L.N. 252 of 2010

MEDICINES ACT
(CAP. 458)

Medicines (Marketing Authorisation) (Amendment) Regulations, 2010

IN exercise of the powers conferred by article 106 of the Medicines Act, the Minister of Health, the Elderly and Community Care, after consultation with the Licensing Authority, has made the following regulations:-

Title and scope.

1. (1) The title of these regulations is the Medicines (Marketing Authorisation) (Amendment) Regulations, 2010 and they shall be read and construed as one with the Medicines (Marketing Authorisation) Regulations, 2007, hereinafter referred to as "the principal regulations".

L.N. 324 of 2007.

(2) These regulations lay out the requirements set in Annex I of Directive 2001/83/EC, as amended by Directive 2003/63/EC and Directive 2009/120/EC.

Amends regulation 2 of the principal regulations.

2. In sub-regulation (1) of regulation 2 of the principal regulations, for the definition "Annex I" there shall be substituted the following:

" "Annex I" means Annex I of Directive 2001/83/EC as subsequently amended and as appearing in the Schedule to these regulations;".

Adds Schedule to the principal regulations.

3. Immediately at the end of the principal regulations, there shall be added the following Schedule:

"SCHEDULE

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

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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 Schedule 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.

(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 pharmacovigilance 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 Schedule 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.

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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*

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 this Schedule.

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 12March 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

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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.

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 humans 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-kineticsWritten 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

P h a r ma c e u t i c a l D e v e l opme n t

— 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.

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(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 Schedule, 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 physicochemical-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 Schedule.

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.

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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 Schedule.

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.

3.2.1.3.1. 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 immunochemical and/or biological methods, as well as information on impurities shall be provided.

3.2.1.3.2. 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.

3.2.1.3.3. 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 summarized

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. Descriotion 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,

— 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 (1) and/or European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs (2).

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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 (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.

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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 ± 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 or 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 summarized;

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
    - Absorption
    - Distribution
    - Metabolism
    - Excretion
    - Pharmaco-kinetic Interactions (non-clinical)
    - Other Pharmaco-kinetic Studies
  - *Toxicology*
    - Single-Dose Toxicity
    - Repeat-Dose Toxicity
    - Genotoxicity
      - In vitro
      - In vivo (including supportive toxico-kinetics 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 evaluation
    - 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, timeeffect 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*

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 anatomo-pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose 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

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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 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 Pharmaco-kinetics 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 Pharmaco-kinetic Studies*
  — Healthy subjects Pharmaco-kinetics and Initial Tolerability Study Reports
  — Patient Pharmaco-kinetics and Initial Tolerability Study Reports
  — Intrinsic Factor Pharmaco-kinetics Study Reports
  — Extrinsic Factor Pharmaco-kinetics Study Reports
  — Population Pharmaco-kinetics Study Reports

— *Reports of Human Pharmaco-dynamic Studies*
  — Healthy Subject Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Study Reports
  — Patient Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic 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 Schedule. 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 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 judgment 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;

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.

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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 bioequivalence 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 Schedule, 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,
- — 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

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*

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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.

PART II

SPECIFIC MARKETING AUTHORISATION DOSSIERS ANDREQUIREMENTS

Some medicinal products present specific features which are such that all the requirements of the marketing authorisation application dossier as laid down in Part I of this Schedule need to be adapted. To take account of these particular situations, an appropriate and adapted presentation of the dossier shall be followed by applicants.

1. WELL-ESTABLISHED MEDICINAL USE

For medicinal products the active substance(s) of which has/have a 'well-established medicinal use' as referred to Article 10(1)(a)(ii), with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Modules 1, 2 and 3 as described in part I of this Schedule.

For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics. The following specific rules shall apply in order to demonstrate the well-established medicinal use:

a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:

— the time over which a substance has been used,
— quantitative aspects of the use of the substance,
— the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and
— the coherence of scientific assessments.

Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

b) The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be communicated. With respect to the provisions on 'well established medicinal use' it is in particular necessary to clarify that 'bibliographic reference' to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

c) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.

d) The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgment must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.

e) Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.

2. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS

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a) Applications based upon Article 10(1) (a) (i) (essentially similar products) shall contain the data described in Modules 1, 2 and 3 of Part I of this Schedule provided the applicant has been granted the consent of the holder of the original marketing authorisation to cross refer to the content of his Modules 4 and 5.

b) Applications based upon Article 10(1) (a) (iii) (essentially similar products i.e. generics) shall contain the data described in Modules 1, 2 and 3 of Part I of this Schedule together with data showing bioavailability and bio-equivalence with the original medicinal product provided the latter is not a biological medicinal product (see Part II, 4 Similar biological medicinal products).

For these products the non-clinical/clinical overviews/summaries shall particularly focus on the following elements:

— the grounds for claiming essential similarity;
— a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities;
— an evaluation of the bio-equivalence studies or a justification why studies were not performed with respect to the guideline on 'Investigation of Bio-availability and Bio-equivalence';
— an update of published literature relevant to the substance and the present application. It may be acceptable for articles in 'peer review' journals to be annotated for this purpose;
— every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.
— if applicable, additional data in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance should be provided by the applicant when he claims essential similarity.

3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS

Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the pharmaco-kinetics of the moiety, pharmaco-dynamics and/or in toxicity which could change the safety/efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered as a new active substance.

Where a medicinal product is intended for a different therapeutic use or presented in a different pharmaceutical form or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.

4. SIMILAR BIOLOGICAL MEDICINAL PRODUCTS

The provisions of Article 10(1)(a) (iii) may not be sufficient in the case of biological medicinal products.
If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided.

When a biological medicinal product as defined in Part I, paragraph 3.2 of this Schedule, which refers to an original medicinal product having been granted a marketing authorisation in the Community, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied.

— Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.

— Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.

The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

5. FIXED COMBINATION MEDICINAL PRODUCTS

Applications based upon Article 10 (1) (b) shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product.

For those applications a full dossier (Modules 1 to 5) shall be provided for the fixed combination medicinal product. Where applicable, information regarding the manufacturing sites and the adventitious agents, safety evaluation shall be provided.

5. DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES

When, as provided for in Article 22, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

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

— in the present state of scientific knowledge, comprehensive information cannot be provided, or

— it would be contrary to generally accepted principles of medical ethics to collect such information, marketing authorisation may be granted subject to certain specific obligations.

These obligations may include the following:

— the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/ risk profile,

— the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,

— the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

7. MIXED MARKETING AUTHORISATION APPLICATIONS

Mixed marketing-authorisation applications shall mean marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Schedule. The competent authority shall accept the proposed format presented by the applicant on a case by case basis.

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PART III
PARTICULAR MEDICINAL PRODUCTS

This Part lays down specific requirements related to the nature of identified medicinal products.

1. BIOLOGICAL MEDICINAL PRODUCTS

1.1. **Plasma-derived medicinal product**

For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in 'Information related to the starting and raw materials', for starting materials made of human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.

a) Principles

For the purposes of this Schedule:

— Plasma Master File shall mean a stand-alone documentation, which is separate from the dossier for marketing authorisation which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices referred to in Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or human plasma (1).

— Every centre or establishment for fractionation/processing of human plasma shall prepare and keep updated the set of detailed relevant information referred to in the Plasma Master File.

— The Plasma Master File shall be submitted to the Agency or to the competent authority by the applicant for a marketing authorisation or the holder of the marketing authorisation. Where the applicant for a marketing authorisation or the marketing authorisation holder differs from the holder of the Plasma Master File, the Plasma Master File shall be made available to the applicant or marketing authorisation holder for submission to the competent authority. In any case, the applicant or marketing authorisation holder shall take responsibility for the medicinal product.

— The competent authority that is evaluating the marketing authorisation shall await for the Agency to issue the certificate before deciding on the application.

— Any marketing authorisation dossier containing a human plasma-derived constituent shall refer to the Plasma Master File corresponding to the plasma used as a starting/raw material.

b) Content

In accordance with the provisions of Article 109, as amended by Directive 2002/98/EC, which refers to the requirements for donors and the testing of donations, the Plasma Master File shall include information on the plasma used as starting/raw material, in particular:

(1) Plasma origin

(i) information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.

(ii) information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.

(iii) selection/exclusion criteria for blood/plasma donors.

(iv) system in place which enables the path taken by each donation to be traced from the blood/ plasma collection establishment through to finished products and vice versa.

(2) Plasma quality and safety

(i) compliance with European PharmacopoeiaMonographs.

(ii) testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used.

(iii) technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used.

(iv) conditions of storage and transport of plasma.

(v) procedures for any inventory hold and/or quarantine period.

(vi) characterisation of the plasma pool.

(3) System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.

In addition, the Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorisation or are in the process of being granted such an authorisation, including medicinal products referred to in Article 2 of Directive 2001/20/EC of the European Parliament and of the Council relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

c) Evaluation and Certification

— For medicinal products not yet authorised, the marketing authorisation applicant shall submit a full dossier to a competent authority, which shall be accompanied by a separate Plasma Master File where one does not already exist.

— The Plasma Master File is subject to a scientific and technical evaluation carried out by the Agency. A positive evaluation shall result in a certificate of compliance with Community legislation for the Plasma Master File, which shall be accompanied by the evaluation report. The certificate issued shall apply throughout the Community.

— The Plasma Master File shall be updated and re-certified on an annual basis.

— Changes subsequently introduced to the terms of a Plasma Master File must follow evaluation procedure laid down by Commission Regulation (EC) No 542/95 (1) concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Council regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (2). Conditions for the assessment of these changes are laid down by Regulation (EC) No 1085/2003.

— As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Plasma Master File on the concerned medicinal product(s).

— By derogation from the provisions of the second indent of the present point (evaluation and certification), where a Plasma Master File corresponds only to blood/plasma-derived medicinal products the marketing authorisation of which is restricted to a single Member State, the scientific and technical evaluation of the said Plasma Master File shall be carried out by the national competent authority of that Member State.

1.2. **Vaccines**

For vaccines for human use and by derogation from the provisions of Module 3 on ‘Active substance(s)’, the following requirements when based on the use of a Vaccine Antigen Master File system shall apply. The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.

a) Principles

For the purposes of this Schedule:

— Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

— A vaccine may contain one or several distinct vaccine antigens. There are as many active substance(s) as vaccine antigen(s) present in a vaccine.

— A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.

— A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

b) Content

The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on 'Quality Data' as delineated in Part I of this Schedule:

Active Substance

1. General Information, including compliance with the relevant monograph(s) of the European Pharmacopoeia.

2. Information on the manufacture of the active substance: this heading must cover the manufacturing process, information on the starting and raw materials, specific measures on TSEs and adventitious agents safety evaluation and facilities and equipment.

3. Characterisation of the active substance

4. Quality control of the active substance

5. Reference standard and materials

6. Container and closure system of the active substance

7. Stability of the active substance.

c) Evaluation and Certification

— For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing-authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen that is part of the novel vaccine where no master file already exists for the single vaccine antigen.A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance to the European legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Community.

— The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorised in the Community.

— Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Community shall be subject to a scientific and technical evaluation carried out by the Agency in accordance with the procedure laid down in Commission Regulation (EC) No 1085/2003. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Community legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Community.

— By derogation from the provisions of the first, second and third indents of the present point (evaluation and certification), where a Vaccine Antigen Master File corresponds only to a vaccine which is the subject of a marketing authorisation which has not been/will not be granted according to a Community procedure, and, provided the authorised vaccine includes vaccine antigens which have not been evaluated through a Community procedure, the scientific and technical evaluation of the said Vaccine Antigen Master File and its subsequent changes, shall be carried out by the national competent authority that has granted the marketing authorisation.

— As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Vaccine Antigen Master File on the concerned medicinal product(s).

2. RADIO-PHARMACEUTICALS AND PRECURSORS

2.1. **Radio-pharmaceuticals**

For the purposes of this chapter, applications based upon Articles 6 (2) and 9 shall provide a full dossier in which the following specific details shall be included:

Module 3

a) In the context of a radio-pharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radio-nuclide. The description of the manufacturing method of radiopharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia . In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.

For radio-nuclides, the nuclear reactions involved shall be discussed.

In a generator, both mother and daughter radio-nuclides shall be considered as active substances.

b) Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.

c) Starting materials include irradiation target materials.

d) Considerations on chemical/radiochemical purity and its relationship to bio-distribution shall be provided.

e) Radio-nuclide purity, radiochemical purity and specific activity shall be described.

f) For generators, details on the testing for mother and daughter radio-nuclides are required. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided.

g) The requirement to express the content of active substances in terms of the mass of active entities shall onlyapply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.

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h) For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on radiochemical and radio-nuclidic purity of the radiolabelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.

i) Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radiolabelled products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.

Module 4

It is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognised system by a particular route of administration.

Module 5

The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews.

2.2. **Radio-pharmaceutical precursors for radio-labelling purposes**

In the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labeling efficiency or in vivo dissociation of the radio-labeled conjugate, i.e. questions related to the effects produced in the patient by free radio-nuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment.

In particular, the following information where applicable shall be provided:

Module 3

The provisions of Module 3 shall apply to the registration of radio-pharmaceutical precursors as defined above (indents a) to i)), where applicable.

Module 4

Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the provisions related to good laboratory practice laid down in Council Directives 87/18/EEC and 88/320/EEC shall be provided, unless otherwise justified.

Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.

Information relating to the chemical toxicity and disposition of the relevant ‘cold’ nuclide shall be presented.

Module 5

Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.

However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.

3. HOMEOPATHIC MEDICINAL PRODUCTS

This section sets out specific provisions on the application of Modules 3 and 4 to homeopathic medicinal products as defined in Article 1(5).

Module 3

The provisions of Module 3 shall apply to the documents submitted in accordance with Article 15 in the simplified registration of homeopathic medicinal products referred to in Article 14(1) as well as to the documents for authorisation of other homeopathic medicinal products referred to in Article 16(1) with the following modifications.

a) Terminology

The Latin name of the homeopathic stock described in the marketing authorisation application dossier must be in accordance with the Latin title of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.

b) Control of starting materials

The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished medicinal product, accompanying the application shall be supplemented by additional data on the homeopathic stock.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished medicinal product. If possible, an assay is required if toxic components are present and if the quality cannot be controlled on final dilution to be incorporated because of the high dilution degree. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished medicinal product must be fully described.

In case dilutions are involved, these dilution steps should be done in accordance with the Homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State.

c) Control tests on the finished medicinal product

The general quality requirements shall apply to the homeopathic finished medicinal products, any exception needs to be duly justified by the applicant.

Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that an identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

d) Stability tests

The stability of the finished medicinal product must be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

Module 4

The provisions of Module 4 shall apply to the simplified registration of homeopathic medicinal products referred to in Article 14(1) with the following specifications.

Any missing information must be justified, e.g., justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.

4. HERBAL MEDICINAL PRODUCTS

Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.

Module 3

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The provisions of Module 3, including compliance with monograph(s) of the European Pharmacopoeia, shall apply to the authorisation of herbal medicinal products. The state of scientific knowledge at the time when the application is lodged shall be taken into account.

The following aspects specific to herbal medicinal products shall be considered:

(1) Herbal substances and herbal preparations

For the purposes of this Schedule the terms 'herbal substances and preparations' shall be considered equivalent to the terms 'herbal drugs and herbal drug preparations', as defined in the European Pharmacopoeia.

With respect to the nomencRlature of the herbal substance, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

To document the section of the structure for herbal substance(s) and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass) as well as other constituent(s) shall be provided.

To document the section on the manufacturer of the herbal substance, the name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance shall be provided, where appropriate.

To document the section on the manufacturer of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.

With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.

With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing, solvents and reagents, purification stages and standardisation.

With respect to the manufacturing process development, a brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s), where applicable, contained as active substance(s) in the herbal medicinal product applied for shall be discussed, where appropriate.

With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phyto-chemical characterisation, and biological activity if necessary, shall be provided.

With respect to the elucidation of the structure and other characteristics of the herbal preparation, information on the phyto- and physicochemical characterisation, and biological activity if necessary, shall be provided.

The specifications for the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

The analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

With respect to batch analyses, description of batches and results of batch analyses for the herbal substance(s) and herbal preparation(s) where applicable shall be provided, including those for pharmacopoeial substances.

Justification for the specifications of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Information on the reference standards or reference materials used for testing of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant can apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines.

(2) Herbal Medicinal Products

With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed, where appropriate.

5. ORPHAN MEDICINAL PRODUCTS

— In the case of an orphan medicinal product in the meaning of Regulation (EC) No 141/2000, general provisions of Part II-6 (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.

— When an applicant for an marketing authorisation for an orphan medicinal product invokes the provisions of Article 10 (1)(a)(ii) and Part II-1 of this Schedule (well-established medicinal use), the systematic and documented use of the concerned substance can refer —as way of derogation —to the use of that substance in accordance with the provisions of Article 5 of this Directive.

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PART IV
ADVANCED THERAPY MEDICINAL PRODUCTS

1. INTRODUCTION

Marketing authorisation applications for advanced therapy medicinal products, as defined in point (a) of Article 2(1) of Regulation (EC) No 1394/2007, shall follow the format requirements (Modules 1, 2, 3, 4 and 5) described in Part I of this Schedule.

The technical requirements for Modules 3, 4 and 5 for biological medicinal products, as described in Part I of this Schedule, shall apply. The specific requirements for advanced therapy medicinal products described in sections 3, 4 and 5 of this part explain how the requirements in Part I apply to advanced therapy medicinal products. In addition, where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.

Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products referred to in point 4 of the "Introduction and general principles".

The risk analysis may cover the entire development. Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the extent of replication competence of viruses or micro-organisms used *in vivo*, the level of integration of nucleic acids sequences or genes into the genome, the long time functionality, the risk of oncogenicity and the mode of administration or use.

Relevant available non-clinical and clinical data or experience with other, related advanced therapy medicinal products may also be considered in the risk analysis.

Any deviation from the requirements of this Schedule shall be scientifically justified in Module 2 of the application dossier. The risk analysis described above, when applied, shall also be included and described in Module 2. In this case, the methodology followed, the nature of the identified risks and the implications of the risk based approach for the development and evaluation program shall be discussed and any deviations from the requirements of this Schedule resulting from the risk analysis shall be described.

2. DEFINITIONS

For the purposes of this Schedule, in addition to the definitions laid down in Regulation (EC) No 1394/2007, the definitions set out in sections 2.1 and 2.2 shall apply.

2.1. **Gene therapy medicinal product**

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence. Gene therapy medicinal products shall not include vaccines against infectious diseases.

2.2. **Somatic cell therapy medicinal product**

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

3. SPECIFIC REQUIREMENTS REGARDING MODULE 3

3.1. **Specific requirements for all advanced therapy medicinal products**

A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.

The traceability system shall be complementary to, and compatible with, the requirements established in Directive 2004/23/EC of the European Parliament and of the Council, as regards human cells and tissues other than blood cells, and Directive 2002/98/EC, as regards human blood cells.

3.2. **Specific requirements for gene therapy medicinal products**

3.2.1. *Introduction: finished product, active substance and starting materials*

3.2.1.1. Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).

The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.

The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).

3.2.1.2. Gene therapy medicinal product containing genetically modified cells

The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.

The active substance shall consist of cells genetically modified by one of the products described in section 3.2.1.1 above.

3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.

3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.

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3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.

3.2.2. Specific requirements

In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Schedule, the following requirements shall apply:

(a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps;

(b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;

(c) process-related impurities and product-related impurities shall be described in the relevant sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;

(d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;

(e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, shall be tested.

For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for somatic cell therapy medicinal products and tissue engineered products (see section 3.3) shall apply.

3.3. **Specific requirements for somatic cell therapy medicinal products and tissue engineered products**

3.3.1. *Introduction: finished product, active substance and starting materials*

The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.

The active substance shall be composed of the engineered cells and/or tissues.

Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.

Materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.

3.3.2. *Specific requirements*

In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Schedule, the following requirements shall apply:

3.3.2.1. Starting materials

(a) Summary information shall be provided on donation, procurement and testing of the human tissue and cells used as starting materials and made in accordance with Directive 2004/23/EC. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified.

(b) If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.

(c) The potential variability introduced through the human or animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterisation of the active substance and the finished product, development of assays, setting of specifications and stability.

(d) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents, including vertically transmitted microorganisms and viruses, and evidence of the suitability of the animal facilities shall be provided.

(e) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of the transgenic animal shall be provided.

(f) For the genetic modification of the cells, the technical requirements specified in section 3.2 shall apply.

(g) The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with engineered cells of which they form an integral part, shall be described and justified.

(h) For scaffolds, matrices and devices that fall under the definition of a medical device or active implantable medical device, the information required under section 3.4 for the evaluation of the combined advanced therapy medicinal product shall be provided.

3.3.2.2. Manufacturing process

(a) The manufacturing process shall be validated to ensure batch and process consistency, functional integrity of the cells throughout manufacturing and transport up to the moment of application or administration, and proper differentiation state.

(b) If cells are grown directly inside or on a matrix, scaffold or device, information shall be provided on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination.

3.3.2.3. Characterisation and control strategy

(a) Relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity (e.g. adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated.

(b) Qualitative and, where possible, quantitative information on product- and process-related impurities, as well as on any material capable of introducing degradation products during production, shall be provided. The extent of the determination of impurities shall be justified.

(c) If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this shall be justified.

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(d) Where biologically active molecules (such as growth factors, cytokines) are present as components of the cell based product, their impact and interaction with other components of the active substance shall be characterised.

(e) Where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for these cell-based products. Where needed, non-clinical investigations shall complement the physicochemical characterisation.

3.3.2.4. Excipients

For excipient(s) used in cell or tissue-based medicinal products (e.g. the components of the transport medium), the requirements for novel excipients, as laid down in Part I of this Schedule, shall apply, unless data exists on the interactions between the cells or tissues and the excipients.

3.3.2.5. Developmental studies

The description of the development program shall address the choice of materials and processes. In particular, the integrity of the cell population as in the final formulation shall be discussed.

3.3.2.6. Reference materials

A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised.

3.4. **Specific requirements for advanced therapy medicinal products containing devices**

3.4.1. *Advanced therapy medicinal product containing devices as referred to in Article 7 of Regulation (EC) No 1394/2007*
A description of the physical characteristics and performance of the product and a description of the product design methods shall be provided.

The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.

3.4.2. *Combined advanced therapy medicinal products as defined in Article 2(1)(d) of Regulation (EC) No 1394/2007*

For the cellular or tissue part of the combined advanced therapy medicinal product, the specific requirements for somatic cell therapy medicinal products and tissue engineered products set out in section 3.3 shall apply and, in the case of genetically modified cells, the specific requirements for gene therapy medicinal products set out in section 3.2 shall apply.

The medical device or the active implantable medical device may be an integral part of the active substance.

Where the medical device or active implantable medical device is combined with the cells at the time of the manufacture or application or administration of the finished products, they shall be considered as an integral part of the finished product.

Information related to the medical device or the active implantable medical device (which is an integral part of the active substance or of the finished product) which is relevant for the evaluation of the combined advanced therapy medicinal product shall be provided. This information shall include:

(a) information on the choice and intended function of the medical device or implantable medical device and demonstration of compatibility of the device with other components of the product;

(b) evidence of conformity of the medical device part with the essential requirements laid down in Annex I to Council Directive 93/42/EEC, or of conformity of the active implantable device part with the essential requirements laid down in Annex 1 to Council Directive 90/385/EEC;

(c) where applicable, evidence of compliance of the medical device or implantable medical device with the BSE/TSE requirements laid down in Commission Directive 2003/32/EC;

(d) where available, the results of any assessment of the medical device part or the active implantable medical device part by a notified body in accordance with Directive 93/42/EEC or Directive 90/385/EEC.

The notified body which has carried out the assessment referred to in point (d) of this section shall make available on request of the competent authority assessing the application, any information related to the results of the assessment in accordance with Directive 93/42/EEC or Directive 90/385/EEC. This may include information and documents contained in the conformity assessment application concerned, where necessary for the evaluation of the combined advanced therapy medicinal product as a whole.

4. SPECIFIC REQUIREMENTS REGARDING MODULE

4.1. **Specific requirements for all advanced therapy medicinal products**

The requirements of Part I, Module 4 of this Schedule on the pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of advanced therapy medicinal products. The technical requirements in sections 4.1, 4.2 and 4.3 below explain how the requirements in Part I of this Schedule apply to advanced therapy medicinal products. Where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.

The rationale for the non-clinical development and the criteria used to choose the relevant species and models (*in vitro* and *in vivo*) shall be discussed and justified in the non-clinical overview. The chosen animal model(s) may include immuno-compromised, knockout, humanised or transgenic animals. The use of homologous models (e.g. mouse cells analysed in mice) or disease mimicking models shall be considered, especially for immunogenicity and immunotoxicity studies.

In addition to the requirements of Part I, the safety, suitability and biocompatibility of all structural components (such as matrices, scaffolds and devices) and any additional substances (such as cellular products, biomolecules, biomaterials, and chemical substances), which are present in the finished product, shall be provided. Their physical, mechanical, chemical and biological properties shall be taken into account.

4.2. **Specific requirements for gene therapy medicinal products**

In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.

4.2.1. *Pharmacology*

(a) *In vitro* and *in vivo* studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic "proof of concept" studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.

(b) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of functionality and activity in target cells and tissues shall be provided.

4.2.2. *Pharmacokinetics*

(a) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.

(b) Investigations of shedding and risk of transmission to third parties shall be provided with the environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.

4.2.3. *Toxicology*

(a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the *in vivo* effect of expressed nucleic acid sequence-related products which are not intended for the physiological function shall be evaluated.

(b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.

(c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.

(d) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.

(e) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant *in vivo/in vitro* models.

(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly justified in the application on the basis of the type of product concerned.

(g) *Additional toxicity studies*

— Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be performed, if biodistribution data indicate a risk for germline transmission.

— Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.

4.3. **Specific requirements for somatic cell therapy medicinal products and tissue engineered products**

4.3.1. *Pharmacology*

(a) The primary pharmacological studies shall be adequate to demonstrate the proof of concept. The interaction of the cell-based products with the surrounding tissue shall be studied.

(b) The amount of product needed to achieve the desired effect/the effective dose, and, depending on the type of product, the frequency of dosing shall be determined.

(c) Secondary pharmacological studies shall be taken into account to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product, of the tissue

engineered product or of additional substances, as biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.

4.3.2. *Pharmacokinetics*

(a) Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion shall not be required. However, parameters such as viability, longevity, distribution, growth, differentiation and migration shall be investigated, unless otherwise duly justified in the application on the basis of the type of product concerned.

(b) For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and amount of expression of these molecules shall be studied.

4.3.3. *Toxicology*

(a) The toxicity of the finished product shall be assessed. Individual testing of active substance(s), excipients additional substances and any process-related impurities shall be taken into consideration.

(b) The duration of observations may be longer than in standard toxicity studies and the anticipated lifespan of the medicinal product, together with its pharmacodynamic and pharmacokinetic profile, shall be taken into consideration. A justification of the duration shall be provided.

(c) Conventional carcinogenicity and genotoxicity studies shall not be required, except with regard to the tumourigenic potential of the product.

(d) Potential immunogenic and immunotoxic effects shall be studied.

(e) In the case of cell-based products containing animal cells, the associated specific safety concerns such as transmission to humans of xenogeneic pathogens shall be addressed.

5. SPECIFIC REQUIREMENTS REGARDING MODULE 5

5.1. **Specific requirements for all advanced therapy medicinal products**

5.1.1. The specific requirements in this section of Part IV are additional requirements to those set in Module 5 in Part I of this Schedule.

5.1.2. Where the clinical application of advanced therapy medicinal products requires specific concomitant therapy and involve surgical procedures, the therapeutic procedure as a whole shall be investigated and described. Information on the standardisation and optimisation of those procedures during clinical development shall be provided.

Where medical devices used during the surgical procedures for application, implantation or administration of the advanced therapy medicinal product may have an impact on the efficacy or safety of the advanced therapy product, information on these devices shall be provided.

Specific expertise required to carry out the application, implantation, administration or follow-up activities shall be defined. Where necessary, the training plan of health care professionals on the use, application, implantation or administration procedures of these products shall be provided.

5.1.3. Given that, due to the nature of advanced therapy medicinal products, their manufacturing process may change during clinical development, additional studies to demonstrate comparability may be required.

5.1.4. During clinical development, risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk shall be addressed.

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5.1.5. Dose selection and schedule of use shall be defined by dose-finding studies.

5.1.6. The efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions, evidence of long-term efficacy may be required. The strategy to evaluate long-term efficacy shall be provided.

5.1.7. A strategy for the long-term follow-up of safety and efficacy shall be included in the risk management plan.

5.1.8. For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed for and performed on the combined product as a whole.

5.2. **Specific requirements for gene therapy medicinal products**

5.2.1. *Human pharmacokinetic studies*

Human pharmacokinetic studies shall include the following aspects:

(a) shedding studies to address the excretion of the gene therapy medicinal products;

(b) biodistribution studies;

(c) pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).

5.2.2. *Human pharmacodynamic studies*

Human pharmacodynamic studies shall address the expression and function of the nucleic acid sequence following administration of the gene therapy medicinal product.

5.2.3. *Safety studies*

Safety studies shall address the following aspects:

(a) emergence of replication competent vector;

(b) emergence of new strains;

(c) reassortment of existing genomic sequences;

(d) neoplastic proliferation due to insertional mutagenicity.

5.3. **Specific requirements for somatic cell therapy medicinal products**

5.3.1. *Somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s)*

For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of those molecules shall be addressed, if feasible.

5.3.2. *Biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components*

The biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components shall be addressed during the clinical development.

5.3.3. *Safety studies*

Safety studies shall address the following aspects:

(a) distribution and engrafting following administration;

(b) ectopic engraftment;

(c) oncogenic transformation and cell/tissue lineage fidelity.

5.4. **Specific requirements for tissue engineered products**

5.4.1. *Pharmacokinetic studies*

Where conventional pharmacokinetic studies are not relevant for tissue engineered products, the biodistribution, persistence and degradation of the tissue engineered product components shall be addressed during the clinical development.

5.4.2. *Pharmacodynamic studies*

Pharmacodynamic studies shall be designed and tailored to the specificities of tissue engineered products. The evidence for the “proof of concept” and the kinetics of the product to obtain the intended regeneration, repairing or replacement shall be provided. Suitable pharmacodynamic markers, related to the intended function(s) and structure shall be taken into account.

5.4.3. *Safety studies*

Section 5.3.3 shall apply.”.

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