

[^{F1}ANNEX I

ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

Textual Amendments

- F1** Substituted by [Commission directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use \(Text with EEA relevance\)](#).

PART I

STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS

1. MODULE 1: ADMINISTRATIVE INFORMATION

1.1. Table of contents

A comprehensive table of contents of Modules 1 to 5 of the dossier submitted for marketing authorisation application shall be presented.

1.2. Application form

The medicinal product, which is the subject of the application, shall be identified by name and name of the active substance(s), together with the pharmaceutical form, the route 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 substance(s)), and where relevant the name and address of the importer.

The applicant shall identify the type of application and indicate what samples, if any, are also provided.

Annexed to the administrative data shall be copies of the manufacturing authorisation as defined in Article 40, together with a list of countries in which authorisation has been granted, copies of all the summaries of product characteristics in accordance with Article 11 as approved by Member States and a list of countries in which an application has been submitted.

As outlined in the application form, the applicants shall provide, inter alia, details of the medicinal product subject of the application, the legal basis of the application, the proposed marketing authorisation holder and manufacture(s), information on orphan medicinal product status, scientific advice and paediatric development program.

1.3. Summary of product characteristics, labelling and package leaflet

1.3.1. Summary of product characteristics

The applicant shall propose a summary of the product characteristics, in accordance with Article 11.

1.3.2. Labelling and package leaflet

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A proposed labelling text for immediate and outer packaging as well as for the package leaflet shall be provided. These shall be in accordance with all mandatory items listed in Title V on the labelling of medicinal products for human use (Article 63) and on package leaflet (Article 59).

1.3.3. Mock-ups and specimens

The applicant shall provide specimen and/or mock-ups of the immediate and outer packaging, labels and package leaflets for the medicinal product concerned.

1.3.4. Summaries of product characteristics already approved in the Member States

Annexed to the administrative data of the application form shall be copies of all the summaries of product characteristics in accordance with Articles 11 and 21 as approved by Member States, where applicable and a list of countries in which an application has been submitted.

1.4. Information about the experts

In accordance with Article 12 (2) experts must provide detailed reports of their observations on the documents and particulars which constitute the marketing authorisation dossier and in particular on Modules 3, 4 and 5 (chemical, pharmaceutical and biological documentation, non-clinical documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product and of the investigations carried out on animals and human beings and bring out all the data relevant for evaluation.

These requirements shall be met by providing a quality overall summary, a non-clinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorisation application dossier. A declaration signed by the experts together with brief information on their educational background, training and occupational experience shall be presented in Module 1. The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.

1.5. Specific requirements for different types of applications

Specific requirements for different types of applications are addressed in Part II of the present Annex.

1.6. Environmental risk assessment

Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the environment due to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products containing or consisting of GMOs (Genetically Modified Organisms) within the meaning of Article 2 of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of modified organisms and repealing Council Directive 90/220/EEC⁽¹⁾ shall be addressed.

Information pertaining to the environmental risk shall appear as an appendix to Module 1.

The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive.

The information shall consist of:

- an introduction;

- a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;
- the information requested in Annexes II to IV of the Directive 2001/18/EC, including detection and identification methods as well as unique code of the GMO, plus any additional information on the GMO or the product of relevance to evaluating the environmental risk;
- an environment risk assessment (ERA) report prepared on basis of the information specified in Annexes III and IV of Directive 2001/18/EC and in accordance with Annex II of Directive 2001/18/EC;
- taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet;
- appropriate measures in order to inform the public.

A dated signature of the author, information on the author's educational, training and occupational experience, and a statement of the author's relationship with the applicant, shall be included.

2. MODULE 2: SUMMARIES

This Module aims to summarise the chemical, pharmaceutical and biological data, the non-clinical data and the clinical data presented in Modules 3, 4 and 5 of the dossier for marketing authorisation, and to provide the reports/overviews described in Article 12 of this Directive.

Critical points shall be addressed and analysed. Factual summaries including tabular formats shall be provided. Those reports shall provide cross-references to tabular formats or to the information contained in the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 (non-clinical documentation) and Module 5 (clinical documentation).

Information contained in Module 2 shall be presented in accordance with the format, content and numbering system delineated in the Volume 2 of the Notice to Applicants. The overviews and summaries shall comply with the basic principles and requirements as laid down herewith:

2.1. Overall table of contents

Module 2 shall contain a table of contents for the scientific documentation submitted in Modules 2 to 5.

2.2. Introduction

Information on the pharmacological class, mode of action and proposed clinical use of the medicinal product for which a marketing authorisation is requested shall be supplied.

2.3. Quality overall summary

A review of the information related to the chemical, pharmaceutical and biological data shall be provided in a quality overall summary.

Key critical parameters and issues related to quality aspects shall be emphasised as well as justification in cases where the relevant guidelines are not followed. This document shall follow the scope and outline of the corresponding detailed data presented in Module 3.

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2.4. Non-clinical overview

An integrated and critical assessment of the non-clinical evaluation of the medicinal product in animals/in vitro shall be required. Discussion and justification of the testing strategy and of deviation from the relevant guidelines shall be included.

Except for biological medicinal products, an assessment of the impurities and degradation products shall be included along with their potential pharmacological and toxicological effects. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the non-clinical studies and the product to be marketed shall be discussed.

For biological medicinal products, comparability of material used in non-clinical studies, clinical studies, and the medicinal product for marketing shall be assessed.

Any novel excipient shall be the subject of a specific safety assessment.

The characteristics of the medicinal product, as demonstrated by the non-clinical studies shall be defined and the implications of the findings for the safety of the medicinal product for the intended clinical use in human shall be discussed.

2.5. Clinical overview

The clinical overview is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5. The approach to the clinical development of the medicinal product, including critical study design, decisions related to and performance of the studies shall be provided.

A brief overview of the clinical findings, including important limitations as well as an evaluation of benefits and risks based on the conclusions of the clinical studies shall be provided. An interpretation of the way the efficacy and safety findings support the proposed dose and target indications and an evaluation of how the summary of product characteristics and other approaches will optimise the benefits and manage the risks is required.

Efficacy or safety issues encountered in development and unresolved issues shall be explained.

2.6. Non-clinical summary

The results of pharmacology, pharmaco-kinetics and toxicology studies carried out in animals/in vitro shall be provided as factual written and tabulated summaries which shall be presented in the following order:

- Introduction
- Pharmacology Written Summary
- Pharmacology Tabulated Summary
- Pharmaco-kinetics Written Summary
- Pharmaco-kinetics Tabulated Summary
- Toxicology Written Summary
- Toxicology Tabulated Summary.

2.7. Clinical Summary

A detailed, factual summary of the clinical information on the medicinal product included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutics studies, of clinical pharmacology studies, and of clinical efficacy and safety studies. A synopsis of the individual studies is required.

Summarised clinical information shall be presented in the following order:

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- Summary of Bio-pharmaceutics and Associated Analytical Methods
 - Summary of Clinical Pharmacology Studies
 - Summary of Clinical Efficacy
 - Summary of Clinical Safety
 - Synopses of Individual Studies
3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES

3.1. Format and presentation

The general outline of Module 3 is as follows:

- Table of contents
- Body of data
 - *Active substance*
 - General Information*
 - Nomenclature
 - Structure
 - General Properties
 - Manufacture*
 - Manufacturer(s)
 - Description of Manufacturing Process and Process Controls
 - Control of Materials
 - Controls of Critical Steps and Intermediates
 - Process Validation and/or Evaluation
 - Manufacturing Process Development
 - Characterisation*
 - Elucidation of Structure and other Characteristics
 - Impurities
 - Control of Active Substance*
 - Specification
 - Analytical Procedures
 - Validation of Analytical Procedures
 - Batch Analyses
 - Justification of Specification
 - Reference Standards or Materials*
 - Container Closure System*
 - Stability*
 - Stability Summary and Conclusions
 - Post-approval Stability Protocol and Stability Commitment
 - Stability Data
 - *Finished Medicinal Product*
 - Description and Composition of the Medicinal Product*
 - Pharmaceutical Development*
 - Components of the Medicinal Product

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- Active Substance
- Excipients
- Medicinal Product
 - Formulation Development
 - Overages
 - Physicochemical and Biological Properties
- Manufacturing Process Development
- Container Closure System
- Microbiological Attributes
- Compatibility
- Manufacture*
 - Manufacturer(s)
 - Batch Formula
 - Description of Manufacturing Process and Process Controls
 - Controls of Critical Steps and Intermediates
 - Process Validation and/or Evaluation
- Control of Excipients*
 - Specifications
 - Analytical Procedures
 - Validation of Analytical Procedures
 - Justification of Specifications
 - Excipients of Human or Animal Origin
 - Novel Excipients
- Control of Finished Medicinal Product*
 - Specification(s)
 - Analytical Procedures
 - Validation of Analytical Procedures
 - Batch Analyses
 - Characterisation of Impurities
 - Justification of Specification(s)
- Reference Standards or Materials*
- Container Closure System*
- Stability*
 - Stability Summary and Conclusion
 - Post-approval Stability Protocol and Stability Commitment
 - Stability Data
- *Appendices*
 - Facilities and Equipment (Biological Medicinal Products only)
 - Adventitious Agents Safety Evaluation
 - Excipients
- *European Community Additional Information*
 - Process Validation Scheme for the Medicinal Product
 - Medical Device

- Certificate(s) of Suitability
- Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (TSE procedure)
- Literature References

3.2. Content: basic principles and requirements

- (1) The chemical, pharmaceutical and biological data that shall be provided shall include for the active substance(s) and for the finished medicinal product all of relevant information on: the development, the manufacturing process, the characterisation and properties, the quality control operations and requirements, the stability as well as a description of the composition and presentation of the finished medicinal product.
- (2) Two main sets of information shall be provided, dealing with the active substance(s) and with the finished medicinal product, respectively.
- (3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.
- (4) All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests, carried out at the request of the competent authority. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the European Pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).
- (5) The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.

However, where a 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. 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 marketing authorisation holder. The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In the case of analytical procedures included in the European Pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapter(s).

- (6) In case where starting and raw materials, active substance(s) or excipient(s) are 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 by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.

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- (7) Where the active substance and/or a raw and starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European Directorate for the Quality of Medicines, shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines.
- (8) For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the
- (i) detailed description of the manufacturing process,
 - (ii) quality control during manufacture, and
 - (iii) process validation
- to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File.
- In this case, the manufacturer shall, however, provide the applicant with all of 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; these documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.
- (9) Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union. Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by the European Directorate for the Quality of Medicines or by the supply of scientific data to substantiate this compliance.
- (10) For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines as well as in relevant general monograph and general chapter of the European Pharmacopoeia, shall be provided.
- (11) Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product, shall be described in adequate details.
- (12) Where applicable and if needed, a CE marking which is required by Community legislation on medical devices shall be provided.

Special attention shall be paid to the following selected elements.

3.2.1. Active substance(s)

3.2.1.1. General information and information related to the starting and raw materials

- a) Information on the nomenclature of the active substance shall be provided, including recommended International Non-proprietary Name (INN), European Pharmacopoeia name if relevant, chemical name(s).

The structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass shall be provided. For biotechnological medicinal products if appropriate, the schematic amino acid sequence and relative molecular mass shall be provided.

A list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.

- b) For the purposes of this Annex, starting materials shall mean all the materials from which the active substance is manufactured or extracted.

For biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).

A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93; advanced therapy medicinal products as defined in Part IV of this Annex.

Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials.

3.2.1.2. Manufacturing process of the active substance(s)

- a) The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. To adequately describe the manufacturing process and process controls, appropriate information as laid down in guidelines published by the Agency shall be provided.

- b) All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Raw materials shall be listed and their quality and controls shall also be documented.

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

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- c) For biological medicinal products, the following additional requirements shall apply.

The origin and history of starting materials shall be described and documented.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate that the active substance complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.

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.

Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents.

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

Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. 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.

For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the starting material shall be described and documented in accordance with provisions laid down in Part III of this Annex.

The manufacturing facilities and equipment shall be described.

- d) Tests and acceptance criteria carried out at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies shall be provided as appropriate.
- e) If the presence of potentially pathogenic adventitious agents is inevitable, the correspondent material shall be used only when further processing ensures their elimination and/or inactivation and this shall be validated in the section dealing with viral safety evaluation.
- f) A description and discussion of the significant changes made to the manufacturing process during development and/or manufacturing site of the active substance shall be provided.

3.2.1.3. Characterisation of the active substance(s)

Data highlighting the structure and other characteristics of the active substance(s) shall be provided.

Confirmation of the structure of the active substance(s) based on any physico-chemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.

3.2.1.4. Control of active substance(s)

Detailed information on the specifications used for routine control of active substance(s), justification for the choice of these specifications, methods of analysis and their validation shall be provided.

The results of control carried out on individual batches manufactured during development shall be presented.

3.2.1.5. Reference standards or materials

Reference preparations and standards shall be identified and described in detail. Where relevant, chemical and biological reference material of the European Pharmacopoeia shall be used.

3.2.1.6. Container and closure system of the active substance

A description of the container and the closure system(s) and their specifications shall be provided.

3.2.1.7. Stability of the active substance (s)

- a) The types of studies conducted, protocols used, and the results of the studies shall be summarised
- b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format
- c) The post authorisation stability protocol and stability commitment shall be provided

3.2.2. Finished medicinal product

3.2.2.1. Description and composition of the finished medicinal product

A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished medicinal product, their amount on a per-unit basis, the function of the constituents of:

- the active substance(s),
- the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, 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 (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.),
- these particulars shall be supplemented by any relevant data concerning the type of 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 medicinal product.

The ‘usual terminology’, to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions in Article 8 (3) (c):

- 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,

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- in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation, or, failing this, 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 of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorised for use in medicinal products⁽²⁾ and/or European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs⁽³⁾.

In order to give the 'quantitative composition' of the active substance(s) of the finished 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 substance.

Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule.

For medicinal products containing an active substance, which is the subject of an application for marketing authorisation in any Member State for the first time, the quantitative statement of an active substance, 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 authorised medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.

Units of biological activity shall be used for substances, which cannot be defined molecularly. Where an International Unit of biological activity has been defined by the World Health Organisation, 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 by using where applicable the European Pharmacopoeia Units.

3.2.2.2. Pharmaceutical development

This chapter shall be devoted to information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier.

The studies described in this chapter are distinct from routine control tests conducted according to specifications. Critical parameters of the formulation and process attributes that can influence batch reproducibility, medicinal product performance and medicinal product quality shall be identified and described. Additional supportive data, where appropriate, shall be referenced to the relevant chapters of Module 4 (Non Clinical Study Reports) and Module 5 (Clinical Study Reports) of the marketing authorisation application dossier.

- a) The compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished product or the compatibility of different active substances with each other in the case of combination products, shall be documented.
- b) The choice of excipients, in particular relative to their respective functions and concentration shall be documented.

- c) A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.
- d) Any overages in the formulation(s) shall be warranted.
- e) As far as the physiochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.
- f) The selection and optimisation of the manufacturing process as well as differences between the manufacturing process(es) used to produce pivotal clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided.
- g) The suitability of the container and closure system used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product and container may need to be considered.
- h) The microbiological attributes of the dosage form in relation with non-sterile and sterile products shall be in accordance with and documented as prescribed in the European Pharmacopoeia.
- i) In order to provide appropriate and supportive information for the labelling the compatibility of the finished product with reconstitution diluent(s) or dosage devices shall be documented.

3.2.2.3. Manufacturing process of the finished medicinal product

- a) The description of the manufacturing method accompanying the application for Marketing Authorisation pursuant to Article 8 (3) (d), 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 including process controls and corresponding acceptance criteria, 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,
- 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 medicinal products, details of the sterilisation processes and/or aseptic procedures used,
- a detailed batch formula.

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

- b) 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 production process shall be included.

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 active substances

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(or of all the excipient constituents subject to the same requirements as the active substances).

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

- c) Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.

3.2.2.4. Control of excipients

- a) All the materials needed in order to manufacture the excipient(s) shall be listed identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Colouring matter shall, in all cases, satisfy the requirements of Directives 78/25/EEC and/or 94/36/EC. In addition, colouring matter shall meet purity criteria as laid down in Directive 95/45/EC, as amended.

- b) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and duly validated.
- c) Specific attention shall be paid to excipients of human or animal origin.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.

Demonstration of compliance with the aforementioned Note for Guidance can be done by submitting either preferably a certificate of suitability to the relevant monograph on Transmissible Spongiform Encephalopathies of the European Pharmacopoeia, or by the supply of scientific data to substantiate this compliance.

- d) Novel excipients:

For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data, both non-clinical and clinical, shall be provided according to the active substance format previously described.

A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the chapter devoted to Active Substance(s) of Module 3.

Information on novel excipient(s) may be presented as a stand-alone document following the format described in the former paragraphs. Where the applicant differs from the novel excipient manufacturer the said stand-alone document shall be made available to the applicant for submission to the competent authority.

Additional information on toxicity studies with the novel excipient shall be provided in Module 4 of the dossier.

Clinical studies shall be provided in Module 5.

3.2.2.5. Control of the finished medicinal product

For the control of the finished medicinal product, a batch of a medicinal product is an entity which 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 sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

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

Detailed information on the specifications, (release and shelf life) justification for their choice, methods of analysis and their validation shall be provided.

3.2.2.6. Reference standards or materials

Reference preparations and standards used for testing of the finished medicinal product shall be identified and described in detail, if not previously provided in the section related to the active substance.

3.2.2.7. Container and closure of the finished medicinal product

A description of the container and the closure system(s) including the identity of each immediate packaging material and their specifications shall be provided. The specifications shall include description and identification. Non-pharmacopoeial methods (with validation) shall be included where appropriate.

For non-functional outer packaging materials only a brief description shall be provided. For functional outer packaging materials additional information shall be provided.

3.2.2.8. Stability of the finished medicinal product

- a) The types of studies conducted, protocols used, and the results of the studies shall be summarised;
- b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format; in case of vaccines, information on cumulative stability shall be provided where appropriate;
- c) The post authorisation stability protocol and stability commitment shall be provided.

4. MODULE 4: NON-CLINICAL REPORTS

4.1. Format and Presentation

The general outline of Module 4 is as follows:

- Table of contents
- Study reports
 - *Pharmacology*
 - Primary Pharmaco-dynamics
 - Secondary Pharmaco-dynamics
 - Safety Pharmacology
 - Pharmaco-dynamic Interactions
 - *Pharmaco-kinetics*
 - Analytical Methods and Validation Reports

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- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetic Interactions (non-clinical)
- Other Pharmacokinetic Studies
- *Toxicology*
 - Single-Dose Toxicity
 - Repeat-Dose Toxicity
 - Genotoxicity
 - In vitro
 - In vivo (including supportive toxicokinetics evaluations)
 - Carcinogenicity
 - Long-term studies
 - Short- or medium-term studies
 - Other studies
 - Reproductive and Developmental Toxicity
 - Fertility and early embryonic development
 - Embryo-fetal development
 - Prenatal and postnatal development
 - Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
 - Local Tolerance
- *Other Toxicity Studies*
 - Antigenicity
 - Immuno-toxicity
 - Mechanistic studies
 - Dependence
 - Metabolites
 - Impurities
 - Other
- Literature references

4.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

- (1) The pharmacological and toxicological 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 and toxicological potential of the product.

- (2) For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to be adapted for individual products; therefore the testing program carried out shall be justified by the applicant.

In establishing the testing program, 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 peri-natal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.

- (3) The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.
- (4) Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

4.2.1. Pharmacology

Pharmacology study shall follow two distinct lines of approach.

- Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both in vivo and in vitro, shall be used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action.
- Secondly, the applicant shall investigate the potential undesirable pharmaco-dynamic effects of the substance on physiological functions. These investigations shall be performed at exposures in the anticipated therapeutic range and above. 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. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.

For the pharmaco-dynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmaco-dynamic 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.

4.2.2. Pharmaco-kinetics

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Pharmaco-kinetics means the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, metabolism (bio-transformation) and excretion of these substances.

The study of these different phases may be carried mainly by means of physical, chemical or possibly by biological methods, and by observation of the actual pharmaco-dynamic activity of the substance itself.

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

In vitro studies also can be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).

Pharmaco-kinetic investigation of all 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, pharmaco-kinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

The pharmaco-kinetic program shall be design to allow comparison and extrapolation between animal and human.

4.2.3. Toxicology

a) Single-dose toxicity

A single-dose toxicity test shall mean 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 single-dose toxicity test must be carried out in accordance with the relevant guidelines published by the Agency.

b) Repeat-dose toxicity

Repeated dose toxicity tests are intended to reveal any physiological and/or anatomopathological 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 is to describe potential adverse effects to which attention should be paid in clinical studies. The duration is defined in the relevant guidelines published by the Agency.

c) Geno-toxicity

The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance.

d) Carcino-genicity

Tests to reveal carcinogenic effects shall normally be required:

1. These studies shall be performed for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner.
2. These studies are recommended for some medicinal products if there is concern about their carcinogenic potential, e.g. from product of the same class or similar structure, or from evidence in repeated dose toxicity studies.
3. Studies with unequivocally geno-toxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product is intended to be administered chronically to humans a chronic study may be necessary to detect early tumorigenic effects.

e) Reproductive and developmental toxicity

Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.

These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicinal product under investigation has been administered to the female during pregnancy.

Omission of these tests must be adequately justified.

Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring may be warranted.

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

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

f) Local tolerance

The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the medicinal product 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 pharmaco-dynamic ones.

Local tolerance testing shall be conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control group(s). Positive controls/reference substances shall be included where necessary.

The design of local tolerance tests (choice of species, duration, frequency and route of administration, doses) will depend upon the problem to be investigated and the

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proposed conditions of administration in clinical use. Reversibility of local lesions shall be performed where relevant.

Studies in animals can be substituted by validated in vitro tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation.

For chemicals applied to the skin (e.g. dermal, rectal, vaginal) the sensitising potential shall be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).

5. MODULE 5: CLINICAL STUDY REPORTS

5.1. Format and Presentation

The general outline of Module 5 is as follows:

- Table of contents for clinical study reports
- Tabular listing of all clinical studies
- Clinical study reports
 - *Reports of Bio-pharmaceutical Studies*
 - Bio-availability Study Reports
 - Comparative Bio-availability and Bio-equivalence Study Reports
 - In vitro — In vivo Correlation Study Report
 - Reports of Bio-analytical and Analytical Methods
 - *Reports of Studies Pertinent to Pharmacokinetics Using Human Bio-materials*
 - Plasma Protein Binding Study Reports
 - Reports of Hepatic Metabolism and Interaction Studies
 - Reports of Studies Using Other Human Bio-materials
 - *Reports of Human Pharmacokinetic Studies*
 - Healthy subjects Pharmacokinetics and Initial Tolerability Study Reports
 - Patient Pharmacokinetics and Initial Tolerability Study Reports
 - Intrinsic Factor Pharmacokinetics Study Reports
 - Extrinsic Factor Pharmacokinetics Study Reports
 - Population Pharmacokinetics Study Reports
 - *Reports of Human Pharmacodynamic Studies*
 - Healthy Subject Pharmacodynamic and Pharmacokinetics/Pharmacodynamic Study Reports
 - Patient Pharmacodynamic and Pharmacokinetics/Pharmacodynamic Studies Study Reports
 - *Reports of Efficacy and Safety Studies*
 - Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
 - Study Reports of Uncontrolled Clinical Studies
 - Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses
 - Other Study Reports
 - *Reports of Post-marketing Experience*
- Literature references

5.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

- a) The clinical particulars to be provided pursuant to Articles 8 (3) (i) and 10 (1) 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 authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.
- b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 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, pharmaco-kinetic and pharmaco-dynamic 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.
- c) Marketing authorisation holders must arrange for essential clinical trial documents (including case report forms) other than subject's medical files, to be kept by the owners of the data:
 - for at least 15 years after completion or discontinuation of the trial,
 - or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community,
 - or for at least two years after formal discontinuation of clinical development of the investigational product.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these documents no longer need to be retained.

The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation 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. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.

In addition for trials conducted within the European Community, the marketing authorisation holder shall make any additional arrangements for archiving of

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documentation in accordance with the provisions of Directive 2001/20/EC and implementing detailed guidelines.

Any change of ownership of the data shall be documented.

All data and documents shall be made available if requested by relevant authorities.

d) 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 medicinal 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 multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.

e) 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.

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 tolerance, 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 over dosage. 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 medicinal product on behalf of all centres.

f) The clinical observations shall be summarised for each trial indicating:

- 1) the number and sex of subjects treated;
- 2) the selection and age-distribution of the groups of patients being investigated and the comparative tests;
- 3) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;
- 4) 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
- 5) the frequency of observed adverse reactions;

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- 6) 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;
 - 7) parameters or evaluation criteria of efficacy and the results in terms of these parameters;
 - 8) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.
- g) In addition, the investigator shall always indicate his observations on:
- 1) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;
 - 2) any interactions that have been observed with other medicinal products administered concomitantly;
 - 3) the criteria determining exclusion of certain patients from the trials;
 - 4) any deaths which occurred during the trial or within the follow-up period.
- h) 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.
- i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre clinical toxicological and pharmacological tests must be undertaken and reviewed.
- j) 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.

5.2.1. Reports of bio-pharmaceutics studies

Bio-availability study reports, comparative bio-availability, bio-equivalence study reports, reports on in vitro and in vivo correlation study, and bio-analytical and analytical methods shall be provided.

In addition, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for the medicinal products referred to in Article 10 (1) (a).

5.2.2. Reports of studies pertinent to pharmaco-kinetics using human bio-materials

For the purposes of this Annex, human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmaco-kinetics properties of drug substances.

In this respect, reports of plasma protein binding study, hepatic metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.

5.2.3. Reports of human pharmaco-kinetic studies

- a) The following pharmaco-kinetic characteristics shall be described:
- absorption (rate and extent),
 - distribution,
 - metabolism,

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— 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 pre clinical studies, shall be described.

In addition to standard multiple-sample pharmaco-kinetics studies, population pharmaco-kinetics analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose- pharmaco-kinetics response relationship. Reports of pharmaco-kinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmaco-kinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmaco-kinetic studies shall be provided.

- b) If the medicinal 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.

Pharmaco-kinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.4. Reports of human pharmaco-dynamic studies

- a) The pharmaco-dynamic 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 pharmaco-dynamic action not related to efficacy shall be described.

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

- b) If the medicinal 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.

Pharmaco-dynamic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.5. Reports of efficacy and safety studies

5.2.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

In general, clinical trials shall be done as ‘controlled clinical trials’ if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; 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.

- (1) 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 randomisation 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 randomisation, 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.

The safety data shall be reviewed taking into account guidelines published by the Commission, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.

- 5.2.5.2. Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports

These reports shall be provided.

- 5.2.6. Reports of post-marketing experience

If the medicinal product is already authorised in third countries, information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.

- 5.2.7. Case reports forms and individual patient listings

When submitted in accordance with the relevant Guideline published by the Agency, case report forms and individual patient data listings shall be provided and presented in the same order as the clinical study reports and indexed by study.]

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- (1) [^{F1}OJ L 106, 17.4.2001, p. 1.]
- (2) [^{F1}OJ L 11, 14.1.1978, p. 18.]
- (3) [^{F1}OJ L 237, 10.9.1994, p. 13.]

Textual Amendments

- F1** Substituted by [Commission directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use \(Text with EEA relevance\).](#)