Annex-1

PARTICULARS AND DOCUMENTS TO BE SUBMITTED AT THE MARKETING AUTHORIZATION APPLICATION FOR MEDICINAL PRODUCTS FOR HUMAN USE

Introduction and general principles

The particulars and documents accompanying an application for marketing authorization pursuant to the provisions of this Regulation, shall be presented to the Agency in accordance with the requirements set out in this Annex. While preparing the application dossier, the Common Technical Document (CTD) Guideline published by the Agency shall be followed.

(2) The particulars and documents shall be presented as five modules:

Module 1 Administrative Data

Module 2 Quality Information, Pre-clinical and Clinical Summaries,

Module 3 Chemical, Pharmaceutical and Biological Information,

Module 4 Pre-clinical Reports,

Module 5 Clinical Study Reports.

These five Modules shall be presented in full compliance with the format, content and numbering system detailed in the CTD Guideline published by the Agency.

(3) Submission of the CTD to the Agency is applicable irrespective of whether it is a full or abbreviated application for all type of marketing authorisation applications, and it is also applicable for all types of products including new chemical entities, radiopharmaceuticals, human medicinal products obtained from human blood or plasma, vaccines and herbal medicinal products.

(4) In assembling the dossier for application for marketing authorization, applicants shall also take into account the scientific guidelines on quality, safety and efficacy and other legislation published by the Agency, pertaining to medicinal products for human use.

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

(6) The manufacturing process shall comply with the requirements of the Regulation on the Manufacturing Plants of Medicinal Products for Human Use, and with the principles set forth in the guidelines prepared on the basis of this Regulation.

(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 for human use and/or completed trials concerning therapeutic indications not covered by the application.

(8) All clinical trials conducted in Turkey, must fully comply with the requirements of the Regulation on Clinical Trials of Pharmaceuticals and Biological Products. During the assessment of an application, clinical trials, conducted outside Turkey, which relate to medicinal products for human use intended to be used in Turkey, shall be designed, implemented and reported on the basis of good clinical practice and ethical principles which have been set forth in accordance with the principles specified in the relevant Regulation.

(9) Pre-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions specified in the Regulation on Good Laboratory Practice Principles and the

Harmonisation of Test Units, Inspection of Good Laboratory Practice and the Control of the Studies published on the Official Gazette dated 9/3/2020, with no. 27516.

(10) All tests performed on animals for experimental and other scientific purposes are carried out within the framework of legal regulations regarding the protection of animals.

(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 Agency. After marketing authorization has been granted, any change to the data in the dossier shall be submitted to the Agency, in accordance with the provisions of the relevant guidelines and, if relevant, pharmacovigilance implementations.

This Annex has been divided into three different parts:

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

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

Part III deals with ‘Particular application requirements’ for biological medicinal products (Plasma Master File, PMF); (Vaccine Antigen Master File, VAMF)], radio-pharmaceuticals, herbal medicinal products and allergen products.

PART I

STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS

1. MODULE 1: ADMINISTRATIVE INFORMATION

1.1. Table of contents

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

1.2. Application form

The applicant shall submit diploma or its notarised copy showing that applicant may practice one of the professions specified in article 7 of this Regulation, or a graduation certificate from the Higher Education Council; certified document indicating that the applicant is authorised to submit an application; in the event of the applicant being a legal entity, the original version or a copy of the commercial registry gazette indicating the relevant partners, duties and titles of the persons responsible.

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

The applicant shall identify the type of application.

Annexed to the administrative data shall be other documents of the manufacturing site, as defined in the Regulation Regarding the Manufacturing Plants of Medicinal Products for

Human Use, together with a list of countries in which marketing authorisation has been submitted, copies of certified product certificates granted by the other country or countries where the product has been placed on market and the summaries of product characteristics.

As outlined in the application form, the applicants shall provide, details of the medicinal product for human use subject of the application, the proposed marketing authorization holder and information on manufacturing site for all manufacturing steps and information on issues such as the product being in the pediatric 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 10 of this Regulation.

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 the provisions of the relevant legislation on the labelling and package leaflet.

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 for human use concerned.

1.4. Information About the Experts

In accordance with Article 11 of the Regulation, 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, pre-clinical documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product for human use 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 pre-clinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorisation application dossier. A declaration signed by the experts together with brief information on their educational background, training and occupational experience shall be presented in Module 1 The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.

1.5. Specific Requirements for Different Types of Applications

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

1.6. Environmental Risk Assessment

Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the environment due to the use and/or disposal of the medicinal product for human use and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products for human use containing

or consisting of GMOs (Genetically Modified Organisms) shall be assessed in accordance with the relevant legislation of the Ministry of Agriculture and Forestry.

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

In the presentation of the information, the relevant legislation of the Ministry of Agriculture and Forestry and any guidelines published in relation to this legislation, shall be taken into consideration during the submission of the documents.

The documents to be submitted consist of:

- Introduction,

- any consent of the competent authority pertaining to the deliberate release into the environment of the GMOs for research and development purposes according to the relevant legislation,

- the detection and identification methods of GMOs in accordance with the relevant legislation, GMO codes, plus any additional information on the GMOs or the product of relevance to evaluating of the environmental risk,

- an environmental risk assessment report prepared on the basis of relevant legislation,

- taking into account the above information and the environmental risk assessment report, a conclusion report 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 statement with a dated signature of the expert, information on the expert's educational, training and occupational experience, and the expert's relationship with the applicant, shall be included in the report submitted.

2. MODULE 2: SUMMARIES

This Module aims to summarize the chemical, pharmaceutical and biological data, pre-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.

Critical points shall be addressed and analyzed. Factual summaries including tabular formats shall be provided. Summaries in tabular format and other information shall provide cross-references to the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 (pre-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 CTD Guideline.

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 human use 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 emphasized 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. Preclinical Overview

An integrated and critical assessment of the preclinical *in vitro* evaluation of the medicinal product for human use in animals 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 preclinical studies and the medicinal product for human use to be marketed shall be discussed.

For biological medicinal products, comparability of material used in preclinical 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 for human use, as demonstrated by the preclinical studies shall be defined and the implications of the findings for the safety of the medicinal product for human use 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 for human use, including critical study design, decisions and assessments related to and performance of the studies shall be provided.

A brief overview of the clinical findings, as well as the 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. Summary of Preclinical Studies

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

- Introduction
- Pharmacology summary
- Pharmacology tabulated summary
- Pharmaco-kinetics summary

- Pharmaco-kinetics tabulated summary
- Toxicology summary
- Toxicology tabulated summary

2.7. Clinical Summary

A detailed, factual summary of the clinical information on the medicinal product for human use 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 studies 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 FOR HUMAN USE CONTAINING CHEMICAL OR BIOLOGICAL ACTIVE SUBSTANCES

3.1. Format and Presentation

The general outline of Module 3 is as follows:

A) TABLE OF CONTENTS

B) BODY OF DATA

1) Active substance

a) General Information

- Nomenclature
- Structure
- General Properties

b) Manufacture

- Manufacturing site
- Description of manufacturing process and process controls
- Control of materials
- Controls of critical steps and intermediates
- Process validation or evaluation
- Manufacturing process development

c) Charactherisation

- Elucidation of structure and other characteristics
- Impurities

ç) Control of active substance(s)

- Specifications
- Analytical procedures
- Validation of analytical procedures
- Batch analyses
- Justification of specifications

d) Reference standards or materials

e) Immediate packaging (container closure system)

f) Stability (in line with the guideline on stability tests)
-Stability summary and conclusions
- Post-approval stability protocol and stability commitment
- Stability data
2) Finished product
a) Definition and composition of medicinal products for human use
b) Pharmaceutical development
- Components of the medicinal product for human use
• Active substance(s)
• Excipient(s)
- Medicinal product for human use
• Formulation development
• Overages (Excess) dose
• Physicochemical and biological properties
- Manufacturing process development
- Immediate packaging (container closure system)
- Microbiological attributes
- Compatibility
c) Manufacture
- Manufacturing site(s)
- Batch formula
- Description of manufacturing process and process controls
- Controls of critical steps and intermediates
- Process validation or evaluation
ç) Control of excipient(s)
- Specifications
- Analytical procedures
- Validation of analytical procedures
- Justification of specifications
- Excipients of human or animal origin
- Novel excipients
d) Control of the finished product
- Specifications
- Analytical procedures
- Validation of analytical procedures
- Batch analyses
- Characterisation of impurities
- Justification of specification(s)
e) Reference standards or materials
f) Immediate packaging (container closure system)
g) Stability (in line with the guideline on stability tests)
- Stability summary and conclusions
- Post-approval stability protocol and stability commitment
- Stability data

3) Appendices

- Manufacturing site and equipment (only for biological medicinal products)
- Adventitious agents safety evaluation
- Excipient(s)

4) Other Additional Information

- Process validation scheme for the medicinal product
- Medical device (if used)
- Certificate(s) of suitability to pharmacopoeia, of the active substance(s)
- Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (TSE procedure)

C) LITERATURE REFERENCES

3.2. Contents: Basic Principles and Requirements

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.

Information dealing with active substance(s) with finished product shall be provided, respectively.

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.

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 Agency. All test methods 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 pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).

The monographs of the Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in the monographs. In respect of other substances, observance with national pharmacopoeia shall be required. However, where a material in the pharmacopoeia 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 the specifications contained in the pharmacopoeia might be insufficient to ensure the quality of the substance, the Agency may request more appropriate specifications from the marketing authorization holder. The Agency shall inform the authorities responsible for the pharmacopoeia in question. The applicant 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 contained in the pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapter(s).

In case where described starting and raw materials, active substances or excipients are not described in the pharmacopoeia compliance with the pharmacopoeia of a third country can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical methods contained in the monograph and by a translation where appropriate.

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 ensure in writing to the applicant that no changes have been made in the manufacturing process since the issuance of the certificate of suitability by the EDQM.

For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the;

(a) detailed description of the manufacturing process,

(b) quality control of the manufacturing process and,

(c) process validation of the manufacturing process,

to be supplied in a separate document directly to the Agency by the manufacturer of the active substance as an Active Substance Master File.

In this case, however, the manufacturer provides the applicant with all the data that may be necessary for him to take responsibility for the medicinal product.

The manufacturer shall confirm in writing to the applicant that he will ensure batch-to-batch consistency and not modify the manufacturing process and specifications without informing in advance the applicant. Documents and particulars supporting the application for such a change shall be supplied to the Agency. Documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.

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.

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/communiques as well as in relevant general monograph and general chapter of the pharmacopoeia, shall be provided.

Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product for human use, shall be described in adequate details.

For medical device part of medicinal products for human use with medical devices considered within the scope of this Regulation pursuant to Article 1 of the Regulation on Medical Devices published in the Official Gazette dated 2/6/2021 and numbered 31499, the relevant general safety and performance requirements stated in the Annex 1 of the Regulation on Medical Devices shall apply. An EU Declaration of Conformity or EC Certificate of Conformity is submitted for assessment of compliance with the requirements. If the results of the conformity assessment cannot be submitted and the device is used separately, in case a notified body is required for conformity assessment pursuant to the Medical Device Regulation, for the device type in question, the Agency shall request the applicant to submit an opinion issued by a notified body designated in accordance with the Medical Device Regulation on the conformity of the device part with the relevant requirements.

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(s) shall be provided, including recommended International Non-proprietary Name (INN), pharmacopoeia name if relevant and chemical name(s).

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

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

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

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

A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

The following shall be considered as biological medicinal products:

a) Immunological medicinal products for human use and blood products as defined respectively in paragraphs (o) and (p) of the first paragraph of Article 4 of this Regulation,

b) Advanced therapy medicinal products,

c) Medicinal products for human use developed through one of the following biotechnological processes:

- Recombinant DNA technology,
- Controlled expression of genes encoding biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells,
- Hybridoma and monoclonal antibody methods.

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

3.2.1.2. Manufacturing process of the active substance(s)

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

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

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

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

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

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

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

When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for the production and beyond.

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

If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated. Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed. If this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.

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

The manufacturing facilities and equipment shall be described.

ç) 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.

d) 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.

e) A description and discussion of the significant changes made to the manufacturing process during development and/or manufacturing site of the active substance(s) shall be provided.

3.2.1.3. Characterization of the active substance (s)

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

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

3.2.1.4. Control of active substance(s)

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

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

3.2.1.5. Reference standards or materials

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

3.2.1.6. Container and closure system of the active substance(s)

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

3.2.1.7. Stability of the active substance(s)

In line with the guideline on stability tests:

a) The types of studies conducted, protocols used, and the results of the studies shall be summarised.

b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format.

c) The post marketing authorization stability protocol and stability commitment shall be provided.

3.2.2. Finished medicinal product

3.2.2.1. Description and composition of the finished medicinal product

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

- 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 of the medicinal product for human use, 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.

Within the scope of the usual terminology, to be used in describing the structure of medicinal products for human use;

- in respect of substances, reference shall be made to the pharmacopoeia concerned, with the main title at the head of the monograph in question.

- in respect of other substances, the common name, or failing this, 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 the Turkish Food Codex Regulation on Specifications of Food Additives published in the Official Gazette dated 3/4/2017 and numbered 30027 shall be used. In addition, it must meet the criteria set out in the same Regulation. 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 substance(s) 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, 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.

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, immediate packaging (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 section 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 for human use performance and medicinal product quality shall be identified and described. Additional supportive data, where appropriate, shall be referenced to the relevant sections of Module 4 (Preclinical Study Reports) and Module 5 (Clinical Study Reports) of the marketing authorization 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 the excipient(s), 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.

ç) Any overage(s) in the formulation(s) shall be warranted.

d) As far as the physiochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.

e) The selection and optimization 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.

f) The suitability of the immediate packaging (container/closure system) used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product for human use and container may need to be considered.

g) 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 pharmacopoeia.

ğ) 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 authorization pursuant to the first paragraph of Article 8 this Regulation, shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed and 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 a change in the constituents,

- in case of continuous manufacture, specification of full details concerning the 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 medicinal product for human use,

- for sterile medicinal products for human use, 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 excipient(s)

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.

In respect of colouring matter, designation by the 'E' code assigned to them in the Turkish Food Codex Regulation on Specifications of Food Additives shall be used. In addition, it shall meet the criteria set out in the same Regulation.

b) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and duly validated.

c) Specific attention shall be paid to excipients of human or animal origin.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product for human use 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.

ç) Novel excipient(s):

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 pre-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 Agency.

Additional information on toxicity studies of new excipient(s)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 for human use 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(s).

3.2.2.7. Immediate packaging (container and closure) system of the finished medicinal product

A description of the container and the closure system 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 product

In line with the guideline on stability tests:

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 marketing authorization stability protocol and stability commitment shall be provided.

4. MODULE 4: PRE-CLINICAL REPORTS

4.1. Format and Presentation

The general outline of Module 4 is as follows:

A - TABLE OF CONTENTS

B -STUDY REPORTS

1- Pharmacology

- Primary Pharmaco-dynamics

- Secondary Pharmaco-dynamics
- Safety pharmacology
- Pharmaco-dynamic interactions

2 - Pharmaco-kinetics

- Analytical Methods and Validation Reports
- Absorption
- Distribution
- Metabolism
- Excretion
- Pre-clinical pharmaco-kinetic interactions
- Other Pharmaco-kinetic Studies

3- Toxicology

a) Single-dose toxicity

b) Repeated dose toxicity

c) Genotoxicity

- *In vitro*
- *In vivo* (including supportive toxicokinetic assessments)

ç) Carcinogenicity

- Long-Term studies
- Short- or Medium-Term Studies
- Other studies

d) Reproductive and Developmental Toxicity

- Fertility and early embryonic development
- Embryo/fetal development
- Prenatal and Postnatal Development
- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

e) Local tolerance

4 -Other Toxicity Studies

- Antigenicity
- Immunotoxicity
- Mechanistic studies
- Dependence
- Metabolites
- Impurities
- Other

C - LITERATURE REFERENCES

4.2. Contents: Basic Principles and Requirements

Special attention shall be paid to the following elements:

(1) The pharmacological and toxicological tests must show:

a) The potential toxicity of the medicinal product for human use and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human being should be evaluated in relation to the pathological condition concerned.

b) The pharmacological properties of the medicinal product for human use, shall be presented 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 for human use and medicinal products derived from human blood or plasma, the requirements 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 medicinal product for human use 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 for human use, the toxicology of degradation products must be considered.

4.2.1. Pharmacology

Pharmacology study shall follow two distinct lines of approach:

- Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both *in vivo* and *in vitro* shall be used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action.

- Secondly, the applicant shall investigate the potential undesirable pharmaco-dynamic effects of the substance on physiological functions. These investigations shall be performed at exposures in the anticipated therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.

For the pharmaco-dynamic medicinal product interaction, tests on combinations of active substance(s) 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. Pharmacokinetics

Pharmacokinetics refers to studies that examine the status of the active substance(s) and their metabolites in the organism and covers the absorption, distribution, metabolism (biotransformation) and excretion of these substances.

The study of these different phases may be carried out mainly by means of physical, chemical or possibly biological methods and by observation of the actual pharmacodynamic 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 chemotherapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmacodynamic effects (e.g. numerous diagnostic agents, etc.).

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

All substances with pharmacological activity must be investigated in terms of pharmacokinetics. For new combinations of known substances that have been investigated in accordance with the provisions of this Regulation, pharmacokinetic studies may not be required when justified by toxicity tests and therapeutic trials.

The pharmacokinetic program shall be designed to allow comparison between humans and animals and extrapolation of the information obtained.

4.2.3. Toxicology

a) Single-dose toxicity

Single-dose toxicity test refers to the qualitative and quantitative studies of the toxic reactions that may result from only one application of the active substance(s) in the human medicinal product, in the proportions they are present in the human medicinal product and in the physicochemical condition.

Single-dose toxicity test is carried out in accordance with the relevant guidelines determined by the Agency.

b) Repeated dose toxicity

The purpose of repeated-dose toxicity tests is to reveal the physiological or anatomical and pathological changes resulting from repeated administration of the active substance or combination of active substance under investigation and to determine the connection of these changes with 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 of the test must comply with the relevant guidelines determined by the Agency.

c) Genotoxicity

The aim of studies on mutagenic and clastogenic potential is to reveal the changes that substances can create in the genetics 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. The conduct of these studies is obligatory for any new substance.

ç) Carcinogenicity

Tests to reveal carcinogenic effects shall normally be required:

1. These studies shall be performed for any medicinal product for human use 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 for human use if there is concern about their carcinogenic potential, such as from products of the same class or similar structure or from evidence in repeated dose toxicity studies.

3. Studies with unequivocally genotoxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product for human use is intended to be administered on a chronic basis to humans, a chronic study may be necessary to detect early tumorigenic effects.

d) 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 the 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 for human use under investigation has been administered to the female during pregnancy.

Conduct of these tests must be adequately justified.

Depending on the established indication of the medicinal product for human use, additional studies showing improvements when administered to the neonate may be warranted.

Embryo/fetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Perinatal and postnatal studies shall be conducted in at least one species. If the metabolism of a medicinal product for human use 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.

e) Local tolerance

The purpose of local tolerance studies is to ascertain whether medicinal products for human use (both active substance(s) and excipient(s)) 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 physicochemical actions of the product can be distinguished from toxicological or pharmacodynamic 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 groups.

The design of local tolerance tests (choice of species, duration, frequency, route of administration and 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.

Validated *in vitro* tests may be performed instead of animal studies, provided that the test results are of comparable quality and useful for safety assessment.

For chemicals applied to the skin (e.g. dermal, rectal, vaginal) the sensitizing 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:

A - Table of Contents for Clinical Study Reports

B - Tabular Listing of All Clinical Studies

C - Clinical study reports

1- Reports of Bio-pharmaceutical Studies

- Bioavailability Study Reports
- Comparative Bioavailability and Bioequivalence Study Reports
- *In vitro-In vivo* Correlation Study Reports
- Reports of Bioanalytical and Analytical Methods

2 - Reports of Studies Pertinent to Pharmacokinetics Using Human Bio-materials

- Plasma Protein Binding Study Reports
- Hepatic Metabolism Reports and Interaction Study Reports
- Reports of Studies Using Other Human Bio-materials

3 - Reports of Human Pharmacokinetic Studies

- Healthy Subjects' Pharmacokinetics and Initial Tolerability Study Reports
- Patients' Pharmacokinetics and Initial Tolerability Study Reports
- Intrinsic Factor Pharmacokinetic Study Reports
- Extrinsic Factor Pharmacokinetic Study Reports
- Population Pharmacokinetic Study Reports

4- Reports of Human Pharmacodynamic Studies

- Healthy Subjects' Pharmacodynamic and Pharmacokinetic/Pharmacodynamic Study Reports
- Patients' Pharmacodynamic and Pharmacokinetic/Pharmacodynamic Studies Study Reports

5 - Efficacy and Safety Study Reports

- 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

6- Reports of Post-Marketing Experience

C - Literature References

5.2. Contents: Basic Principles and Requirements

The following are particularly important:

a) Pursuant to subparagraphs (j), (k) and (l) of the first paragraph of the 8th article of this Regulation and the first paragraph of the 9th article, it should allow the formation of a well-founded and scientifically valid opinion showing whether the clinical information to be provided meets the criteria for the registration of the medicinal product for human use. As a result, all positive or negative results of clinical trials must be reported.

b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex. The investigator should have knowledge of the results obtained from pharmacological and toxicological tests. The applicant must therefore provide the investigator's brochure with all known relevant information prior to initiation of the clinical trial and the data necessary to justify the nature, scale and duration of the proposed trial, including chemical, pharmaceutical and biological data, toxicological, pharmacokinetic and pharmacodynamic data in animals, and data from previous clinical studies The complete pharmacological and toxicological reports shall be provided upon 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 authorization holders must arrange for essential clinical trial documents (including case report forms) other than the volunteer's medical files.

- Data holders must keep the data for at least 14 (fourteen) years pursuant to the completion or discontinuation of the trial.

- Relevant documents shall be kept for at least five years pursuant to the completion or discontinuation of the trial.

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

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

The sponsor or data holders shall retain all other documentation pertaining to the trial as long as the product is authorized. 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 pursuant to the medicinal product for human use is no longer authorized.

The applicant makes the necessary additional arrangements to ensure the archiving of documents and the implementation of the guidelines to be prepared based on this Regulation, in accordance with the provisions of the Regulation on Clinical Trials of Pharmaceuticals and Biological Products.

Any change of ownership of the clinical data shall be documented.

All documents are submitted if requested by the Agency.

ç) The documents belonging to each clinical study must be at a level sufficient to make an objective decision:

-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 the investigator(s) and each investigator shall give his name, address, appointments, curriculum vitae, and the documents indication the distribution of the clinical duties, specify where the trial was carried out, and assemble the information in respect of each patient individually (including case report forms on each volunteer;

- Final report signed by the investigator and for multi-center trials, by all the investigators or the coordinating (principal) investigator,

d) It shall be sufficient to submit the final report of the clinical trial during the application. However, in case the abovementioned information and documents are requested, they shall be kept ready to be submitted to the Agency.

In his conclusions regarding the experimental evidence, the investigator provides an opinion on the safety, tolerance, and efficacy of the product in normal use, as well as useful information on indications and contraindications, dosage and mean duration of treatment, special precautions to be taken in treatment, and clinical symptoms in overdose. In reporting the results of a multi-center study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product for human use on behalf of all centers.

e) The clinical observations of each trial are summarized by stating the following:

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 any treatment
- received any placebo
- received another medicinal product of known effect
- received treatment other than therapy using medicinal products

5) 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) Efficacy parameters or evaluation criteria and the results obtained according to 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.

f) 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 for human use;

2) Any interactions that have been observed with other medicinal products for human use 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,

g) Documents relating to a new combination of medicinal substances must be the same as those required for new medicinal products and must prove the safety and efficacy of the combination.

ğ) The reasons for the partially or completely extracted data should be explained. If unexpected results occur during the investigation, further preclinical toxicological and pharmacological tests are performed and reviewed.

h) If the medicinal product for human use 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 Biopharmaceutical Studies

Bioavailability study reports, comparative bioavailability, bioequivalence study reports, *in vitro* and *in vivo* correlation study reports, bioanalytical and analytical methods are provided.

In addition, evaluations regarding bioavailability are carried out when necessary to demonstrate the bioequivalence of medicinal products for human use specified in the first paragraph of Article 9 of this Regulation.

5.2.2. Reports of Pharmacokinetic Studies using Human Bio-materials

Human biomaterials in this annex refer to proteins, cells, tissues and related substances of human origin that are used *in vitro* or *ex vivo* to determine the pharmacokinetic properties of a medicine substance.

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

5.2.3. Reports of Human Pharmacokinetic Studies

a) The following pharmacokinetic properties are defined

- absorption (rate and degree),
- distribution
- metabolism
- excretion

Features of clinical importance are identified, including the meaning of kinetic data for dosing regimens for patients particularly at risk, and the differences between human and preclinical animal species.

In addition to standard multiple-sample pharmacokinetic studies, population pharmacokinetic 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-pharmacokinetic response relationship. Reports of pharmacokinetic and initial tolerability studies in healthy subjects and patients, reports of pharmacokinetic studies to assess effects of intrinsic and extrinsic factors and reports of population pharmacokinetic studies shall be provided.

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

Pharmacokinetic interactions between the active substance(s) and other medicinal products for human use or substances shall be investigated.

5.2.4. Reports of Human Pharmacodynamic Studies

a) The pharmacodynamic effect associated with efficacy includes the following information:

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

The pharmacodynamic effect not related to efficacy shall be described.

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

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

Pharmacodynamic interactions between the active substance(s) and other medicinal products for human use or substances shall be investigated.

5.2.5 - Efficacy and Safety Study Reports

5.2.5.1. Study reports of controlled clinical studies pertinent to the claimed indication

In general, clinical trials shall be conducted as “controlled clinical trials” if possible. These studies shall be randomized, in comparison with placebo and an established medicinal product for human use of proven therapeutic value, where possible. Other study designs are justified. Treatments of control groups differ from case to case, ethical considerations, and therapeutic area. Thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product for human use with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

(1) Whenever possible, and especially in studies where the effect of the product cannot be measured objectively, measures to prevent subjective biases, including randomization methods and blinding methods, should be taken.

(2) The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomization, shall be documented. The 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 relevant guidelines, 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 results of the safety assessments regarding the possible uses of the medicinal product for human use are disclosed.

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 must be submitted.

5.2.6. Reports of post-marketing experience

If the medicinal product for human use is already authorized in third countries, the information shall be given in respect of adverse reactions of the medicinal product for human

use concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.

5.2.7. Case Report Forms and Individual Patient Lists

When submitted in accordance with the relevant Guideline, 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.

SECTION II

SPECIFIC MARKETING AUTHORIZATION DOSSIERS AND REQUIREMENTS

Some medicinal products for human use contain specific features that require adaptation of all the requirements of the registration application dossier set out in Part I of this Annex. Applicants shall present the dossier upon consideration of these particular situations.

1. ESTABLISHED MEDICAL USE

As specified in the second sub-clause of sub-clause (a) of the first paragraph of Article 9 of this Regulation, the following issues are valid for medicinal products for human use containing active substance(s) with "established medical use", known efficacy and acceptable safety level.

The applicant submits Modules 1, 2 and 3 described in Part I of this annex.

A detailed scientific bibliography is provided for modules 4 and 5, which covers preclinical and clinical features.

The following specific rules shall apply in order to demonstrate the established medicinal use:

a) Factors which have to be taken into account in order to establish a established medicinal use of constituents of medicinal products for human use 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 an established medicinal use of a constituent of a medicinal product for human use must not be less than 10 (ten) years from the first systematic and documented use of that substance as a medicinal product.

b) Documentation submitted by the applicant should cover all aspects of safety or efficacy assessments. Relevant literature summaries are found or cited, taking into account pre- and post-marketing studies and the published scientific literature on experiences presented as epidemiological studies, particularly comparative epidemiological studies. All positive and negative documents must be submitted. With respect to the provisions on “established medicinal use”, it is in particular necessary to clarify that not just data related to tests and trials but also other evidences are indicated as “bibliographic reference” (post-marketing studies, epidemiological studies, etc.). If the use of such sources of information in the application is appropriately justified, it can be accepted as valid evidence for the safety and efficacy of the product.

c) Particular attention should be given to missing information and justification should be provided as to why an acceptable level of safety or efficacy can be demonstrated despite the lack of studies.

ç) Preclinical or clinical overview explains the link between the information of a medicinal product for human use other than the medicinal product intended to be marketed, and the product applied for. A judgement must be made whether the medical product for human use considered can be regarded as similar to the product for which a marketing authorization application has been submitted, in spite of the existing differences.

d) Post-marketing experience in medicinal products for human use containing the same components is particularly important and applicants should pay special attention to this issue.

2. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS FOR HUMAN USE

a) Applications based on the first sub-clause of the first subparagraph (a) of the first paragraph of Article 9 of this Regulation (basically similar products) contains the data specified in Modules 1, 2 and 3 and Part I of this annex, provided that the application made by the marketing authorization holder of the reference medicinal product for human use to the applicant is allowed to make reference to the information contained in Modules 4 and 5.

b) Applications made based on the fourth sub-clause (a) of the first paragraph of Article 9 of this Regulation (basically similar products, eg generic medicinal products) include data described in Modules 1, 2 and 3 of the section of this Annex, in addition to data showing bioavailability and bioequivalence with the reference medicinal product, provided that the reference medicinal product for human use is not a biological medicinal product (see Chapter II, 4 Biosimilar medicinal products)

In particular, the following should be noted in the preclinical/clinical overview/summaries of these products:

- The grounds for claiming essential similarity,

- A summary of impurities present in batches of the active substance(s) proposed to be used in the product to be marketed and finished medicinal products (and where relevant, decomposition products arising in products during storage) and an evaluation of these impurities,

- Evaluation of bioequivalence studies or the reasons why the studies were not carried out in accordance with the provisions of the applicable Bioavailability and Bioequivalence legislation,

- It is acceptable to update the published literature related to the active substance(s) of the medicinal product for human use subject to the application, and to reference the articles in the 'peer review' journals for this purpose,

- Any claim that is unknown or inferred from the characteristics of the medicinal product for human use or treatment group in the summary of product characteristics should be discussed in the preclinical/clinical overview/summaries and supported by published literature or additional studies,

- Where possible, the applicant provides additional evidence that the safety and efficacy properties of different salts, esters or derivatives of an active substance(s) which he claims are essentially similar to the existing active substance(s) are equivalent.

3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS

Where the active substance(s) of an essentially similar medicinal product for human use contains the same therapeutic effect as the original authorized product associated with a different salt/ester complex/derivative, evidence proving that there is no change in the pharmacokinetics, pharmacodynamics and/or in toxicity which lead to the modification of the safety/efficacy profile shall be demonstrated. In case of failure to present such evidence, this association shall be considered as a new active substance.

Where a medicinal product for human use 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. BIOSIMILAR MEDICINAL PRODUCTS

For biological medicinal products, the requirements specified in subparagraph (c) of the first paragraph of Article 9 of this Regulation must be fulfilled. If the information required in the case of essentially similar products (bio-similar medical products) 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.

If a separate application for a biological medicinal product is made by a separate applicant for a biological medicinal product that references the reference medicinal product authorized in Turkey and is defined in paragraph 3.2. of Part I of this Annex, the following applies.

- The information to be provided will not be limited to the information requested in Modules 1, 2 and 3 (pharmaceutical, chemical and biological data) and is supported by bioavailability and bioequivalence data. The type and amount of additional information (toxicological and other preclinical and appropriate clinical data) is determined on a case-by-case basis in accordance with relevant scientific guidelines.

- Due to the diversity of biological medicinal products, defined studies envisaged in Modules 4 and 5 are requested by the Agency, taking into account the specific characteristics of each biological medicinal product.

The general principles to be applied are specified in the relevant guide, which takes into account the characteristics of the relevant biological medicinal product. If the authorized reference medicinal product has more than one indication, the efficacy and safety of the biological medicinal product claimed to be similar must be proven or, if necessary, demonstrated separately for each indication.

5. FIXED COMBINATION MEDICINAL PRODUCTS

Applications made based on subparagraphs (ç) and (d) of the first paragraph of Article 9 of this Regulation are valid for new medicinal products for human use consisting of at least two active substances, which were not previously authorized as fixed combination medicinal products for human use.

The complete dossier (Modules 1 to 5) shall be submitted for such fixed component medicinal product for human use applications. Where applicable, information on production sites and incidental substances and safety assessment shall be provided.

6. REQUIRED DOCUMENTS FOR MARKETING AUTHORIZATION APPLICATIONS IN EXCEPTIONAL SITUATIONS

As stated in Article 36 of this Regulation;

- The therapeutic indications for the medicinal product for human use are too rare to expect the applicant to provide comprehensive evidence, or

- Inability to provide detailed information in the light of available scientific data, or

- The Agency may grant marketing authorization to a medicinal product for human use subject to certain conditions, when the applicant proves objectively and verifiablely that it cannot provide comprehensive data on efficacy and safety under normal use conditions, due to the fact that collecting such information is contrary to the generally accepted medical ethical principles.

These obligations may include the following:

- The applicant will carry out the scheduled studies determined by the Agency within a certain period of time, the results of which will form the basis for the re-evaluation of the benefit/risk balance.

- The medicinal product for human use must be available only by prescription and, in certain cases, it must be administered under strict medical supervision, possibly in a hospital and by a person authorized for radiopharmaceuticals.

- Instructions for use and other medical information guides should be prepared in a way that draws the attention of medical personnel to the lack of some aspects of the properties of the medicinal product for human use.

7. MIXED MARKETING AUTHORIZATION APPLICATIONS

Mixed marketing authorization applications refer to registration application files, which are a combination of limited clinical or preclinical study reports made by the applicant in Module 4 or 5 of this Regulation, and contain bibliographic references. Other modules will follow the pattern outlined in Part I of this annex. The Agency accepts the form submitted by the applicant by evaluating it on a per-application basis.

PART III

PARTICULAR MEDICINAL PRODUCTS

This Chapter sets out the specific requirements regarding the nature of identified medicinal products for human use.

1. BIOLOGICAL MEDICINAL PRODUCTS

1.1. Plasma-Derived Medicinal Products For Human Use

For medicinal products for human use 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 obtained from human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.

a) Principles

For the purposes of this Annex:

- They are stand-alone documents submitted separately from the PMF authorization dossier and are the information and documents containing detailed information about the sub/main fractions of a for human use medicinal product or the medical device specified in the Medical Device Regulation and the whole human plasma used as a starting material or raw material for the production of active substance(s) and excipient(s).

- Centers or institutions where human plasma is fractionated/processed maintain and update the information specified in the PMF.

- PMF is given to the Agency by the applicant or the marketing authorization holder. In cases where the PMF holder is different from the applicant or marketing authorization holder, the PMF must be given to the applicant or marketing authorization holder to be submitted to the Agency. In any case, the applicant or the marketing authorization holder assumes responsibility for the medicinal product for human use.

- While making a decision on the application for an imported product, the Agency seeks to have the certificate of the competent health authority of the country to be imported.

- For the marketing authorization application dossier of a medicinal product for human use containing a component derived from human plasma, reference is made to the PMF of the plasma used as the starting material/raw material.

b) Content

In particular, it contains the following information on plasma used as PMF starting material/raw material in accordance with the provisions of the relevant Regulation on testing of donors or donations:

I. Plasma origin

1.Information on centers or establishments in which blood/plasma collection is carried out, including inspection and approval and epidemiological data on blood transmissible infections,

2. Information on centers or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status,

3. Selection/exclusion criteria for blood/plasma donors,

4. 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.

II. Plasma quality and safety

1. Compliance with Pharmacopoeia monographs,

2. 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,

3. Technical characteristics of bags for blood and plasma collection, including information on anticoagulant solutions used,

4. Conditions of storage and transport of plasma,

5. Procedures for any inventory hold and/or quarantine period,

6. Definition of the plasma pool.

III. System that defines the conditions of interaction and accepted specifications between the place of manufacture or plasma fractionator/processor of medicinal products for human use derived from plasma and, on the other hand, blood plasma collection centers, testing centers or establishments.

In addition, the Plasma Master File contains a list of medicinal products for human use for which the Plasma Master File is valid, including clinical trial products covered by the Regulation on Clinical Trials of Medicines and Biological Products.

c) Evaluation and Certification

- For products that have not been authorized yet, the applicant submits a complete and complete dossier to the Agency, together with a separate PMF, if it is not already available to the Agency.

- The Agency evaluates PMF scientifically and technically.

- The PMF is updated annually by the applicant and the application for variation is evaluated and the applicant is notified of eligibility by the Agency.

- Changes to be made after the approval of the PMF are subject to the provisions of the Regulation on Changes in Medicinal Products for Human Use, which was published in the Official Gazette dated 23/5/2005 and numbered 25823.

- In line with the above-mentioned provisions, the Agency re-evaluates the related medicinal products for human use authorized on the basis of the PMF, taking into account the certification, re-certification and changes of the related PMF.

1.2. Vaccines

By derogation from the provisions of Module 3 on active substance(s) of vaccines, the following requirements shall apply when based on the use of a Vaccine Antigen Master File (VAMF) system:

The marketing authorization application dossier of a vaccine other than the 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 annex:

- VAMF refers to the document submitted separately from the marketing authorization application dossier, containing relevant information on the biological, pharmaceutical and chemical structure of each active substance that is a part of the medicinal product for human use. The stand-alone documentation may also be utilized by the same applicant or marketing authorization holder for one or more monovalent and/or combined vaccines.

- 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 VAMF contains information from the relevant section of Module 3 (active substance) on 'Quality Data' referred to in Part I of this Annex:

Active Substance

1. General information, including information demonstrating compliance with the relevant monograph(s) of the Pharmacopoeia.

2. Information on the production of the active substance: this heading covers the production process, information on starting and raw materials, special precautions regarding TSEs, safety assessment of unexpected agents, and plant and equipment.

3. Characterization 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 new vaccines containing a new vaccine antigen, the applicant submits to the Agency a complete and complete file with the VAMF of each vaccine antigen that is part of the new vaccine. The Agency evaluates each of the Vaccine Antigen Master File from a scientific and technical point of view.

- The provisions of the above paragraph apply to all vaccines consisting of a new combination of vaccine antigens, regardless of whether the vaccine antigens are part of currently authorized vaccines.

- Changes to be made after the approval of the Vaccine Antigen Master File are subject to the provisions of the Regulation on Changes in Medicinal Products for Human Use that have been Authorized or Application for Authorization has been made. The application for variation is evaluated and the applicant is notified of eligibility by the Agency.

- As the second step of the provisions specified in the first, second and third paragraphs above, the Agency approves the VAMF regarding the human medicinal product(s) for which the same Vaccine Antigen Master File is used and evaluates the variation applications regarding it.

2. Radiopharmaceuticals and precursors

2.1. Radio-pharmaceuticals

Within the scope of this section, a complete and complete dossier containing the following information is submitted for applications made in accordance with Article 5 and Article 8 of this Regulation, subparagraph (v) and related articles:

Module 3

a) In radiopharmaceutical kits that will be marked with radioactive substance after being procured from the production site, the part of the formulation intended to bind to or carry the radionuclide is considered as active substance(s). Descriptions of the production methods of radiopharmaceutical kits also include details on the manufacture of the kit and the proposed final processes to obtain the radioactive medicinal product. Required specifications of the radionuclide shall be defined in accordance with the general monograph or special monograph of the pharmacopoeia, where possible. In addition, any compounds essential for the radio-labelling shall also be described. The structure of the radio labelled compound shall also be defined.

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

In the generator, both parent and daughter radionuclides shall be considered active substance(s).

b) Information on the nature of the radionuclide, the definition of the isotope, possible impurities, carrier, use and specific activity shall be provided.

c) Starting materials shall include irradiation materials.

ç) Opinions on chemical/radiochemical purity and its relation with biodistribution shall be provided.

d) Radionuclidic purity, radiochemical purity and specific activity shall be defined.

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

f) The requirement to express the content of active substance(s) in terms of the mass of active entities shall only apply 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.

g) For kits, the specifications of the finished product shall include tests on the performance of products after radio-labeling. Controls for the radiochemical and radionuclidic purity of the radiolabeled compound will be included. Any material essential for radio-labelling shall be identified and assayed.

ğ) Stability information shall be provided for radionuclide generators, kits and radioactively labeled products. Radiopharmaceuticals presented in multiple dose vials shall be documented stability during use.

Module 4

It is envisaged 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 desired property. Therefore, assessments of the efficacy and safety of radiopharmaceuticals consider requirements for medicinal products and radiation dosimetry considerations. Organs/tissues exposed to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognized system by a particular route of administration.

Module 5

Results of clinical trials shall be presented where applicable, otherwise justified in the clinical overview.

2.2. Radiopharmaceutical Precursors for Radioactive Labeling

In the specific case of a radio-pharmaceutical precursor intended solely for radio-labeling purposes, the primary objective shall be to present information that would address the possible consequences of poor radio-labeling efficiency or *in vivo* dissociation of the radio-labeled conjugate (eg., 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 (eg., radiation exposure to hospital staff and to the environment).

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

Module 3

Where applicable, the provisions of Module 3 for the registration of radiopharmaceutical precursors Chapter III, 2.1. It is valid as stated in articles (a) and (ğ).

Module 4

Regarding single-dose and repeated-dose toxicity, the results of studies performed in accordance with the Principles of Good Laboratory Practices, Harmonization of Test Units, Regulation on Good Laboratory Practices and Inspection of Studies shall be provided and verified.

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 the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labeling purposes.

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

3. HERBAL MEDICINAL PRODUCTS

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

Module 3

The provisions of Module 3 also apply to the registration of herbal medicinal products, including compliance with the pharmacopoeial monograph(s). 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 taken into account:

1. Herbal substances and herbal preparations:

The terms related to "herbal substances and preparations" in this annex shall be considered equivalent to the terms of "herbal medicines and herbal medicine preparations" specified in the pharmacopoeia.

With respect to the nomenclature of the herbal substance, the binomial scientific name of the plant (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 (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.

For the purpose of documenting 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.

For the purpose of documenting the section on the manufacturing site of the herbal substance, the name, address and responsibility of each supplier (including toll manufacturing sites) and each proposed site or facility involved in production/collection and testing of the herbal substance shall be provided, where appropriate.

For the purpose of documenting the section on the manufacturing site of the herbal preparation, the name, address and responsibility of each manufacturer (including toll manufacturing site) and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.

For the purpose of describing the manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection. This information includes the geographical source of the herbal medicinal product and the conditions of sowing, harvesting, drying and storage.

For the purpose of describing the manufacturing process and process controls for the herbal preparation, the information shall be provided to adequately describe the manufacturing process of the herbal preparation. This information includes processing, solvents and reagents (reagents), purification steps and standardization.

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 characterization 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-chemical and physicochemical characterization and biological activity if necessary, shall be provided.

Specifications of herbal substance(s) and herbal preparation(s) shall be provided where applicable.

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 preparations 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 pharmacopoeia substances.

The specifications for 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.

4. ALLERGEN PRODUCTS

Within the scope of this section, a complete and complete file containing all the information specified in the applications made pursuant to Article 5 and Article 8 of this Regulation and related articles is submitted.

General principles to be applied for allergen extracts from the allergen group that are in close structural relationship with each other are produced by the same manufacturer, the place of production of the finished product is the same, extraction and the reference allergen product, which is representatively selected among the products with the same production processes, and the allergen extracts from the allergen group that are closely related to each other, produced by the same manufacturer, with the same place of production of the finished product, extraction and the associated allergen product, which refers to a representative selected product among products whose manufacturing processes are exactly the same shall be stated in the guide published by the Agency regarding allergen products.