

General Requirements to the Materials of Registration Dossier (in Format of Common Technical Document)

Module 1: Administrative information

1.1 Table of contents

A comprehensive table of contents of models 1-5 of the dossier submitted for state registration of medicinal product shall be presented.

1.2. Registration form

Name of medicinal product, name of active substance(s), pharmaceutical form, route of administration, strength (dose) and presentation of finished medicinal product including packaging shall be provided in registration form.

Name and location of the applicant shall be indicated together with name and location of manufacturers and manufacturing sites involved in different manufacturing stages (including manufacturer of finished medical product and manufacturer(s) of active substance(s)) and where relevant name and location of importer.

The applicant shall identify the type of medicinal product and indicate what samples (if any) are provided.

Annexed to the administrative data shall be: copy of manufacturing license (if according to manufacturer's country legislation the manufacturing license is available in electronic form only (e.g. USA), the printout with reference to appropriate official site certified by applicant's signature/stamp (if any) should be provided) or other licensing document to manufacture the applied pharmaceutical form in the manufacturer's country and certified copy of the document issued by the State Administration of Ukraine on Medicinal Products confirming the compliance of manufacture of medicinal products with requirements to manufacture of medicinal products in Ukraine (GMP) or applicant's letter of guarantee to submit such document during the specialized expert evaluation; list of countries where the medicinal product has been issued a license, copies of all summaries of product characteristics/instructions for medical use developed and approved according to the national legislation of applicant/manufacturer and list of countries where the applications for registration have been submitted.

As indicated in registration form, the applicant shall submit details of the medicinal product subject of the registration form, justification for submitting application for registration, proposed holder of registration certificate and manufacturer(s), information on medicinal product of limited use status, scientific consultations and pediatric development programs.

1.3. Summary of product characteristics, labelling and instructions for medical use:

1.3.1. Copy of summary of product characteristics/instructions for medical use approved in the manufacturer's/applicant's country or according to the official information for use of medicinal product approved in compliance with the legislation of country of the applicant/manufacturer or

country which regulatory authority follows high quality standards complying with the WHO standards and/or according to the results of clinical trials.

Applicant proposes draft summary of product characteristics drawn up according to the requirements of Annex 22 of the Procedure.

1.3.2. Labelling.

The applicant shall submit the proposed labelling for immediate and outer packaging of finished medicinal product drawn up according to the requirements of Annex 17 of the Procedure as a separate document.

For in bulk product the proposed labelling shall bear data specified by the manufacturer within data management system at manufacturing site according to GMP for intermediate product. This labelling shall be provided in appropriate section of MQC.

1.3.3. Instructions for medical use.

The applicant shall submit draft instruction for medical use (hard or electronic copy) drawn up according to the requirements of Annex 20 of the Procedure.

1.3.4. Summary of product characteristics.

1.4. Information about the independent experts:

Experts must submit summary of their observations on the documents and materials of registration dossier in particular on Modules 3-5 (chemical, pharmaceutical and biological documentation, preclinical and clinical documentation respectively). Summary of independent expert shall highlight critical points related to quality of medicinal product, preclinical studies and clinical trials and contain all data relevant for evaluation.

These requirements shall be met by providing a quality overall summaries, preclinical and clinical overviews given in Module 2 of the registration dossier for medicinal product. The data on education, specialty and experience being signed by the independent experts shall be provided in Module 1.

The experts shall have suitable technical and professional qualification. The professional relationships between expert and applicant shall be declared.

1.5 Specific requirements for different types of medicinal products.

Specific requirements for different types of medicinal products are given in section III of the Procedure and Annexes 7-11 of the Procedure.

1.5.1. Information for medicinal product with well-established medical use

For medicinal products with well-established medical use as specified in subitem 1.4, item 1, section III of the Procedure the applicant shall submit in this section a brief summary (up to 5 pages) with all grounds and evidences used to demonstrate that the active substance of medicinal product being reviewed has a well-established medical use with an acceptable level of safety and efficacy.

1.5.2. Information for generic, hybrid medicinal product or biosimilar.

For generic, hybrid medicinal product or biosimilar the applicant shall submit in this section a brief summary (up to 5 pages) with all grounds and evidences used to demonstrate that medicinal product is

a) generic of reference medicinal product

This brief summary should include details on the medicinal product: its qualitative and quantitative composition in active substances, its pharmaceutical form; and its safety/efficacy profile of the active substance(s) in comparison to the active substance(s) of the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the generic medicinal product.

The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and efficacy.

b) hybrid of reference medicinal product

This brief summary should include details on the medicinal product: its qualitative and quantitative composition in active substance, pharmaceutical form; strengths; therapeutic indications, route of administration as appropriate in comparison to the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the hybrid medicinal product.

c) similar biological medicinal product – biosimilar

This brief summary should include details on the similar biological medicinal product, its active substance, raw materials and manufacturing process. Differences with relevant attributes of the reference medicinal product should be included. Any other changes introduced during development, which could affect comparability, should be highlighted.

The comparability exercise versus the reference medicinal product for quality, safety and efficacy should be described, and the reference medicinal product used throughout the quality, safety and efficacy development programme (as appropriate) should be defined.

The applicant should include “Overview of choice of reference product” table in this section.

1.6. Environmental risk assessment

The registration dossier shall include a risk assessment overview, evaluating possible risks to the environment due to the use and/or disposal of medicinal products and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products containing GMOs (genetically modified organisms) shall be considered according to the current legislation of Ukraine related to GMO.

The information related to environmental risk shall be presented as an Annex of Module 1.

The information shall consist of:

- introduction;
- copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to the current legislation of Ukraine related to GMO;
- detection and identification methods and the unique code of GMO and any additional information about GMO or medicinal product of relevance to evaluating the environmental risk;
- environmental risk assessment (ERA) report prepared based on available information;
- a conclusion based on the above information and the ERA, related to the appropriate risk management strategy pertinent to ERA and medicinal 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 instruction for medical use;
- appropriate measures in order to inform the public.

The above information should be dated and signed by the author, providing information on his educational, training and occupational experience. A statement of the author's relationship with the applicant shall be provided.

1.7. Information relating to exclusivity of medicinal products of limited use (orphan products).

This section may be submitted if applicant has information on exclusivity at the territory of EC of applied for registration orphan products and when type II changes introduce new therapeutic indication or indications which are already approved for registered orphan product according to Art. 8.3 of Regulation (EC) №141/2000.

1.8. Information relating to pharmacovigilance

1.8.1. Pharmacovigilance system

A brief description of the pharmacovigilance system of the applicant must be provided, including:

- A proof that the applicant has the services of a qualified person responsible for pharmacovigilance and/or contact person in Ukraine of a qualified person of the applicant responsible for pharmacovigilance;
- Contact details of a qualified person responsible for pharmacovigilance and/or contact person in Ukraine of a qualified person of the applicant responsible for pharmacovigilance if different from qualified person responsible for pharmacovigilance and address where the main activity on pharmacovigilance takes place;
- Letter of guarantee of the applicant that he has the necessary means to perform tasks and commitments related to pharmacovigilance in Ukraine according to legislation indicating the location of pharmacovigilance system master file, where it is kept and its number, if available.

The brief description of the pharmacovigilance system should comply with the requirements envisaged in legislation.

1.8.2. Risk management system*

The detailed description of a risk management system should be provided in the form of a risk management plan (hereinafter - RMP), the format and structure of which approved in legislation. In particular RMP or its updated version should be submitted in the following cases:

- for registration of any medicinal product except for traditional and homeopathic medicinal products registered through simplified procedure;
{Paragraph 3, subitem 1.8.2., item 1.8, section 1 amended by MoH Ukraine Order № 1528 of 27.06.2019}
- for changes requiring new registration, in particular new pharmaceutical form, new method of administration, new process of manufacture of biotechnologically-derived medicinal product, pediatric indications and other significant changes in indications;
- for new data affecting benefit/risk ratio of medicinal product, current specifications, pharmacovigilance plan, measures for minimizing risks or their efficacy or within 60 days after important results related to pharmacovigilance or risk minimization have been obtained;
- on demand of the Center within 60 days after submitting the request.

RMP shall be submitted in format of separate document (separate volumes in hard or electronic copy) according to the structure envisaged by the legislation.

Applicant may consult with the Center on the need for and content of RMP before submitting the application for registration or introducing change.

Note. * Risk management plan must be submitted in 2 years after implementation of Procedure. Until the specified term, the risk management plan shall be submitted, if available.

Module 2: Common technical document summaries

This module includes summaries of chemical, pharmaceutical and biological documentation, preclinical and clinical data given in Modules 3, 4 and 5 of registration dossier for medicinal product and CV of independent experts.

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

Overviews and summaries shall comply with the basic principles and requirements specified below.

2.1. Overall table of contents.

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

2.2. Introduction.

The information on the pharmacological class, mode of action and the proposed clinical use of medicinal product shall be provided.

2.3. Quality overall summary.

Quality overall summary shall review the information related to chemical, pharmaceutical and biological data.

Special attention shall be paid to critical parameters and issues related to quality and justified in cases where relevant requirements of guidelines are not followed. This document shall cover issues and outline of the corresponding detailed data presented in Module 3.

2.4. Pre-clinical overview.

Presented should be an integrated and critical assessment of preclinical studies of medicinal product in animals/in vitro as well as discussion and justification of testing strategy and deviations from the relevant guideline requirements, if required.

Except for biotechnology-derived products, an assessment of the impurities and degradants of medicinal product should be included along with their potential pharmacological and toxicological effects. Any differences in the chirality, chemical form, and impurity profile between the compound used in the preclinical studies and the medicinal product to be produced should be discussed.

For biotechnology-derived medicinal products, comparability of material used in preclinical studies, clinical studies, and in composition of medicinal product to be registered shall be assessed.

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

There should be defined the characteristics of medicinal product as demonstrated by the preclinical studies and discussed the implications of the findings for the safety of the medicinal product for the intended clinical use in humans.

2.5. Clinical Overview

The Clinical Overview shall contain a critical analysis of the clinical data included in summary and Module 5. Specified shall be the approach to the clinical development of a medicinal product, including critical study design, decisions taken related to and performance of the studies.

Provided shall be a brief overview of the clinical findings, including important limitations and evaluation of benefits/risks ratio based upon the conclusions of the clinical studies. Justify the proposed dose and indication for use based on obtained clinical data related to efficacy and safety and evaluate how summary of product characteristics and other approaches will optimise benefits and limit risks.

Explain the efficacy or safety issues encountered in development, and unresolved issues.

2.6. Pre-clinical summary

The pre-clinical summary should be submitted based on actual results of pharmacology, pharmacokinetics and toxicology studies in animals/in vitro as written and tabulated summaries in the following order.

Introduction.

Pharmacology written summary.

Pharmacology tabulated summary.

Pharmacokinetics written summary.

Pharmacokinetics tabulated summary.

Toxicology written summary.

Toxicology tabulated summary.

2.7. Clinical summary:

Provided shall be a detailed, factual summary of the clinical information on medicinal product in Module 5. The summary shall include the results of all biopharmaceutics, clinical pharmacology, clinical efficacy and safety studies. A synopsis of individual studies is required.

Summarised clinical information shall be provided in the following order:

Summary of biopharmaceutics studies and associated analytical methods.

Summary of clinical pharmacology studies.

Summary of clinical efficacy.

Summary of clinical safety.

Synopses of individual studies.

3. Module 3: Quality. Chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances

3.1. Format and presentation

General outline of Module 3:

Table of contents.

Body of data.

Active pharmaceutical ingredient (API)*.

General information:

Nomenclature.

Structure.

General properties.

Manufacture

Manufacturer(s).

Description of manufacturing process and process controls.

Control of materials.

Controls of critical steps and intermediates.

Process validation and/or evaluation.

Manufacturing process development.

Characterization

Elucidation of structure and other characteristics.

Impurities.

Control of API.

Specification.

Analytical procedures.

Validation of analytical procedures.

Batch analyses.

Justification of specification.

Reference standards or materials.

Container/closure system.

Stability:

Stability summary and conclusions.

Post-approval stability protocol and stability commitment.

Stability data.

Finished medicinal product:

Description and composition of the medicinal product.

Pharmaceutical development:

Components of the medicinal product.

API.

Excipients.

Medicinal product.

Formulation development.

Overages.

Physicochemical and biological properties.

Manufacturing process development.

Container/closure system.

Microbiological attributes.

Compatibility.

Manufacture

Manufacturer(s).

Batch formula.

Description of manufacturing process and process controls.

Controls of critical steps and intermediates.

Process validation and/or evaluation.

Control of excipients:

Specifications.

Analytical procedures.

Validation of analytical procedures.

Justification of specifications.

Excipients of human or animal origin.

Novel excipients.

Control of finished medicinal product:

Specification(s).

Analytical procedures.

Validation of analytical procedures.

Batch analyses.

Characterisation of impurities.

Justification of specification(s).

Reference standards and materials.

Container/closure system.

Stability:

Stability summary and conclusion

Post-approval stability protocol and stability commitment.

Stability data.

Appendices:

Facilities and equipment (biological medicinal products only).

Adventitious agents safety evaluation.

Excipients.

Additional information.

Process validation scheme for medicinal product.

Device for administration of medicinal product.

Certificate of suitability.

For medicinal products containing or using in the manufacturing process materials of animal and/or human origin a certificate of suitability for TSE shall be issued.

Literature references.

3.2 Contents: basic principles and requirements

1. The chemical, pharmaceutical and biological data that shall be provided shall include for API and for the finished medicinal product all information on the development, the manufacturing process, the characterisation and properties, quality control operations and requirements, the stability and a description of composition and presentation of the finished medicinal product (form and pack).

2. Two main sets of information shall be provided dealing with the API and with the finished medicinal product respectively.

3. This module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of API incorporated in the formulation of the finished medicinal product.

4. All the procedures and methods used for manufacturing and controlling the API and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests carried out at the request of the competent authority. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the State Pharmacopeia of Ukraine (hereinafter – SPhU) or European pharmacopeia, this description shall be replaced by the appropriate reference to monograph(s) and general section(s) of pharmacopeia.

5. The monographs of European Pharmacopeia or SPhU shall be applicable to all API appearing in it.

However, where API in SPhU or Ph.Eur. or other national pharmacopoeias has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their limits must be declared and a suitable test procedure must be described. In cases where a specification contained in a monograph of the SPhU or Ph.Eur. or other national pharmacopoeia might be insufficient to ensure the quality of API and more detailed specification may be required, the competent authority may request a more detailed specification from the applicant. The competent authorities shall inform the authorities responsible for pharmacopoeia. Furthermore, the holder of registration certificate shall provide the authorities responsible for the above pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In the case of analytical procedures included in the SPhU or Ph.Eur. there is no need to give their full description it will be sufficient in each section where the description of this method is planned to make the appropriate reference to monograph(s) and general article(s).

6. In case where starting and raw materials, API or excipients are described neither in SPhU nor in Ph.Eur., the reference to monograph of other national pharmacopeias can be accepted. In such cases the applicant shall submit a copy of monograph accompanied by the validation of analytical methods described in the monograph and by a translation, where appropriate.

7. Where API and/or excipient(s) or starting material are the subject of a Ph.Eur. monograph the applicant may present a certificate of suitability granted by the European Directorate for the Quality of Medicines in the relevant item of this Module. The certificates of suitability to the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The substance manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of certificate of suitability by the European Directorate for the Quality of Medicines.

8. For a well-defined API the manufacturer or the applicant may arrange for the:

Detailed description of the manufacturing process;

Quality control during manufacture;

Process validation

to be supplied in a separate document directly to the competent authority by the manufacturer as an API master file.

However, in this case the API manufacturer shall provide the applicant with all of the data, which may be necessary for the latter to take responsibility for medical product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the introduction of such change shall be submitted to the competent authority; these documents and particulars will be also supplied to the applicant when they concern the open part of API master file.

9. Specific measures concerning the prevention of the transmission of animal spongiform encephalopathy shall be described (raw material from ruminant origin): at each step of the manufacturing process the applicant must demonstrate the compliance of the materials used referring to EMA Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (2011/C 73/01) (current edition published by the European Commission in the Official Journal of the European Union). The compliance with the above document may be confirmed by submitting either, preferably the 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 supply of scientific data to substantiate this compliance.

10. Information assessing the risk with respect to potential contamination with adventitious agents (regardless whether they are viral or non-viral) as laid down in relevant guidelines as well as general monographs and general sections of SPhU or Ph.Eur. shall be provided.

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

12. For devices intended for administration of medicinal product the CE-certificate (justification of conformity to Directive 93/42/EEC concerning medical devices) (if any) or the MoH conclusion pertinent to safety of device applied with medicinal product shall be provided.

Special attention shall be paid to the following subitems.

3.2.S. Active Pharmaceutical Ingredient*

* If there is an API master file, materials related only to the open part of master file shall be submitted for expert evaluation.

3.2.S.1 General information related to starting and raw material

1) information about the API name shall be provided, including recommended INN, if any – pharmacopoeial name specified in SPhU, Ph.Eur. and chemical name.

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided. For biotechnologically-derived medicinal products the schematic amino acid sequence and relative molecular mass should be provided, as appropriate;

2) in the context of this Annex starting materials shall mean all the materials from which API 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 API of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma; medicinal products developed by means of biotechnological processes (e.g. recombinant DNA technology; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells; hybridoma and monoclonal antibody methods, etc.); advanced therapy medicinal products.

Any other substances used for manufacturing or extracting API but from which this API 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.S.2 Manufacturing process of API

- 1) Applicant shall describe API manufacturing process. To adequately describe the manufacturing process and process controls, appropriate information as laid down in guidelines shall be provided.
- 2) All materials needed in order to manufacture API shall be listed, identifying where each material is used in the process. Information on the quality and control of these materials and information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Starting (raw) materials shall be listed and their quality and controls shall also be documented.

The name, location, and responsibility of each manufacturer, including contractors, and information about each of the proposed production site or laboratory shall be provided.

3) 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 spongiform encephalopathy, the applicant must demonstrate that the active substance complies with the EMA Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (2011/C 73/01) (current edition, 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 starting materials from which they are derived shall be tested for adventitious agents.

If the presence of potentially pathogenic adventitious agents is inevitable, the starting 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 Annex 10 of the Procedure.

The manufacturing facilities and equipment shall be described.

4) Tests and acceptance criteria at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies shall be provided as appropriate.

5) If the presence of potentially pathogenic adventitious agents is inevitable, the starting material shall be used only when further processing ensures their elimination and/or inactivation and this shall be validated in the section dealing with viral safety evaluation.

6) A description and discussion of the significant changes made to the manufacturing process during development and/or manufacturing site of API shall be provided.

3.2.S.3. Characterisation of API

Data highlighting the structure and other characteristics of API shall be provided.

Confirmation of the structure of API based on current physico-chemical and/or biological methods, as well as information on impurities shall be provided.

3.2.S.4. Control of API

Detailed information on the specifications used for routine control of API, 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.S.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 SPhU or European Pharmacopoeia shall be used.

3.2.S.6. Container and closure system

A description of the container and the closure system(s) and their specifications shall be provided. Packaging material complying with SPhU or Ph.Eur. shall be used, if possible.

3.2.S.7. Stability of API

- 1) The types of studies conducted, protocols used, and the results of the studies shall be summarised;
- 2) 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;
- 3) The post authorisation stability protocol and applicant's stability commitment shall be provided.

3.2.P. Finished medicinal product

3.2.P.1. Description and composition of the 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 in medicinal product:

- API;
- 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 pharmaceutical form of the outer covering of the medicinal products intended to be ingested or otherwise administered to the patient (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.).

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

The 'usual terminology', to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions:

- in respect of substances which appear in SPhU or European Pharmacopoeia or in the national pharmacopoeia, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,
- in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation, or, failing this, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,
- in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorised for use in medicinal products and/or European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs.

In order to give the 'quantitative composition' of API 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 API.

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

For medicinal products containing API, which is declared in composition of medicinal product for the first time, the quantitative statement of API, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity in the molecule. This quantitative composition must be the same in all registration documents irrespective of country of submission.

For API, which cannot be defined molecularly the units of biological activity shall be used or International Units of biological activity defined by the World Health Organisation, if any. 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 API by using where applicable the European Pharmacopoeia Units. The biological activity per mass unit shall be specified, if possible.

3.2.P.2. Pharmaceutical development

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

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 performance and medicinal product quality shall be identified and described. Additional supportive data, where appropriate, shall be referenced to the relevant items of Module 4 (Preclinical Study Reports) and Module 5 (Clinical Study Reports) of the registration dossier.

1. The compatibility of the API with excipients as well as key physicochemical characteristics of the API that can influence the performance of the finished medicinal product or the compatibility of different API with each other in the case of combination medicinal products, shall be documented.
2. The choice of excipients, in particular relative to their respective functions and concentration shall be documented.
3. A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.
4. Any overages in the formulation(s) shall be justified.
5. The physicochemical and biological properties and any parameter relevant to the performance of finished medicinal product shall be indicated and justified.
6. The selection and optimisation of the manufacturing process as well as differences between the manufacturing process(es) used to produce clinical batches and the process used for manufacturing the finished medicinal product shall be provided.
7. The suitability of the container and closure system used for the storage, shipping and use of the finished medicinal product shall be justified. A possible interaction between medicinal product and container may need to be specified.
8. The microbiological attributes of the dosage form in relation with non-sterile and sterile medicinal products shall be in accordance with and documented as prescribed in SPhU and the European Pharmacopoeia.
9. In order to provide appropriate and supportive information for the labelling pertinent to the use of diluent(s) or dosage device the compatibility of the finished medicinal product with reconstitution diluent(s) or dosage devices shall be justified.

3.2.P.3. Manufacturing process of the medicinal product

1. The description of the manufacturing method accompanying the registration form of medicinal product (Annex 1 of the Procedure), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose it shall include at least:

- description 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 might have produced an adverse change in the constituents of the pharmaceutical form,
- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished medicinal 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 sterile medicinal products, details of the sterilisation processes and/or aseptic procedures used,

— a detailed batch formula.

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

2. Particulars relating to the medicinal product quality 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 medicinal product which does not include the assay of all API (or of all the excipients subject to the same requirements as API).

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

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

3.2.P.4. Control of excipients

1. All starting 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 and information demonstrating that materials meet standards appropriate for their intended use shall be provided.

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

2. For each excipient, the specifications and their justifications shall be detailed. The analytical procedures used for their quality control shall be described and duly validated.

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

Regarding the specific measures for the prevention of the transmission of animal spongiform encephalopathies, the applicant must demonstrate also for excipients that the medicinal product is manufactured in accordance with the EMA Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (2011/C 73/01) (current edition, published by the European 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.

4. Novel excipients:

For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data, both preclinical and clinical, shall be provided. This information 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 section devoted to API of Module 3.

Information on novel excipient 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 latter shall make available the said stand-alone document to the applicant for submission to the competent authority.

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

The results of clinical studies for novel excipient shall be provided in Module 5.

3.2.P.5. Control of the finished medicinal product

For the control of the finished medicinal product, a batch of a finished medicinal product is an entity which comprises all the units of a pharmaceutical form which are made from the same quantity of raw 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 of the finished product manufactured in a given period of time.

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

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

3.2.P.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 API.

3.2.P.7. Container and closure 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 control methods. 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.

For devices intended for administration of medicinal product the CE-certificate (justification of conformity to Directive 93/42/EEC concerning medical devices) (if any) or the MoH conclusion pertinent to safety of device applied with medicinal product shall be provided.

3.2.P.8. Stability of the finished medicinal product

1. The types of studies conducted, protocols used, and the results of the studies shall be summarised. Additionally recommendations pertinent to transportations may be provided, which can be included in MQC.

2. 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.

3. The postregistration stability protocol and applicant's stability commitment shall be provided.

4. Module 4: Preclinical study reports

4.1. Format and presentation of Module 4 data should be the following:

Table of contents.

Study reports

Pharmacology:

Primary pharmaco-dynamics

Secondary pharmaco-dynamics

Safety pharmacology

Pharmaco-dynamic interactions

Pharmacokinetics:

Analytical methods and validation reports

Absorption

Distribution

Metabolism

Excretion

Pharmaco-kinetic interactions (preclinical)

Other pharmaco-kinetic studies

Toxicology:

Single-dose toxicity

Repeat-dose toxicity

Genotoxicity

In vitro

In vivo (including supportive toxico-kinetics evaluations)

Carcinogenicity

Long-term studies

Short- or medium-term studies

Other studies

Reproductive and developmental toxicity

Fertility and early embryonic development

Embryotoxicity

Prenatal and postnatal toxicity

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Local tolerance

Other toxicity studies

Antigenicity

Immuno-toxicity

Mechanistic studies

Dependence

Metabolites toxicity

Impurities toxicity

Other

Literature references

4.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

1. The pharmacological and toxicological tests must show:

1) the potential toxicity of the medicinal product and any dangerous or undesirable toxic reactions that may be observed under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;

b) the pharmacological properties of the medicinal product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general

applicability. Mathematical and statistical methods of results processing shall be used in designing the experimental studies and in evaluating the obtained data.

Additionally, it is necessary to give information about the therapeutic and toxicological potential of the medicinal product.

2. For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to be adapted for individual medicinal product; 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 shall be designed to take account of the possible induction of, and interference by, antibodies;

the suitability of studies 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 a toxicity, validation of their removal from medicinal product may replace the study.

3. The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.

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

4.2.1. Pharmacology

Pharmacology study shall follow two distinct lines of approach.

Firstly, the pharmacodynamics activity of medicinal product 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. The results shall be compared with data relating to a substance or substances with a similar therapeutic action.

Secondly, the investigator shall study the potential undesirable pharmaco-dynamic effects of the active substance on physiological functions. If the doses of medicinal product causing negative adverse reactions are close to doses recommended for medical use the studies shall be extended.

The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and their validity to be established. The results of experiment shall be stated in detail and their statistical validity to be proved. Any quantitative modification of responses resulting from repeated administration of the active substance shall be investigated.

Tests on fixed combinations of active substances for the pharmaco-dynamic interaction, may be prompted either by pharmacological premises or by indications for use. 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 of active substances is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination of active substances can be demonstrated in animals, and at least the importance of any adverse reactions.

4.2.2. Pharmaco-kinetics

Pharmaco-kinetic study includes analysis of all processes with the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, bio-transformation and excretion of these active substances.

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

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

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

Pharmaco-kinetic investigation of all pharmacologically active substances is necessary. In the case of new fixed combinations of known active substances, which have been investigated in accordance with the requirements of the Procedure, pharmaco-kinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

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

4.2.3. Toxicology

1) Single-dose toxicity

A single-dose toxicity test shall mean a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the finished medicinal product.

The single-dose toxicity test must be carried out in accordance with the current requirements and methodical recommendations.

2) Repeat-dose toxicity

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

Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the duration of clinical use. Its purpose is to determine experimentally and to describe potential adverse reactions to which attention should be paid in clinical studies.

3) Geno-toxicity

The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which active substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to human health since exposure to a mutagen causes germ-line mutation, with the inherited disorders, and somatic mutations, which may lead to the development of malignant neoplasms. These studies are obligatory for any new active substance.

4) Carcino-genicity

Tests to reveal carcinogenic effects shall normally be required:

These studies shall be performed for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner.

These studies are recommended if there is concern about their carcinogenic potential, e.g. from medicinal product of the same class or similar structure, or from evidence in repeated dose toxicity studies.

Studies with unequivocally geno-toxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product is intended to be administered chronically to patients a chronic study may be necessary to detect early tumorigenic effects.

5) Reproductive and developmental toxicity

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

These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well

as latent effects, when the medicinal product under investigation has been administered to the female during pregnancy.

Omission of these tests must be adequately justified.

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

Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri- and postnatal toxicity studies shall be conducted in at least one species. If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species in studies. 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 registration dossier is submitted shall be taken into account when determining the study design.

6) Local tolerance

The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the medicinal product as a result of its administration in clinical use.

The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the medicinal product can be distinguished from toxicological or pharmacodynamic ones.

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

The design of local tolerance tests (choice of species, duration, frequency and route of administration, doses) will depend upon the problem to be investigated and the proposed conditions of clinical use of medicinal product. Reversibility of local lesions shall be performed where relevant.

Studies in animals can be substituted by validated in vitro tests provided that the test results allow to determine risk/benefit ratio.

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

Module 5: Clinical study reports

5.1. Format and presentation.

The general outline of Module 5 is as follows:

Table of contents for clinical study reports.

Tabular listing of all clinical studies.

Clinical study reports.

Reports of biopharmaceutical studies.

Bio-availability study reports.

Comparative bio-availability and bio-equivalence study reports.

In vitro-in vivo correlation study report.

Reports of bio-analytical and analytical methods.

Reports of studies pertinent to pharmacokinetics using human biomaterials.

Plasma protein binding study reports.

Reports of hepatic metabolism and interaction studies.

Reports of studies using other human bio-materials.

Reports of human pharmacokinetic studies.

Healthy subjects pharmaco-kinetics and initial tolerability study reports.

Patient pharmaco-kinetics and initial tolerability study reports.

Intrinsic factor pharmaco-kinetics study reports.

Population study reports.

Reports of human pharmacodynamic studies.

Healthy subject pharmaco-dynamic and pharmaco-kinetics/pharmaco-dynamic study reports.

Patient pharmaco-dynamic and pharmaco-kinetics/pharmaco-dynamic studies study reports.

Reports of efficacy and safety studies.

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

Study reports of uncontrolled clinical studies.

Reports of analyses of data from more than one study including any formal integrated analyses, meta-analyses and bridging analyses.

Other study reports.

Reports of post-marketing experience (if any).

Case report forms and individual patient listings.

Literature references.

5.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

1) The clinical particulars to be provided (for different types of medicinal products) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product in question satisfies the criteria governing the granting of a registration certificate. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.

2) 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 the registration dossier. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmaco-kinetic and pharmaco-dynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.

3) applicants must arrange for essential clinical trial documents (including case report forms) other than subject's inpatient/out-patient medical files, to be kept by the owners of the data: for at least 15 years after completion or discontinuation of the trial,

or for at least two years after the expiration of the last registration certificate in Ukraine and when there are no applications for state registration in the MoH authorised body,
or for at least two years after formal discontinuation of clinical development of the investigational medicinal product.

Subject's inpatient/out-patient medical files should be retained in appropriate conditions and within the term envisaged by the current legislation.

The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the medical institutions where study has been conducted as to when these documents no longer need to be retained.

The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the medicinal product is registered. 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 medicinal 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 of registration certificate, for five years after the expiration of registration certificate for medicinal product.

The registration certificate holder shall make any additional arrangements for archiving of documentation in accordance with the current legislation provisions.

Any change of ownership of the data shall be documented.

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

4) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:

the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used;

audit certificate(s), if available;

the list of investigator(s);

data about each investigator (name, address, workplace, title, qualifications and clinical duties);

place where the trial was carried out and information in respect of each patient individually, including case report forms on each trial subject;

final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.

5) The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete documentation shall be provided forthwith upon request.

The investigator shall, based on the experimental evidence, express an opinion on the safety of the medicinal product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. In reporting the results of a multi-centre study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.

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

the number and sex of subjects treated;

the selection and age-distribution of subjects in test and control groups;

the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;

where controlled trials were carried out under the above conditions, whether the control group:

received no treatment

received a placebo

received another medicinal product of known effect

received treatment other than therapy using medicinal products

the frequency of observed adverse reactions;

details concerning trial subjects who may be at increased risk, e.g. elderly people, children, women of childbearing age, or patients whose physiological or pathological condition requires special consideration;

parameters or evaluation criteria of efficacy and the results obtained;

a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.

7) In addition, the investigator shall always indicate his observations on:

any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;

any interactions that have been observed with other medicinal products administered concomitantly;

the criteria determining exclusion of certain patients from the trial subjects;

any deaths which occurred during the trial or within the follow-up period.

8) Particulars concerning a new combination of active substances must be identical to those required for new medicinal product and must substantiate the safety and efficacy of the combination.

9) Total or partial omission of data must be explained. Should unexpected results occur during the course of the clinical trials, further preclinical toxicological and pharmacological tests must be undertaken and reviewed.

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

5.2.1. *Reports of bio-pharmaceutics studies*

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

In addition, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for the generic medicinal products.

If biowaiver procedure is applied the in vitro report shall be provided. The bioequivalence study shall be evaluated and conducted or justified, if not conducted, according to requirements of Guideline on the Investigation of Bioequivalence and Annex 18 of the Procedure.

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

For the purposes of this Annex, human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmaco-kinetics properties of active substances. In this respect, reports of plasma protein binding study, hepatic metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.

5.2.3. Reports of human pharmaco-kinetic studies

1) The following pharmaco-kinetic characteristics shall be described:

absorption (rate and extent),

distribution,

metabolism,

excretion.

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

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

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

Pharmacokinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.4. Reports of human pharmacodynamic studies

1) The pharmacodynamic action correlated to the efficacy shall be demonstrated including: the dose-response relationship and its time course, justification for the dosage and conditions of administration, the mode of action, if possible.

The pharmacodynamic action not related to efficacy shall be described.

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

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

Pharmacodynamic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.5. Reports of efficacy and safety studies

5.2.5.1. Reports of controlled clinical studies pertinent to the claimed indication

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

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

The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.

The safety data shall be reviewed taking into account the events resulting in changes of dose or need for concomitant medication, serious adverse reactions, reactions resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children,

pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.

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

These reports shall be provided.

5.2.6. Reports of post-marketing experience

If the medicinal product is already registered in third countries, information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same API, in relation to the usage rates if possible.

5.2.7. Case reports forms and individual patient listings

Case report forms and individual patient data listings keeping personal data of trial subjects as confidential shall be provided and presented in the same order as the clinical study reports and indexed by study.

{Annex 6 in wording of MoH Ukraine Order №460 as of 23.07.2015; amended by MoH Ukraine Order № 1528 of 27.06.2019}