product concerned is authorised, of the proposal to grant an authorisation under this Article in respect of the product concerned; and

(b) request the competent authority in that State to furnish a copy of the assessment report referred to in Article 21(4) and of the marketing authorisation in force in respect of the said medicinal product.

4. The Commission shall set up a publicly accessible register of medicinal products authorised under paragraph 1. Member States shall notify the Commission if any medicinal product is authorised, or ceases to be authorised, under paragraph 1, including the name or corporate name and permanent address of the authorisation holder. The Commission shall amend the register of medicinal products accordingly and make this register available on their website.

5. No later than 30 April 2008, the Commission shall present a report to the European Parliament and the Council concerning the application of this provision with a view to proposing any necessary amendments.

Article 126b

In order to guarantee independence and transparency, the Member States shall ensure that members of staff of the competent authority responsible for granting authorisations, rapporteurs and experts concerned with the authorisation and surveillance of medicinal products have no financial or other interests in the pharmaceutical industry which could affect their impartiality. These persons shall make an annual declaration of their financial interests.

In addition, the Member States shall ensure that the competent authority makes publicly accessible its rules of procedure and those of its committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions.

Article 127

1. At the request of the manufacturer, the exporter or the authorities of an importing third country, Member States shall certify that a manufacturer of medicinal products is in possession of the manufacturing authorization. When issuing such certificates Member States shall comply with the following conditions:

(a) they shall have regard to the prevailing administrative arrangements of the World Health Organization;

(b) for medicinal products intended for export which are already authorized on their territory, they shall supply the summary of the product characteristics as approved in accordance with Article 21.

2. When the manufacturer is not in possession of a marketing authorization he shall provide the authorities responsible for establishing the certificate referred to in paragraph 1, with a declaration explaining why no marketing authorization is available.

Article 127a

When a medicinal product is to be authorised in accordance with Regulation (EC) No 726/2004 and the Scientific Committee in its opinion refers to recommended conditions or restrictions with regard to the safe and effective use of the medicinal product as provided for in Article 9(4)(c) of that Regulation, a decision addressed to the Member States shall be adopted in accordance with the procedure provided for in Articles 33 and 34 of this Directive, for the implementation of those conditions or restrictions.

Article 127b

Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired.

TITLE XIV

FINAL PROVISIONS

Article 128

Directives 65/65/EEC, 75/318/EEC, 75/319/EEC, 89/342/EEC, 89/343/EEC, 89/381/EEC, 92/25/EEC, 92/26/EEC, 92/27/EEC, 92/28/EEC and 92/73/EEC, amended by the Directives referred to in Annex II, Part A, are repealed, without prejudice to the obligations of the Member States concerning the time-limits for implementation set out in Annex II, Part B.

References to the repealed Directives shall be construed as references to this Directive and shall be read in accordance with the correlation table in Annex III.

Article 129

This Directive shall enter into force on the twentieth day following that of its publication in the Official Journal of the European Communities.

Article 130

This Directive is addressed to the Member States.

Done at Brussels, 6 November 2001

For the European Parliament	*For the Council*
The President	*The President*
N. FONTAINE	D. REYNDERS

DEAD-LINES FOR THE TRANSPOSITION OF AMENDING DIRECTIVES:

Directive 2002/98/EC:

Article 32

1. Member States shall bring into force the laws regulations and administrative provisions necessary to comply with this Directive not later that 8 February 2005. They shall forthwith inform the Commission thereof.

When Member States adopt those provisions, they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the texts of the provisions of national law that they have already adopted or which they adopt in the field governed by this Directive.

Directive 2004/24/EC:

Article 2

1. The Member States shall take the necessary measures to comply with this Directive by 30 October 2005. They shall forthwith inform the Commission thereof.

When Member States adopt these measures, they shall contain a reference to this Directive or shall be accompanied by such a reference on the occasion of their official publication. The methods of making such reference shall be laid down by the Member States.

2. For the traditional herbal medicinal products as referred to in Article 1, which are already on the market on the entry into force of this Directive, the competent authorities shall apply the provisions of this Directive within seven years after its entry into force.

Directive 2004/27/EC:

Article 2

The periods of protection provided for in Article 1, point 8, which amends Article 10(1) of Directive 2001/83/EC, shall not apply to reference medicinal products for which an application for authorisation has been submitted

before the date of transposition to in Article 3 first paragraph.

Article 3

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive no later than 30 October 2005. They shall immediately inform the Commission thereof.

When Member States adopt these measures, they shall contain a reference to this Directive or shall be accompanied by such a reference on the occasion of their official publication. The methods of making such reference shall be laid down by the Member States.

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)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating medicinal products for human use [1], as last amended by Directive 2002/98/EC [2], and in particular Article 120 thereof,

Whereas:

(1) Every medicinal product for human use that is to be placed on the European Community market must be granted a marketing authorisation delivered by a competent authority. With the view to obtaining a marketing authorisation, an application dossier containing particulars and documents relating to the results of tests and trials carried out on this medicinal product must be submitted.

(2) The detailed scientific and technical requirements of Annex I to Directive 2001/83/EC need to be adapted to take account of scientific and technical progress and in particular of a large set of new requirements resulting from recent legislation. The presentation and content of the marketing authorisation application dossier have to be improved in order to facilitate the assessment and the better use of certain parts of the dossier which are common to several medicinal products.

(3) Within the framework of the International Conference on Harmonisation (ICH) a consensus was reached in 2000 to provide a harmonised format and terminology for a Common Technical Document through which a homogeneous organisation and presentation of a marketing authorisation application dossier for human medicinal products could be achieved. Standardised marketing authorisation dossier requirements should therefore be introduced in order to implement the Common Technical Document without delay.

(4) The standardised marketing authorisation dossier requirements (harmonised format) should be applicable to any type of medicinal product for human use, regardless of the procedure for the granting of the marketing authorisation. Some medicinal products present, however, such specific features that all the requirements cannot be fulfilled. To take account of these particular situations, a simplified dossier presentation should be provided for.

(5) The safety of biological medicinal products relies on rigorous control of their starting materials. Requirements for the suitability of human donors and the testing of donations of starting materials for plasma-derived medicinal products are laid down by Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. Article 109 of Directive 2001/83/EC has been amended. Plasma-derived medicinal products per se are biological medicinal products, the manufacture of which is based on the careful handling of human plasma as a starting material. To take account of the fact that the same plasma material is used in most cases for several medicinal products and, as a result, that a substantial part of the marketing authorisation dossier may be common to a great number of other dossiers for totally different plasma-derived medicinal products, it is appropriate to establish a new system aimed at simplifying procedures for both the approval of and subsequent changes to human plasma-derived medicinal products. To this end the concept of a plasma master file (PMF) should be introduced, in particular in order to allow the pooling of national expertise and through the coordination by the EMEA of a single evaluation. A PMF should serve as a stand-alone document, which is separate from the marketing authorisation dossier and through which a harmonised control of the relevant information regarding starting material used for the manufacture of plasma-derived medicinal products could be achieved. The PMF system should consist of a two-step assessment: first, an assessment of the PMF carried out at Community level, the result of which, i.e. a certificate of compliance with the Community legislation for each PMF, must be taken into account by any national competent authority, preventing them of any subsequent reassessment; second, an assessment of the finished plasma-derived medicinal product containing the modified part of the PMF (the two essential parts of the content, plasma origin and plasma quality-safety).

[1] OJ L 311, 28.11.2001, p. 67.
[2] OJ L 33, 8.2.2003, p. 30.

This should remain the task of the competent authority that granted the marketing authorisation for the plasma-derived medicinal product.

(6) In the case of vaccines for human use, the same antigen may be common to several medicinal products (vaccines) and any change to that particular antigen, *ipso facto*, may impact, therefore, on several vaccines authorised by different procedures. In order to simplify the existing procedures for the assessment of such vaccines, both for the granting of a first marketing authorisation and for subsequent changes to it due to modifications to the manufacturing process and testing of individual antigens involved in combined vaccines, a new system based on the concept of a vaccine antigen master file (VAMF) should be introduced. This VAMF will allow the pooling of national expertise, and through the coordination by the EMEA, a single evaluation of the concerned vaccine antigen. The VAMF should serve as a stand-alone part of the marketing authorisation dossier and provide all relevant information of a biological and chemical nature related to one specific antigen, which constitutes one of the active substances of one or several combined vaccines.

(7) The VAMF system should consist of a two-step assessment: first, an assessment of the VAMF carried out at Community level, the result of which, i.e. a certificate of compliance with the Community legislation for each VAMF, must be taken into account by any national competent authority, preventing them from any subsequent reassessment; second, an assessment of the finished medicinal product (combined vaccine) containing the modified antigen which is the task of the competent authority that granted the combined vaccine marketing authorisation.

(8) Herbal medicinal products differ substantially from conventional medicinal products in so far as they are intrinsically associated with the very particular notion of herbal substances and herbal preparations. It is therefore appropriate to determine specific requirements in respect of these products with regard to the standardised marketing authorisation requirements.

(9) The treatment of various acquired and inherited pathological dysfunctions in humans calls upon novel concept-based approaches based on the development of biotechnology techniques. The latter involve the use of advanced therapy medicinal products based on processes focused on various gene-transfer-produced bio-molecules (gene therapy medicinal products) and manipulated or processed cells (cell therapy medicinal products) as active substances.

(10) In so far as they achieve their essential action through metabolic, physiological and immunological means to restore, correct or modify physiological functions in humans, these novel complex therapeutic products representing a new category of biological medicinal products in the sense of Articles 1 and 2 of Directive 2001/83/EC. The general principles already applicable to these products should be specified from a scientific and technical point of view and the specific requirements with regard to the standardised marketing authorisation requirements should be determined.

(11) Directive 2001/83/EC should be amended accordingly.

(12) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee for Medicinal Products for Human Use,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Directive 2001/83/EC is amended as follows:

a) in the second paragraph of Article 22 the words 'Part 4 (G)' are replaced by the following:

'Part II, point 6';

b) Annex I is replaced by the text in the Annex to this Directive.

Article 2

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 31 October 2003 at the latest. They shall forthwith inform the Commission thereof.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

This Directive is applicable as from 1 July 2003.

Article 3

This Directive shall enter into force on the third day following that of its publication in the *Official Journal of the European Union*.

Article 4

This Directive is addressed to the Member States.

Done at Brussels, 25 June 2003.

For the Commission

Erkki LIIKANEN

Member of the Commission

ANNEX

Annex I to Directive 2001/83/EC is replaced by the following:

'ANNEX I

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

TABLE OF CONTENTS

Introduction and general principles

(1) The particulars and documents accompanying an application for marketing authorisation pursuant to Articles 8 and 10 (1) shall be presented in accordance with the requirements set out in this Annex and shall follow the guidance published by the Commission in The rules governing medicinal products in the European Community, Volume 2 B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD).

(2) The particulars and documents shall be presented as five modules: Module 1 provides European Community specific administrative data; Module 2 provides quality, non-clinical and clinical summaries, Module 3 provides chemical, pharmaceutical and biological information, Module 4 provides non-clinical reports and Module 5 provides clinical study reports. This presentation implements a common format for all ICH [1] regions (European Community, United States of America, Japan). These five Modules shall be presented in strict accordance with the format, content and numbering system delineated in details in Volume 2 B of the Notice to Applicants referred to above.

(3) The European Community-CTD-presentation is applicable for all types of marketing authorisation applications irrespective of the procedure to be applied (i.e. centralised, mutual recognition or national) and of whether they are based on a full or abridged application. It is also applicable for all types of products including new chemical entities (NCE), radio-pharmaceuticals, plasma derivatives, vaccines, herbal medicinal products, etc.

(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.

(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

(6) The manufacturing process shall comply with the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for human use [2] and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal products in the European Community, Volume 4.

(7) 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 pharmaco-toxicological or clinical test or trial relating to the medicinal product and/or completed trials concerning therapeutic indications not covered by the application.

(8) All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [3]. To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.

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[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
[2] OJ L 193, 17.7.1991, p. 30.
[3] OJ L 121, 1.5.2001, p. 34.

(9) Non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions related to Good Laboratory Practice laid down in Council Directives 87/18/EEC on the harmonisation of regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their application for tests in chemical substances [1] and 88/320/EEC on the inspection and verification of good laboratory practice (GLP) [2].

(10) Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes.

(11) In order to monitor the benefit/risk assessment, any new information not in the original application and all pharmaco-vigilance information shall be submitted to the competent authority. After marketing authorisation has been granted, any change to the data in the dossier shall be submitted to the competent authorities in accordance with the requirements of Commission Regulations (EC) No 1084/2003 [3] and (EC) No 1085/2003 [4] of the Commission or, if relevant, in accordance with national provisions, as well as the requirements in Volume 9 of Commission publication *The rules governing medicinal products in the European Community*.

This Annex is divided in four different parts:

— Part I describes the application format, the summary of product characteristics, the labelling, the leaflet and presentation requirements for standard applications (Modules 1 to 5).

— Part II provides derogation for 'Specific applications', i.e. well-established medicinal use, essentially similar products, fixed combinations, similar biological products, exceptional circumstances and mixed applications (part bibliographic and part own studies).

— Part III deals with 'Particular application requirements' for biological medicinal products (Plasma Master File; Vaccine Antigen Master File), radio-pharmaceuticals, homeopathic medicinal products, herbal medicinal products and orphan medicinal products.

— Part IV deals with 'Advanced therapy medicinal products' and concerns specific requirements for gene therapy medicinal products (using human autologous or allogeneic system, or xenogeneic system) and cell therapy medicinal products both of human or animal origin and xenogeneic transplantation medicinal products.

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.

[1] OJ L 15, 17.1.1987, p. 29.
[2] OJ L 145, 11.6.1988, p. 35.
[3] See p. 1 of this Official Journal.
[4] See p. 24 of this Official Journal.

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*

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).

[1] OJ L 106, 17.4.2001, p. 1.

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.

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:

— 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

  — 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.

(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.

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.