of age and clinical condition, particularly hepatic or renal function impairment.

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 and 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 weighting factors established by the International Commission for 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 to target tissues/organs are used, details should be given with reference to the original reports.

The absorbed dose to the organ receiving the highest exposure and to 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 should 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.

10. LABELLING AND PACKAGING

10.1 Labelling

The label on the container should state:

- the name of the product and the name of any 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 state the time zone used), and the volume of liquid in the container;
- for solid preparations, such as freeze-dried preparations, the total radioactivity at a stated date and, if necessary, hour (and state the time zone used);
- for capsules, the radioactivity of each capsule at a stated date and, if necessary, hour (and state the time zone used), and the number of capsules in the container;
- where relevant, the international symbol for radioactivity.

In addition the label on the container 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.

10.2 Packaging material

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

10.3 Package leaflets

Package leaflets play a particularly important role for semi-manufactured products such as preparation kits for radiolabelled monoclonal antibodies. This is the responsibility of the antibody manufacturer and should at least show:

- the name of the product and a description of its use;
- a list of the contents of the kit;
- the name and 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;
- warnings and precautions in respect of the components and the prepared radiopharmaceutical including radiation safety aspects;
- indications and contraindications in respect of 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;
- precautions to be taken if the patient has received monoclonal antibodies previously, with regard to interference by antibodies and hypersensitivity;
- where applicable, the pharmacology and toxicology of the prepared radiopharmaceutical including the route of elimination and effective half-life;
- the radiation dose to the patient from the prepared radiopharmaceutical;
- a statement of recommended use for the prepared radiopharmaceutical and the recommended dose;
- 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 specification needed to check radiochemical purity.