

II

(Acts whose publication is not obligatory)

COMMISSION

COMMISSION DIRECTIVE

of 19 July 1991

modifying the Annex to Council Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products

(91/507/EEC)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community,

Having regard to Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products⁽¹⁾, as last amended by Directive 89/341/EEC⁽²⁾,

Having regard to Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens⁽³⁾, and in particular Article 5 thereof,

Having regard to Council Directive 89/343/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals⁽⁴⁾, and in particular Article 7 thereof,

Having regard to Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulations or administrative action relating to proprietary medicinal products and laying down special

provisions for medicinal products derived from human blood or human plasma⁽⁵⁾, and in particular Article 6 thereof,

Whereas following the adoption of Directives 89/342/EEC, 89/343/EEC and 89/381/EEC, it is necessary to amend the Annex to Directive 75/318/EEC in order to lay down special requirements for the testing of immunological medicinal products, radiopharmaceuticals and medicinal products derived from human blood or human plasma;

Whereas it is further necessary to adapt to technical progress the existing requirements laid down in the Annex to Directive 75/318/EEC, in particular with regard to the special nature of medicinal products obtained through processes mentioned in list A and in the first indent of list B of the Annex of Council Directive 87/22/EEC⁽⁶⁾;

Whereas the provisions of this Directive are in accordance with the opinion of the Committee on the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Medicinal Products Sector established pursuant to Article 2b of Directive 75/318/EEC,

HAS ADOPTED THIS DIRECTIVE:

Article 1

The text of the Annex to Directive 75/318/EEC is hereby replaced by the text of the Annex to this Directive.

⁽¹⁾ OJ No L 147, 9. 6. 1975, p. 1.

⁽²⁾ OJ No L 142, 25. 5. 1989, p. 11.

⁽³⁾ OJ No L 142, 25. 5. 1989, p. 14.

⁽⁴⁾ OJ No L 142, 25. 5. 1989, p. 16.

⁽⁵⁾ OJ No L 181, 28. 6. 1989, p. 44.

⁽⁶⁾ OJ No L 15, 17. 1. 1987, p. 38.

Article 2

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive, save Part 2, paragraph A, point 3.3 of the Annex, no later than 1 January 1992; they shall bring into force the provisions necessary to comply with Part 2, paragraph A, point 3.3 of the Annex no later than 1 January 1995. They shall forthwith inform the Commission thereof.

2. When the Member States adopt these provisions, the provisions shall contain a reference to this Directive or shall be accompanied by such a reference when they are

published in official form. The arrangements for this reference shall be decided by the Member States.

Article 3

This Directive is addressed to Member States.

Done at Brussels, 19 July 1991.

For the Commission
Martin BANGEMANN
Vice-President

ANNEX

INTRODUCTION

The particulars and documents accompanying an application for marketing authorization pursuant to Article 4 of Council Directive 65/65/EEC ⁽¹⁾ shall be presented in four parts, in accordance with the requirements set out in this Annex and taking account of the guidance published by the Commission in *The rules governing medicinal products in the European Community*, Volume II : *Notice to applicants for marketing authorizations for medicinal products for human use in the Member States of the European Community*.

In assembling the dossier for application for marketing authorization, applicants shall take into account the Community guidelines relating to the quality, safety and efficacy of medicinal products published by the Commission in *The rules governing medicinal products in the European Community*, Volume III and its supplements : *Guidelines on the quality, safety and efficacy of medicinal products for human use*.

All information which is relevant to the evaluation of the medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmacotoxicological or clinical test or trial relating to the medicinal product. Moreover, in order to monitor the benefit/risk assessment after marketing authorization has been granted, any change to the data in the dossier, any new information not in the original application and all pharmacovigilance reports, shall be submitted to the competent authorities.

The general sections of this Annex give the requirements for all categories of medicinal products ; they are supplemented by sections containing additional special requirements for radiopharmaceuticals and for biological medicinal products, such as vaccines, serums, toxins, allergen products, medicinal products derived from human blood or plasma. The additional special requirements for biological medicinal products are also applicable to medicinal products obtained through processes mentioned in List A and the first indent of List B of the Annex to Directive 87/22/EEC.

Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC ⁽²⁾.

⁽¹⁾ OJ No 22, 9. 2. 1965, p. 369/65.

⁽²⁾ OJ No L 358, 18. 12. 1986, p. 1.

PART 1

SUMMARY OF THE DOSSIER

A. Administrative data

The medicinal product which is the subject of the application shall be identified by name and name of the active ingredient(s), together with the pharmaceutical form, the method of administration, the strength and the final presentation, including packaging.

The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture (including the manufacturer of the finished product and the manufacturer(s) of the active ingredient(s)), and where relevant the name and address of the importer.

The applicant shall identify the number of volumes of documentation submitted in support of the application and indicate what samples, if any, are also provided.

Annexed to the administrative data shall be copies of the manufacturing authorization as defined in Article 16 of Council Directive 75/319/EEC⁽¹⁾, together with a list of countries in which authorization has been granted, copies of all the summaries of product characteristics in accordance with Article 4a of Directive 65/65/EEC as approved by Member States and a list of countries in which an application has been submitted.

B. Summary of product characteristics

The applicant shall propose a summary of the product characteristics, in accordance with Article 4a of Directive 65/65/EEC.

In addition the applicant shall provide samples or mock-ups of the packaging, labels and package leaflets for the medicinal product concerned.

C. Expert reports

In accordance with Article 2 of Directive 75/319/EEC, expert reports must be provided on the chemical, pharmaceutical and biological documentation, the pharmacotoxicological documentation and the clinical documentation respectively.

The expert report shall consist of a critical evaluation of the quality of the product and the investigations carried out on animals and human beings and bring out all the data relevant for evaluation. It shall be worded so as to enable the reader to obtain a good understanding of the properties, quality, the proposed specifications and control methods, the safety, the efficacy, the advantages and disadvantages of the product.

All important data shall be summarized in an appendix to the expert report, whenever possible including report formats in tabular or in graphic form. The expert report and the summaries shall contain precise cross references to the information contained in the main documentation.

Each expert report shall be prepared by a suitably qualified and experienced person. It shall be signed and dated by the expert, and attached to the report shall be brief information about the educational background, training and occupational experience of the expert. The professional relationship of the expert to the applicant shall be declared.

⁽¹⁾ OJ No L 147, 9. 6. 1975, p. 13.

PART 2

CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL TESTING OF MEDICINAL PRODUCTS

All the test procedures shall correspond to the state of scientific progress at the time and shall be validated procedures; results of the validation studies shall be provided.

All the test procedure(s) shall be described in sufficiently precise detail so as to be reproducible in control tests, carried out at the request of the competent authority; any special apparatus and equipment which may be used shall be described in adequate detail, possibly accompanied by a diagram. The formulae of the laboratory reagents shall be supplemented, if necessary, by the method of preparation. In the case of test procedures included in the *European Pharmacopoeia* or the pharmacopoeia of a Member State, this description may be replaced by a detailed reference to the pharmacopoeia in question.

A. Qualitative and quantitative particulars of the constituents

The particulars and documents which must accompany applications for marketing authorization, pursuant to point 3 of Article 4 (2) of Directive 65/65/EEC shall be submitted in accordance with the following requirements.

1. *Qualitative particulars*

1.1. 'Qualitative particulars' of all the constituents of the medicinal product shall mean the designation or description of:

- the active ingredient(s),
- the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilizers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,
- the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products — capsules, gelatine capsules, rectal capsules, etc.

These particulars shall be supplemented by any relevant data concerning the container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the product.

1.2. In the context of a radiopharmaceutical kit, which is to be radiolabelled after supply by the manufacturer, the active ingredient is considered to be that part of the formulation which is intended to carry or bind the radionuclide. Details of the source of the radionuclide shall be stated. In addition, any compounds essential for the radiolabelling shall be stated.

In a generator, both mother and daughter radionuclides are to be considered as active ingredients.

2. The 'usual terminology', to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions of point 3 of Article 4 (2) of Directive 65/65/EEC:

- in respect of substances which appear in the *European Pharmacopoeia* or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,
- in respect of other substances, the international non-proprietary name recommended by the World Health Organization, which may be accompanied by another non-proprietary name, or, failing these, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,
- in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC⁽¹⁾ of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorized for use in medicinal products.

⁽¹⁾ OJ No L 11, 14. 1. 1978, p. 18.

3. *Quantitative particulars*

- 3.1. In order to give 'quantitative particulars' of the active ingredients of the medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active ingredient.

Units of biological activity shall be used for substances which cannot be defined chemically. Where an International Unit of biological activity has been defined by the World Health Organization, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances.

Whenever possible, biological activity per units of mass shall be indicated.

This information shall be supplemented :

- in respect of injectable preparations, by the mass or units of biological activity of each active ingredient in the unit container, taking into account the usable volume of the product, after reconstitution, where appropriate,
 - in respect of medicinal products to be administered by drops, by the mass or units of biological activity of each active ingredient contained in the number of drops corresponding to 1 ml or 1 g of the preparation,
 - in respect of syrups, emulsions, granular preparations and other pharmaceutical forms to be administered in measured quantities, by the mass or units of biological activity of each active ingredient per measured quantity.
- 3.2. Active ingredients present in the form of compounds or derivatives shall be described quantitatively by their total mass, and if necessary or relevant, by the mass of the active entity or entities of the molecule.
- 3.3. For medicinal products containing an active ingredient which is the subject of an application for marketing authorization in any Member State for the first time, the quantitative statement of an active ingredient which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorized medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active ingredient.
- 3.4. For allergen products, the quantitative particulars shall be expressed by units of biological activity, except for well defined allergen products for which the concentration may be expressed by mass/unit of volume.
- 3.5. The requirement to express the content of active ingredients in terms of the mass of active entities, as in point 3.3. above, may not apply to radiopharmaceuticals. For radionuclides, radioactivity shall be expressed in becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.

4. *Development pharmaceuticals*

- 4.1. An explanation should be provided with regard to the choice of composition, constituents and container and the intended function of the excipients in the finished product. This explanation shall be supported by scientific data on development pharmaceuticals. The overage, with justification thereof, should be stated.
- 4.2. For radiopharmaceuticals, this should include a consideration of chemical/radiochemical purity and its relationship to biodistribution.

B. *Description of method of preparation*

1. The description of the method of preparation accompanying the application for marketing authorization pursuant to point 4 of Article 4 (2) of Directive 65/65/EEC, shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose it shall include at least :

- mention of the various stages of manufacture, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,
- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,
- the actual manufacturing formula, with the quantitative particulars of all the substances used, the quantities of excipients, however, being given in approximate terms in so far as the pharmaceutical form makes this necessary ; mention shall be made of any substances that may disappear in the course of manufacture ; any overage shall be indicated and justified,

- a statement of the stages of manufacture at which sampling is carried out for in-process control tests, where other data in the documents supporting the application show such tests to be necessary for the quality control of the finished product,
 - experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,
 - for sterile products, details of the sterilization processes and/or aseptic procedures used.
2. For radiopharmaceutical kits, the description of the method of preparation shall also include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product.

For radionuclides, the nuclear reactions involved shall be discussed.

C. Controls of starting materials

1. For the purposes of this paragraph, 'starting materials' shall mean all the constituents of the medicinal product and, if necessary, of its container, as referred to in paragraph A, point 1, above.

In the case of:

- an active ingredient not described in the *European Pharmacopoeia* or in the pharmacopoeia of a Member State, or
- an active ingredient described in the *European Pharmacopoeia* or in the pharmacopoeia of a Member State when prepared by a method liable to leave impurities not mentioned in the pharmacopoeial monograph and for which the monograph is inappropriate to adequately control its quality,

which is manufactured by a person different from the applicant, the latter may arrange for the detailed description of the manufacturing method, quality control during manufacture and process validation to be supplied directly to the competent authorities by the manufacturer of the active ingredient. In this case, the manufacturer shall however provide the applicant with all the data which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities.

The particulars and documents accompanying the application for marketing authorization pursuant to points 7 and 8 of Article 4 (2) of Directive 65/65/EEC shall include the results of the tests, including batch analyses particularly for active ingredients, relating to quality control of all the constituents used. These shall be submitted in accordance with the following provisions.

1.1. *Starting materials listed in pharmacopoeias*

The monographs of the *European Pharmacopoeia* shall be applicable to all substances appearing in it.

In respect of other substances, each Member State may require observance of its own national pharmacopoeia with regard to products manufactured in its territory.

Constituents fulfilling the requirements of the *European Pharmacopoeia* or the pharmacopoeia of one of the Member States shall be deemed to comply sufficiently with point 7 of Article 4 (2) of Directive 65/65/EEC. In this case the description of the analytical methods may be replaced by a detailed reference to the pharmacopoeia in question.

However, where a starting material in the *European Pharmacopoeia* or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described.

Colouring matter shall, in all cases, satisfy the requirements of Directive 78/25/EEC.

The routine tests carried out on each batch of starting materials must be as stated in the application for marketing authorization. If tests other than those mentioned in the pharmacopoeia are used, proof must be supplied that the starting materials meet the quality requirements of that pharmacopoeia.

In cases where a specification contained in a monograph of the *European Pharmacopoeia* or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the person responsible for placing the product on the market.

The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The person responsible for placing the product on the market shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In cases where a starting material is described neither in the *European Pharmacopoeia* nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted; in such cases, the applicant shall submit a copy of the monograph accompanied where necessary by the validation of the test procedures contained in the monograph and by a translation where appropriate.

1.2. *Starting materials not in a pharmacopoeia*

Constituents which are not given in any pharmacopoeia shall be described in the form of a monograph under the following headings:

- (a) The name of the substance, meeting the requirements of paragraph A, point 2, shall be supplemented by any trade or scientific synonyms;
- (b) the definition of the substance, set down in a form similar to that used in the *European Pharmacopoeia*, shall be accompanied by any necessary explanatory evidence, especially concerning the molecular structure where appropriate; it must be accompanied by an appropriate description of the method of synthesis. Where substances can only be described by their method of preparation, the description should be sufficiently detailed to characterize a substance which is constant both in its composition and in its effects;
- (c) methods of identification may be described in the form of complete techniques as used for production of the substance, and in the form of tests which ought to be carried out as a routine matter;
- (d) purity tests shall be described in relation to the sum total of predictable impurities, especially those which may have a harmful effect, and, if necessary, those which, having regard to the combination of substances to which the application refers, might adversely affect the stability of the medicinal product or distort analytical results;
- (e) with regard to complex substances of plant or animal/human origin, a distinction must be made between the case where multiple pharmacological effects render chemical, physical or biological control of the principal constituents necessary, and the case of substances containing one or more groups of principles having similar activity, in respect of which an overall method of assay may be accepted;
- (f) when materials of animal/human origin are used, measures to ensure freedom from potentially pathogenic agents shall be described;
- (g) for radionuclides, the nature of the radionuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be given;
- (h) any special precautions that may be necessary during storage of the starting material and, if necessary, the maximum period of storage before retesting shall be given.

1.3. *Physico-chemical characteristics liable to effect bio-availability*

The following items of information concerning active ingredients, whether or not listed in the pharmacopoeias, shall be provided as part of the general description of the active ingredients if the bio-availability of the medicinal product depends on them:

- crystalline form and solubility coefficients,
- particle size, where appropriate after pulverization,
- state of solvation,
- oil/water coefficient of partition (1).

The first three indents are not applicable to substances used solely in solution.

(1) The competent authorities may also request the pK and pH values if they think this information is essential.

2. For biological medicinal products, such as vaccines, serums, toxins, allergen products and medicinal products derived from human blood or plasma, the requirements of this paragraph shall apply.

For the purposes of this paragraph, starting materials shall mean any substance used in the manufacture of the medicinal product; this includes the constituents of the medicinal product, and, if necessary, of its container, as referred to in paragraph A, point 1 above, as well as source materials such as microorganisms, tissues of either plant or animal origin, cells or fluids (including blood) of human or animal origin, and biotechnological cell constructs. The origin and history of starting materials shall be described and documented.

The description of the starting material shall include the manufacturing strategy, purification/inactivation procedures with their validation and all in-process control procedures designed to ensure the quality, safety and batch to batch consistency of the finished product.

- 2.1. When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for the production and beyond.
- 2.2. Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the source materials from which they are derived shall be tested for adventitious agents.

If the presence of potentially pathogenic adventitious agents is inevitable, the material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

- 2.3. Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks; for serums, defined pools of starting materials shall be used.

For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.

- 2.4. For allergen products, the specifications and control methods for the source materials shall be described. The description shall include particulars concerning collection, pretreatment and storage.
- 2.5. For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the source material shall be described and documented.

Defined pools of source material shall be used.

3. For radiopharmaceuticals, starting materials include irradiation target materials.

D. Control tests carried out at intermediate stages of the manufacturing process

1. The particulars and documents accompanying an application for marketing authorization, pursuant to points 7 and 8 of Article 4 (2) of Directive 65/65/EEC, shall include particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the technical characteristics and the production process.

These tests are essential for checking the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the same requirements as the active ingredients).

The same applies where the quality control of the finished product depends on in-process control tests, particularly if the substance is essentially defined by its method or preparation.

2. For biological medicinal products, such as vaccines, serums, toxins, allergen products and medicinal products derived from human blood or plasma, the procedures and the criteria of acceptability published as recommendations of the WHO (*Requirements for Biological Substances*) shall serve as guidelines for all controls of production stages which are not specified in the *European Pharmacopoeia*, or falling this, in the national pharmacopoeia of a Member State.

For inactivated or detoxified vaccines, effective inactivation or detoxification shall be verified during each production run, unless this control is dependent upon a test for which the availability of susceptible animals is limited. In this case, the test shall be carried out until consistency of production and correlation with appropriate in process controls have been established and thereafter compensated by appropriate in-process controls.

3. For modified or adsorbed allergens, the allergen products shall be qualitatively and quantitatively characterized at an intermediate stage, as late as possible in the manufacturing process.

E. Control tests on the finished product

1. For the control of the finished product, a batch of a finished product comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilization operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

The application for marketing authorization shall list those tests which are carried out routinely on each batch of finished product. The frequency of the tests which are not carried out routinely shall be stated. Release limits shall be indicated.

The particulars and documents accompanying the application for marketing authorization pursuant to points 7 and 8 of Article 4 (2) of Directive 65/65/EEC, shall include particulars relating to control tests on the finished product at release. They shall be submitted in accordance with the following requirements.

The provisions of the monographs for pharmaceutical forms, immunosera, vaccines and radio-pharmaceutical preparations of the *European Pharmacopoeia* or failing that, of a Member State, shall be applicable to all products such as vaccines, serums, toxins, allergen products and medicinal products derived from human blood or plasma which are not specified in the *European Pharmacopoeia* or failing this, in the pharmacopoeia of a Member State, the procedures and the criteria of acceptability published as recommendations in the WHO (*Requirements for Biological Substances*) shall serve as guidelines.

If test procedures and limits other than those mentioned in the monographs of the *European Pharmacopoeia*, or failing this, in the national pharmacopoeia of a Member State, are used, proof shall be supplied that the finished product would, if tested in accordance with those monographs, meet the quality requirements of that pharmacopoeia for the pharmaceutical form concerned.

1.1. *General characteristics of the finished product*

Certain tests of the general characteristics of a product shall always be included among the tests on the finished product. These tests shall, wherever applicable, relate to the control of average masses and maximum deviations, to mechanical, physical or microbiological tests, organoleptic characteristics, physical characteristics such as density, pH, refractive index, etc. For each of these characteristics, standards and tolerance limits shall be specified by the applicant in each particular case.

The conditions of the tests, where appropriate, the equipment/apparatus employed and the standards shall be described in precise details whenever they are not given in the *European Pharmacopoeia* or the pharmacopoeia of the Member States; the same shall apply in cases where the methods prescribed by such pharmacopoeias are not applicable.

Furthermore, solid pharmaceutical forms having to be administered orally shall be subjected to *in vitro* studies on the liberation and dissolution rate of the active ingredient or ingredients; these studies shall also be carried out where administration is by another means if the competent authorities of the Member State concerned consider this necessary.

1.2. *Identification and assay of active ingredient(s)*

Identification and assay of the active ingredient(s) shall be carried out either in a representative sample from the production batch or in a number of dosage-units analysed individually.

Unless there is appropriate justification, the maximum acceptable deviation in the active-ingredient content of the finished product shall not exceed $\pm 5\%$ at the time of manufacture.

On the basis of the stability tests, the manufacturer must propose and justify maximum acceptable tolerance limits in the active-ingredient content of the finished product up to the end of the proposed shelf-life.

In certain exceptional cases of particularly complex mixtures, where assay of active ingredients which are very numerous or present in very low amounts would necessitate an intricate investigation difficult to carry out in respect of each production batch, the assay of one or more active ingredients in the finished product may be omitted, on the express condition that such assays are made at intermediate stages in the production process. This relaxation may not be extended to the characterization of the substances concerned. This simplified technique shall be supplemented by a method of quantitative evaluation, enabling the competent authority to have the conformity of the medicinal product with its specification verified after it has been placed on the market.

An *in vivo* or *in vitro* biological assay shall be obligatory when physico-chemical methods cannot provide adequate information on the quality of the product. Such an assay shall, whenever possible, include reference materials and statistical analysis allowing calculation of confidence limits. Where these tests cannot be carried out on the finished product, they may be performed at an intermediate stage, as late as possible in the manufacturing process.

Where the particulars given in section B show that a significant overage of an active ingredient is employed in the manufacture of the medicinal product, the description of the control tests on the finished product shall include, where appropriate, the chemical and, if necessary, the toxico-pharmacological investigation of the changes that this substance has undergone, and possibly the characterization and/or assay of the degradation products.

1.3. *Identification and assay of excipient constituents*

In so far as is necessary, the excipient(s) shall be subject at least to identification tests.

The test procedure proposed for identifying colouring matters must enable a verification to be made that such matters appear in the list annexed to Directive 78/25/EEC.

An upper and lower limit test shall be obligatory in respect of preserving agents and an upper limit test for any other excipient constituent liable to affect adversely physiological functions; an upper and lower limit test shall be obligatory in respect of the excipient if it is liable to affect the bio-availability of an active substance, unless bio-availability is guaranteed by other appropriate tests.

1.4. *Safety tests*

Apart from the toxico-pharmacological tests submitted with the application for marketing authorization, particulars of safety tests, such as sterility, bacterial endotoxin, pyrogenicity and local tolerance in animals shall be included in the analytical particulars wherever such tests must be undertaken as a matter of routine in order to verify the quality of the product.

2. For all controls of biological medicinal products, such as vaccines, serums, toxins, allergen products and medicinal products derived from human blood or plasma, which are not specified in the European Pharmacopoeia, or failing this, in the national pharmacopoeia of a Member State, the procedures and the criteria of acceptability published as recommendations in the WHO (*Requirements for Biological Substances*) shall serve as guidelines.

3. For radiopharmaceuticals, radionuclidic purity, radiochemical purity and specific activity shall be described. For content of radioactivity, the deviation from that stated on the label should not exceed $\pm 10\%$.

For generators, details on the testing for mother and daughter radionuclides are required. For generator-eluates, tests for mother radionuclides and for other components of the generator system shall be provided.

For kits, the specifications of the finished product shall include tests on performance of products after radiolabelling. Appropriate controls on radiochemical and radionuclidic purity of the radiolabelled compound shall be included. Any material essential for radiolabelling shall be identified and assayed.

F. Stability tests

1. The particulars and documents accompanying the application for marketing authorization pursuant to points 6 and 7 of Article 4 (2) of Directive 65/65/EEC shall be submitted in accordance with the following requirements.

A description shall be given of the investigations by which the shelf life, the recommended storage conditions and the specifications at the end of the shelf-life proposed by the applicant have been determined.

Where a finished product is liable to give rise to degradation products, the applicant must declare these and indicate characterization methods and test procedures.

The conclusions shall contain the results of analyses, justifying the proposed shelf life under the recommended storage conditions and the specifications of the finished product at the end of the shelf-life under these recommended storage conditions.

The maximum acceptable level of degradation products at the end of shelf-life shall be indicated.

A study of the interaction between product and container shall be submitted wherever the risk of such interaction is regarded as possible, especially where injectable preparations or aerosols for internal use are concerned.

2. Where for biological medicinal products, such as vaccines, serums, toxins, allergen products and medicinal products derived from human blood or plasma, stability tests cannot be carried out on the finished products, it is acceptable to carry out stability indicating tests at an intermediate stage of production as late as possible in the manufacturing process. In addition, there should be an evaluation of the stability of the finished product using other secondary tests.
3. For radiopharmaceuticals, information on stability shall be given for generators, kits and radiolabelled products. The stability during use of radiopharmaceuticals in multi-dose vials shall be documented.

PART 3

TOXICOLOGICAL AND PHARMACOLOGICAL TESTS

I. Introduction

1. The particulars and documents accompanying the application for marketing authorization pursuant to point 8 of Article 4, second paragraph, Directive 65/65/EEC shall be given in accordance with the requirements below.

Member States shall ensure that the safety tests are carried out in conformity with the provisions relating to good laboratory practice laid down by Directives 87/18/EEC⁽¹⁾ and 88/320/EEC⁽²⁾.

The toxicological and pharmacological tests must show :

- (a) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings ; these should be evaluated in relation to the pathological condition concerned ;
- (b) the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results.

Additionally, it is necessary for clinicians to be given information about the therapeutic potential of the product.

2. Where a medicinal product is intended for topical use, systemic absorption must be investigated, due account also being taken of the possible use of the product on broken skin and absorption through other relevant surfaces. Only if it is proved that systematic absorption under these conditions is negligible may repeated dose systematic toxicity tests, foetal toxicity tests and studies of reproductive function be omitted.

If, however, systematic absorption is demonstrated during therapeutic experimentation, toxicity tests shall be carried out on animals, including where necessary, foetal toxicity tests.

In all cases, tests of local tolerance after repeated application shall be carried out with particular care and include histological examinations ; the possibility of sensitization shall be investigated and any carcinogenic potential investigated in the cases referred to in paragraph II E of this Part.

3. For biological medicinal products such as vaccines, serums, toxins, allergen products and medicinal products derived from human blood or plasma, the requirements of this Part may have to be adapted for individual products ; therefore the testing programme carried out shall be justified by the applicant.

In establishing the testing programme, the following shall be taken into consideration :

- all tests requiring repeated administration of the product shall be designed to take account of the possible induction of, and interference by, antibodies ;
- examination of reproductive function, of embryo/foetal and perinatal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where components other than the active ingredient(s) are incriminated, validation of their removal may replace the study.

4. For radiopharmaceuticals, it is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radiopharmaceuticals ; in therapy, it is the wanted property. The evaluation of safety and efficacy of radiopharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognized system by a particular route of administration.
5. The toxicology and pharmacokinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.

⁽¹⁾ OJ No L 15, 17. 1. 87, p. 29.

⁽²⁾ OJ No L 145, 11. 6. 88, p. 35.

6. Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

II. Performance of tests

A. Toxicity

1. Single dose toxicity

An acute test is a qualitative and quantitative study of the toxic reactions which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.

The acute toxicity test must be carried out in two or more mammalian species of known strain unless a single species can be justified. At least two different routes of administration shall normally be used, one being identical with or similar to that proposed for use in human beings and the other ensuring systemic exposure to the substance.

This study will cover the signs observed, including local reactions. The period during which the test animals are observed shall be fixed by the investigator as being adequate to reveal tissue or organ damage or recovery, usually for a period of 14 days but not less than seven days, but without exposing the animals to prolonged suffering. Animals dying during the observation period should be subject to autopsy as also should all animals surviving to the end of the observation period. Histopathological examinations should be considered on any organ showing macroscopic changes at autopsy. The maximum amount of information should be obtained from the animals used in the study.

The single dose toxicity tests should be conducted in such a way that signs of acute toxicity are revealed and the mode of death assessed as far as reasonably possible. In suitable species a quantitative evaluation of the approximate lethal dose and information on the dose effect relationship should be obtained, but a high level of precision is not required.

These studies may give some indication of the likely effects of acute overdosage in man and may be useful for the design of toxicity studies requiring repeated dosing on the suitable animal species.

In the case of active substances in combination, the study must be carried out in such a way as to check whether or not there is enhancement of toxicity or if novel toxic effects occur.

2. Repeated dose toxicity (sub-acute or chronic toxicity)

Repeated dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

Generally, it is desirable that two tests be performed: one short-term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose shall be to determine by experiment the non-toxic dose range of the product and normally it shall last three to six months.

In respect of medicinal products to be administered once only to humans, a single test lasting two to four weeks shall be performed.

If, however, having regard to the proposed duration of use in human beings, the investigator sees fit to carry out experiments of greater or lesser duration than indicated above, he must give adequate reasons for doing so.

Reasons should also be given for the dosages chosen.

Repeated dose toxicity tests shall be carried out on two species of mammals one of which must be a non-rodent. The choice of route(s) of administration employed shall depend on the intended therapeutic use and the possibilities of systemic absorption. The method and frequency of dosage shall be clearly stated.

The maximum dose should be chosen so as to bring harmful effects to light. The lower doses will then enable the animal's tolerance of the product to be determined.

Wherever possible, and always in experiments on small rodents, the design of the experiment and the control procedures must be suited to the scale of the problem being tackled and enable fiducial limits to be determined.

The evaluation of the toxic effects shall be based on observation of behaviour, growth, haematological and biochemical tests, especially those relating to the excretory mechanism, and also on autopsy reports and accompanying histological data. The choice and range of each group of tests will depend on the species of animal used and the state of scientific knowledge at the time.

In the case of new combinations of known substances that have been investigated in accordance with the provisions of this Directive, the long-term tests may, except where acute and sub-acute toxicity tests have demonstrated potentiation or novel toxic effects, be suitable modified by the investigator who shall submit his reasons for such modification.

B. *Examination of reproductive function*

If the results of other tests reveal anything suggesting harmful effects on progeny or impairment of male or female reproductive function, this shall be investigated by appropriate tests.

C. *Embryo/foetal and perinatal toxicity*

This investigation comprises a demonstration of the toxic and especially the teratogenic effects observed in the issue of conception when the substance under investigation has been administered to the female during pregnancy.

Although up to the present these tests have had only a limited predictive value in regard to the application of the results to human beings, they are thought to provide important information where the results show effects such as resorptions and other anomalies.

Omission of these tests, either because the medicinal product will not normally be used by women capable of child-bearing or for other reasons, must be adequately justified.

Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which should be other than a rodent. Peri- and postnatal studies shall be conducted in at least one species. Where metabolism of a medicinal product in a particular species is known to be similar to that in man, it is desirable to include this species. Also, it is desirable that one of the species is the same as in the repeated dose toxicity studies.

The details of the test (number of animals, amounts administered, timing of administration and criteria for evaluation of results) shall depend on the state of scientific knowledge at the time when the application is lodged, and the level of statistical significance that the results must attain.

D. *Mutagenic potential*

The purpose of the study of mutagenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells and which have the effect of making successors permanently and hereditarily different from their predecessors. This study is obligatory for any new substance.

The number and types of results and the criteria for their evaluation shall depend on the state of scientific knowledge at the time when the application is lodged.

E. *Carcinogenic potential*

Tests to reveal carcinogenic effects shall normally be required:

- (a) in respect of substances having a close chemical analogy with known carcinogenic or cocarcinogenic compounds;
- (b) in respect of substances which have given rise to suspicious changes during the long-term toxicological tests;
- (c) in respect of substances which have given rise to suspicious results in the mutagenic-potential tests or in other short-term carcinogenicity tests.

Such tests may also be required in respect of substances to be included in medicinal products likely to be administered regularly over a prolonged period of a patient's life.

The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the details of the tests.

F. *Pharmacodynamics*

This heading covers the variations caused by the substance in the functions of the physiological systems, whether these functions are normal or experimentally modified.

This study shall follow two distinct lines of approach.

Firstly, the actions on which the recommended application in therapeutic practice is based shall be adequately described. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves etc., and wherever possible, compared with data relating to a substance whose activity is known. Where a higher therapeutic potency is being claimed for a substance, the difference shall be demonstrated and shown to be statistically significant.

Secondly, the investigator shall provide a general pharmacological characterization of the substance, with special reference to collateral effects. In general, the main functions of the physiological systems should be investigated. The depth of this investigation must be increased as the doses liable to produce side-effects approach those producing the main effect for which the substance is being proposed.

The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. The experimental results shall be set out clearly and, when relevant to the test, their statistical significance quoted.

Unless good reasons are given to the contrary, any quantitative modification of responses resulting from repeated administration of the substance shall be investigated.

Tests on combinations of active substances may be prompted either by pharmacological premisses or by indications of therapeutic effect.

In the first case, the pharmacodynamic study shall demonstrate those interactions which might make the combination of value in therapeutic use.

In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

If a combination includes a novel active substance, the latter must previously have been studied in depth.

G. *Pharmacokinetics*

Pharmacokinetics means the study of the fate of the active substance within the organism, and covers the study of the absorption, distribution, biotransformation and excretion of the substance.

The study of these different phases may be carried out both by means of physical, chemical or biological methods, and by observation of the actual pharmacodynamic activity of the substance itself.

Information on distribution and elimination (i.e. biotransformation and excretion) shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemotherapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmacodynamic effects (e.g. numerous diagnostic agents, etc.).

Pharmacokinetic investigation of pharmacologically active substances is necessary.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive pharmacokinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

H. *Local tolerance*

The purpose of local tolerance studies is to ascertain whether medicinal products (both active ingredients and excipients) are tolerated at sites in the body which may come into contact with the products as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the product can be distinguished from toxicological or pharmacodynamic ones.

PART 4

CLINICAL DOCUMENTATION

The particulars and documents accompanying applications for marketing authorizations pursuant to point 8 of Article 4 (2) of Directive 65/65/EEC shall be submitted in accordance with the provisions below.

A clinical trial is any systematic study of medicinal products in human subjects whether in patients or non-patient volunteers in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or study their absorption, distribution, metabolism and excretion in order to ascertain the efficacy and safety of the products.

Evaluation of the application for marketing authorization shall be based on clinical trials including clinical pharmacological trials designed to determine the efficacy and safety of the product under normal conditions of use, having regard to the therapeutic indications for use in human beings. Therapeutic advantages must outweigh potential risks.

A. General requirements

The clinical particulars to be provided pursuant to point 8 of Article 4 (2) of Directive 65/65/EEC must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorization. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.

Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Part 3 of this Annex. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmacokinetic and pharmacodynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.

B. Conduct of trials**1. *Good clinical practice***

- 1.1. All phases of clinical investigation, including bioavailability and bioequivalence studies, shall be designed, implemented and reported in accordance with good clinical practice.
- 1.2. All clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinki. In principle, the freely given informed consent of each trial subject shall be obtained and documented.

The trial protocol, procedures (including statistical design) and documentation shall be submitted by the sponsor and/or investigator for an opinion to the relevant ethics committee. The trials shall not begin before the opinion of this committee has been received in writing.

- 1.3. Pre-established, systematic written procedures for the organization, conduct, data collection, documentation and verification of clinical trials shall be required.
- 1.4. In the case of radiopharmaceuticals, clinical trials shall be carried out under the responsibility of a medical doctor authorized to use radionuclides for medical purposes.

2. *Archiving*

The person responsible for placing the medicinal product on the market shall make arrangements for archiving of documentation.

- (a) The investigator shall arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

- (b) Patient files and other source data shall be kept for the maximum period of time permitted by the hospital, institution or private practice.
- (c) The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorized. These procedures shall include :
 - the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used,
 - standard operating procedures,
 - all written opinions on the protocol and procedures,
 - the investigator's brochure,
 - case report forms on each trial subject,
 - final report,
 - audit certificate(s), if available.
- (d) The final report shall be retained by the sponsor or subsequent owner, for five years after the product is no longer authorized.

Any change of ownership of the data shall be documented. All data and documents shall be made available if requested by relevant authorities.

C. Presentation of results

1. The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made :
 - the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product used,
 - audit certificate(s), if available,
 - the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the information in respect of each patient individually, including case report forms on each trial subject,
 - final report signed by the investigator and for multicentre trials, by all the investigators or the coordinating (principal) investigator.
2. The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete documentation shall be provided forthwith upon request.
3. The clinical observations shall be summarized for each trial indicating :
 - (a) the number and sex of patients treated ;
 - (b) the selection and age-distribution of the groups of patients being investigated and the control groups ;
 - (c) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal ;
 - (d) where controlled trials were carried out under the above conditions, whether the control group :
 - received no treatment,
 - received a placebo,
 - received another medicinal product of known effect,
 - received treatment other than therapy using medicinal products ;
 - (e) the frequency of observed side-effects ;
 - (f) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration ;
 - (g) parameters or evaluation criteria of efficacy and the results in terms of these parameters ;
 - (h) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.

4. The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its compatibility, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of overdosage. In reporting the results of a multi-centre study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational product on behalf of all centres.
5. In addition, the investigator shall always indicate his observations on:
 - (a) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;
 - (b) any interactions that have been observed with other medicinal products administered concomitantly;
 - (c) the criteria determining exclusion of certain patients from the trials;
 - (d) any deaths which occurred during the trial or within the follow-up period.
6. Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.
7. Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further preclinical toxicological and pharmacological tests must be undertaken and reviewed.

If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.

D. Clinical pharmacology

1. *Pharmacodynamics*

The pharmacodynamic action correlated to the efficacy shall be demonstrated including:

- the dose-response relationship and its time course,
- justification for the dosage and conditions of administration,
- the mode of action, if possible.

The pharmacodynamic action not related to efficacy shall be described.

The demonstration of pharmacodynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.

2. *Pharmacokinetics*

The following pharmacokinetic characteristics shall be described:

- absorption (rate and extent),
- distribution,
- metabolism,
- excretion.

Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the preclinical studies, shall be described.

3. *Interactions*

If the product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

If pharmacodynamic/pharmacokinetic interactions exist between the substance and other medical products or substances like alcohol, caffeine, tobacco or nicotine, likely to be taken simultaneously, or if such interactions are likely, they should be described and discussed; particularly from the point of view of clinical relevance and the relationship to the statement concerning interactions in the summary of product characteristics presented in accordance with Article 4a, point 5.6 of Directive 65/65/EEC.

E. Bioavailability/bioequivalence

The assessment of bioavailability must be undertaken in all cases where it is necessary, e.g. where the therapeutic dose is near the toxic dose or where the previous tests have revealed anomalies which may be related to pharmacokinetic properties, such as variable absorption.

In addition, an assessment of bioavailability shall be undertaken where necessary to demonstrate bioequivalence for the medicinal products referred to in Article 4 (2) point 8 (i) (ii) and (iii) of Directive 65/65/EEC.

F. Clinical efficacy and safety

1. In general, clinical trials shall be done as 'controlled clinical trials' and if possible, randomized; any other design shall be justified. The control treatment of the trials will vary from case to case and also will depend on ethical considerations; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomization and blinding.

2. The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomization, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.
3. Clinical statements concerning the efficacy or safety of a medicinal product under normal conditions of use which are not scientifically substantiated cannot be accepted as valid evidence.
4. The value of data on the efficacy and safety of a medicinal product under normal conditions of use will be very greatly enhanced if such data come from several competent investigators working independently.
5. For vaccines and serums, the immunological status and age of the trial population and the local epidemiology are of critical importance and shall be monitored during the trial and fully described.

For live attenuated vaccines, clinical trials shall be so designed as to reveal potential transmission of the immunizing agent from vaccinated to non-vaccinated subjects. If transmission is possible, the genotypic and phenotypic stability of the immunizing agent shall be studied.

For vaccines and allergen products, follow-up studies shall include appropriate immunological tests, and where applicable, antibody assays.

6. The pertinence of the different trials to the assessment of safety and the validity of methods of evaluation shall be discussed in the expert report.
7. All adverse events including abnormal laboratory values shall be presented individually and discussed, especially:
 - in terms of overall adverse experience and
 - as a function of the nature, seriousness and causality of effects.
8. A critical assessment of relative safety, taking into account adverse reactions, shall be made in relation to:
 - the disease to be treated,
 - other therapeutic approaches,
 - particular characteristics in sub-groups of patients,
 - preclinical data on toxicology and pharmacology.
9. Recommendations shall be made for the conditions of use, with the intention of reducing the incidence of adverse reactions.

G. Documentation for applications in exceptional circumstances

When, in respect of particular therapeutic indications, the applicant can show that he is unable to provide comprehensive data on the quality, efficacy and safety under normal conditions of use, because:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or

- in the present state of scientific knowledge comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical ethics to collect such information,

marketing authorization may be granted on the following conditions :

- (a) the applicant completed an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,
- (b) the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and for a radiopharmaceutical, by an authorized person,
- (c) the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

H. Post-marketing experience

1. If the medicinal product is already authorized in other countries, information shall be given in respect of adverse drug reactions of the medicinal product concerned and medicinal products containing the same active ingredient(s), in relation to the usage rates if possible. Information from worldwide studies relevant to the safety of the medicinal product shall be included.

For this purpose, an adverse drug reaction is a reaction which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.

2. In the case of vaccines already authorized in other countries, information on the monitoring of vaccinated subjects to evaluate the prevalence of the disease in question as compared to non-vaccinated subjects shall be submitted, when available.
 3. For allergen products, response in periods of increased antigen exposure shall be identified.
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