



MINISTRY OF HEALTH OF UKRAINE

ORDER

26.08.2005 № 426

Registered at the Ministry of Justice of Ukraine
on September 19, 2005 under N 1069/11349

On approval of the Procedure for Conducting Expert Evaluation of Registration Materials Pertinent to Medicinal Products, which are Submitted for State Registration (Re-Registration) and Expert Evaluation of Materials about Introduction of Changes to the Registration Materials during the Validity Period of Registration Certificate

{As amended by MoH Ukraine Orders

№ 95 of 01.03.2006

№ 536 of 11.09.2007

№ 543 of 25.09.2008

№ 3 of 04.01.2013

№ 470 of 07.07.2014

№ 566 of 11.08.2014

№ 460 of 23.07.2015

№ 711 of 13.04.2018

№ 1528 of 27.06.2019

№ 1345 of 09.06.2020

№ 1948 of 21.08.2020}

According to the Decree of the Cabinet of Ministers of Ukraine of May 26, 2005 № 376 “On Approval of the Procedure for State Registration (Re-registration) of Medicinal Products and Amounts of Fees for Their State Registration (Re-Registration)”

I ORDER:

1. To approve the Procedure for Conducting Expert Evaluation of Materials Pertinent to Medicinal Products, which are Submitted for State Registration (Re-Registration) and Expert Evaluation of Materials about Introduction of Changes to the Registration Documents during the Validity Period of Registration Certificate (attached).

2. To consider as void:

2.1. Order of the Ministry of Health of Ukraine dated 19.09.2000 № 220 “On Approval of Procedure for Conducting Expert Evaluation of Materials Pertinent to Medicinal Products which are Submitted for State Registration (Re-Registration) and Expert Evaluation of Materials about Introduction of Changes to the Registration Documents during the Validity Period of Registration Certificate”, registered with the Ministry of Justice of Ukraine on 05.10.2000 under № 685/4906 (amended).

- 2.2. Order of the Ministry of Health of Ukraine dated 03.05 2001 № 163 “On Approval of the Requirements to Information on the Use of Medicinal Product”, registered with the Ministry of Justice of Ukraine on 21.05.01 under № 434/5625 (amended).
3. To revoke the Order of the Ministry of Health of Ukraine dated 04.11.2004 № 536 “On some issues regarding arrangement of registration certificates”.
4. To establish that this order shall come into force starting 01.01.2006.
5. That V.T. Chumak, Director of the State Pharmacological Center MoH Ukraine, submits the present order to the Ministry of Justice of Ukraine for state registration.
6. I hereby authorise V.F. Snisar, Deputy Minister of Health of Ukraine, to supervise execution of this order.

(Item 6 in wording of MoH Ukraine Order № 95 of 01.03.2006)

O. Tolstanov
Deputy Minister

APPROVED
Order of the Ministry of Health
of Ukraine of 26.08.2005 № 426
(in wording of MoH Ukraine Order
of 23.07.2015 № 460)

Registered with the
Ministry of Justice of Ukraine
of September 19, 2005
under № 1069/11349

PROCEDURE
for Conducting Expert Evaluation of Registration Materials Pertinent to
Medicinal Products, which are Submitted for State Registration (Re-Registration) and Expert
Evaluation of Materials about Introduction of Changes to the Registration Materials during
the Validity Period of Registration Certificate

{In the Order's text the words and numbers of "MoH Ukraine document 42-7.1:2014", "MoH Ukraine document 42-7.1:2014" (current version)" are replaced by the words and numbers «the current version of MoH Ukraine document 42-7.2:2018" according to MoH Ukraine Order № 1528 of 27.06.2019}

I. General

1.1 This Procedure has been developed according to the Law of Ukraine "On Medicines" and "On Protection of Population against Infectious Diseases", Procedure for State Registration (Re-registration) of Medicinal Products and Amounts of Fees for Their State Registration (Re-Registration) approved by the Decree of the Cabinet of Ministers of Ukraine of May 26, 2005 № 376.

1.2 This Procedure shall apply to:

active pharmaceutical ingredients, in particular, in the form of pellets, granulate and other presentations;

finished medicinal products;

medicinal products in package in bulk;

medical immunobiological products;

medical devices containing substances which enter systemic blood circulation during their use.

3. This Procedure shall not apply to:

radiopharmaceutical medicinal products produced exclusively from the licensed radionuclide generators, radionuclide kits or radionuclide precursors according to the manufacturer's instructions for use at the accredited health care settings;

products based on blood and plasma which are fractionated from human donor blood according to manufacturer's instructions in relevant accredited establishments;

active pharmaceutical ingredients (API), intermediates, starting materials produced by manufacturers during manufacture of finished medicinal products and not intended for sale by other manufacturer;

{Paragraph 5 of item 3 of section I is deleted. Therefore, paragraphs 6, 7 shall be considered as paragraphs 5, 6 according to MoH Ukraine Order № 1948 of 21.08.2020}

blood and plasma used for commercial production of finished blood products;

vaccine antigens.

4. Requirements to registration materials and their expert evaluations specified by this Procedure shall be applied to homeopathic medicinal products with therapeutic indications or in a pharmaceutical form which may present risk outweighing the intended therapeutic effect.

5. During registration of medical immunobiological products or products derived from human blood or plasma the manufacturer must demonstrate his ability to attain batch-to-batch consistency. During registration of medicinal product derived from human blood or human plasma the manufacturer must also demonstrate the absence of specific viral contamination, to the extent that the state of technology permits.

6. The Ministry of Health of Ukraine (hereinafter – MoH) shall perform state registration of medicinal product based on the positive conclusions on quality, safety and efficacy of medicinal products drawn by the State Enterprise “The State Expert Center of the Ministry of Health of Ukraine” (hereinafter – the Center) based on the results of expert evaluation of registration materials (registration dossier) according to the Procedure, and submitted to MoH for making a decision.

7. MoH performs state re-registration of medicinal product based on conclusions confirming favourable balance of expected benefits in relation to potential risk at use of medicinal products which are made by the Center based on the results of expert evaluation of risk-benefit balance documents according to this Procedure, and submitted to MoH for making a decision.

II. Definition of terms

1. In the Procedure the terms given below shall have the following meaning:

1) Active pharmaceutical ingredient (drug substance, active substance, substance) (hereinafter – API, active substance, substance) - any substance or mixture of substances intended for use in the manufacture of a medicinal product and during this use becomes its active ingredient. Such substances have pharmacological or other direct effect on human body. As part of finished forms of medicinal products they are used for treatment, diagnosis or prevention of disease, for changing the condition, structures or organism's physiological functions, for management, manipulation and relief of symptoms;

API may be: compacted, film-coated, granulated, grinded/crushed to a certain level or treated otherwise, and presented under different names and in different forms (in particular pellets, granules and other presentations);

2) Safety of medicinal product – a profile of a medicinal product based on comparative evaluation of benefits of its use and potential harm which may be caused to a patient using this medicinal product;

3) BCS-based biowaver – an in vitro bioequivalence study, which is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. A BCS-based biowaiver is applicable to immediate release, solid medicinal products for oral administration and systemic action having the same pharmaceutical form;

{Subitem 3 of item 1 of section II in wording of MoH Ukraine Order of 27.06.2019 № 1528}

4) Bioavailability - the rate and extent at which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site(s) of action;

5) Bioequivalence – two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent of absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy.

{Subitem 5 of item 1 of section II in wording of MoH Ukraine Order of 27.06.2019 № 1528}

6) Biological medicinal products – medicinal products containing active substances of biological origin obtained through production from biological source (animal, human, herbal, microbial or biotechnological);

7) Biopharmaceutics Classification System (BCS) – a scientific framework for classifying active substances based upon their aqueous solubility and intestinal permeability;

{Subitem 8 of item 1 of section II is deleted. Therefore, subparagraphs 9 - 61 should be considered as subparagraphs 8 - 60 respectively according to MoH Ukraine Order of 27.06.2019 № 1528}

8) Conclusion of the State Expert Center MoH on efficacy, safety and quality of medicinal product proposed for state registration, and/or expert assessment of benefit/risk balance of medicinal product proposed for state re-registration, and/or introduction of changes to materials of the registration dossier for medicinal product – an integrated result of the expert evaluation of materials of the registration dossier for medicinal product with recommendations regarding its state registration, including a confirmation of the correspondence of the preclinical study reports and clinical trial reports submitted by the applicant to materials of the registration dossier with recommendations regarding their publication on the MoH official website, and/or recommendations regarding state re-registration of medicinal product, and/or introduction of changes to materials of the registration dossier for medicinal product during the validity period of registration certificate or its new registration, or rejection in registration, re-registration, introduction of changes to materials of the registration dossier for medicinal product during the validity period of registration certificate;

{Subitem 8 of item 1 of section II in wording of MoH Ukraine Order of 27.06.2019 № 1528}

9) Advanced (biotechnological) medicinal products – medicinal products containing active substances derived using the following biotechnological methods: gene technology, cell engineering, hybridoma technologies, enzyme technology and engineering immunology, etc;

10) Outer packaging – a packaging into which the immediate packaging is placed and which protects the medicinal product and immediate packaging;

11) Generic medicinal product (generic) (hereinafter – generic) – a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly with regard to safety and/or efficacy. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines;

{Subitem 11 of item 1 of section II in wording of MoH Ukraine Order of 27.06.2019 № 1528}

12) Gene therapy medicinal products – medicinal products obtained through recombinant DNA technologies;

13) Hybrid medicinal product – a medicinal product which does not fall within the definition of a generic medicinal product or where its bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product;

14) Homeopathic medicinal product – any medicinal product made of products, substances or compositions specified as homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the State Pharmacopoeia of Ukraine (hereinafter - SPhU) or the European Pharmacopoeia, or in the absence of such description – in the German Homeopathic (GHP), United States Pharmacopoeia (HPUS), British Homeopathic Pharmacopoeia (BHP), Schwabe's Homeopathic Pharmacopoeia.

Homeopathic medicinal product may also contain a number of active substances;

15) State re-registration of finished medicinal product – procedure that is performed according to requirements of current legislation in order to renew an approval of medicinal product for medical use in Ukraine;

16) State registration of finished medicinal product – procedure that is performed according to requirements of current legislation in order to approve medicinal product for medical use and enter it into the State register of medicinal products of Ukraine.

17) State registration of API – procedure that is performed according to requirements of current legislation in order to classify API as pharmaceutical product to be imported to the customs territory of Ukraine and enter it in the State register of medicinal products of Ukraine.

18) Approval for use of API in manufacture of finished medicinal products – adoption of the API information as a part of registration materials for finished medicinal product (Module 3.2.S) in manufacture of which this API is used, and introduction of the relevant API data into the registration certificate for finished medicinal product according to requirements of current legislation and the Procedure;

19) Equivalence study – test that determines the equivalence between the generic and reference medicinal products using *in vivo* and/or *in vitro* studies;

{Subitem 20 of item 1 of section II is deleted. Therefore, subparagraphs 21 - 60 should be considered as subparagraphs 19 - 59 respectively according to MoH Ukraine Order № 1528 of 27.06.2019 }

20) The Center's expert on registration materials expert evaluation – a natural person with appropriate qualification and knowledge of Ukraine's legislation, rules and standards of the European Union, WHO recommendations related to medicines circulation, provisions of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. At the same time, the expert must not perform activities, including those outside the Center, which cause the conflict of interests.

21) Expert evaluation of registration dossier for medicinal product – a preliminary and specialised expert evaluation of registration materials pertinent to medicinal product in order to prepare motivated conclusions and recommendations on making decision on possibility of its state registration, re-registration, introduction of changes to the registration materials, or rejection in state

registration, re-registration, introduction of changes to the registration materials for medicinal product;

22) Efficacy of medicinal product – a favourable diagnostic, therapeutic or preventive effect of a medicinal product on determination of the nature of a disease, its course, duration or correction of organism's state or functions according to the indications for use specified in the instructions for medical use;

23) Common name – the international non-proprietary name (hereinafter - INN) of active substance recommended by the World Health Organization (hereinafter - WHO), or, in its absence, the usual common name;

24) Applicant (holder of registration certificate) (hereinafter – applicant) – a legal entity or a natural person responsible for efficacy, quality and safety of a medicinal product according to the procedure established by the acting legislation, and having resources to perform pharmacovigilance in Ukraine, and being responsible for reliability of information included in registration dossier submitted by him;

25) Changes that may be made during the validity period of registration certificate – changes proposed by the applicant, which pertain to the registered medicinal product;

26) Instructions for medical use of medicinal product (instructions for use of medicinal product) (hereinafter – instructions for medical use) – a formally approved information on medical use of medicinal product which is formulated according to this Procedure and accompanies the finished medicinal product;

27) Confidential registration information – a scientific and technical information included in registration materials pertinent to a medicinal product, including parts I - IV or modules 1 - 5 of the registration dossier, methods of quality control of medicinal product (except for public information, namely, information on the reference product, name of the medicinal product, composition of active substances, strength, packaging, applicant and/or manufacturer of the medicinal product which are specified in the instructions for medical use, information on unsafe properties of a medicinal product which may cause a patient harm, and except for results of preclinical study and clinical trials of medicinal product (preclinical study reports and clinical trial reports drawn up according to the template established by this Procedure));

{Subitem 27 of item 1 of section II in wording of MoH Ukraine Order of 27.06.2019 № 1528}

28) Herbal medicinal product – any medicinal product exclusively containing as active substance(s) one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more herbal preparations;

29) Medicinal product produced according to the approved specification – a medicinal product containing active substance with well established medicinal use on the territory of Ukraine, with recognized efficacy, and acceptable level of safety, the specification of which has been approved by MoH;

30) Medicinal products obtained from human blood or plasma – medicinal products based on blood constituents which are prepared industrially by state or private establishments; such medicinal products include, in particular, albumin, blood coagulation factors and human immunoglobulins;

31) Medical immunobiological products (hereinafter – MIP) – vaccines, toxoids, immunoglobulins, sera, bacteriophages and other medicinal products intended for use in medical practice for specific prevention of infectious disease;

32) Name of medicinal product – the name given to a medicinal product, which may be either invented by applicant (manufacturer), or a common or scientific name, along with a trade mark or applicant's (manufacturer's) name;

33) Independent expert – a natural person with adequate qualification, special knowledge, who conducts scientific or scientific and technical expert evaluation at Applicant's request and is responsible to the Applicant for reliability and completeness of analysis, validity of recommendations according to the requirements of the Applicant's tasks related to the expert evaluation, but is not an inventor, investigator of the expert evaluation's object; who isn't an expert in agencies or organisations formally designated as expert bodies of scientific and scientific and technical institutions dealing with circulation of medicinal products; or who is not associated otherwise with official expert evaluation authorities, central executive body, which ensures development of state policy for health care or bodies authorized by them;

34) non-comparable biotechnological medicinal product – a medicinal product developed without comprehensive comparability safety and efficacy studies and which doesn't demonstrate its comparability in terms of quality, safety, efficacy to the reference biotechnological medicinal product;

{New subitem is added to item 1 of section II according to the MoH Ukraine Order №711 of 13.04.2018}

35) Illegal use of registration information on safety and efficacy of medicinal product - a reference to or other use of information on efficacy and safety of medicinal product registered according to complete and stand-alone application before the expiration of the five-year period of the day of registration of such medicinal product in Ukraine for state registration of the respective generic medicinal product except for cases when according to the legislation the applicant has obtained the right to refer to and/or use registration information of the reference/original medicinal product, or has submitted his own complete registration information conforming to the registration information of the reference/original medicinal product.

These requirements shall not exclude the subject's rights to carry out within this period an appropriate development of the medicinal product including the equivalence studies of the generic medicinal product and the reference medicinal product and submit a registration dossier to regulatory authority in order to get the registration certificate five years after the registration in Ukraine of the reference medicinal product specified in the previous paragraph;

36) Original (innovator) medicinal product – a medicinal product which was originally registered in the world based on complete documentation related to its quality, safety and efficacy (complete registration dossier);

37) Patented medicinal product – a medicinal product going into circulation under proprietary name of the manufacturer (applicant), the right to manufacture (produce), sell and use of which being covered by the legislation of Ukraine on protection of intellectual property;

38) Immediate packaging – an individual packaging which is in immediate contact with the medicinal product, and contributes to retention of its main properties;

39) Similar biological medicinal product (biosimilar) – a biological medicinal product which is similar in terms of quality, efficacy and safety to the registered reference biological product, which patent protection period expired. The similarity of quality, efficacy and safety of such medicinal product to the reference biological product should be demonstrated by the appropriate comparative quality studies, comparative preclinical and clinical studies;

- 40) Applicant's representative (authorised person acting on behalf of applicant) (hereinafter – applicant's representative) – a legal entity or a natural person who is given by an applicant, according to the respective authorization, a right to represent his interests during procedures of registration, re-registration and/or introduction of changes to registration materials at the territory of Ukraine, and who is responsible as an applicant for reliability of information in materials of the registration dossier submitted by him to the Center;
- 41) Radionuclide precursor – any other radionuclide intended for radiolabelling another substance prior to its administration;
- 42) Product of limited use (orphan product) – a medicinal product which is intended for the diagnosis, prevention or treatment of a rare life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons by the time of submission of the application for state registration;
- 43) “In bulk” product – any medicinal product, which passed all stages of manufacturing process, except for pre-packaging and/or final packaging and labelling;
- 44) Specification (monograph) – information on composition, production technology, quality control and use of medicinal product;
- 45) Radionuclide kit – any medicinal product to be reconstituted or combined with radionuclides in the final radiopharmaceutical medicinal product, usually prior to its administration;
- 46) Radiopharmaceutical medicinal product – any medicinal product, when ready for use, contains one or more radionuclides (radioactive isotopes) included for medical purpose;
- 47) Periodic safety update report on medicinal product (periodic report) – a written report containing periodically updated information on safety of a medicinal product;
- 48) Registration information – a scientific technical information in any format and presentation, stored in any form including illustrations (maps, diagrams, organograms, figures, layouts etc.), photos and any other documented information included in registration materials for medicinal product;
- 49) Registration certificate of medicinal product (medical immunobiological product) – a document containing information on medicinal product (medical immunobiological product) registered in Ukraine and entered into the State register of medicinal products of Ukraine and interdepartmental database of medicinal products registered in Ukraine;
- 50) Registration number – a code mark, assigned to a medicinal product at state registration and reserved for the medicinal product unchanged throughout the whole period of stay of the medicinal product on the pharmaceutical market of Ukraine;
- 51) Registration materials (materials of registration dossier) – a set of documents submitted for state registration, re-registration, introduction of changes into registration materials of a medicinal product based on which the motivated conclusion on its efficacy, safety and quality is made;
- 52) Reference medicinal product – a medicinal product with which the medicinal product in question is to be compared, and which is mainly original (innovator) medicinal product with the established efficacy, safety and quality.
- 53) Herbal preparations – preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates;

54) Herbal substances – whole, fragmented or cut plants, plants parts, algae, fungi, lichen in an unprocessed, usually dried form, but sometimes fresh. Certain exudates from plants (for example, tars) that have not been designed for specific treatment are also considered to be herbal substances. Herbal substances are to be precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author);

55) Strength of the medicinal product – the content of the active substance (-s) expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form;

56) Bridging summary report – a written report integrating the safety information about a medicinal product presented in two or more periodic safety updated reports for medicinal products.

57) Pharmaceutical alternative medicinal products – medicinal products containing different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the same active moiety of the molecule of the same active substance (s) or differ in dosage form or strength;

58) Pharmaceutical equivalent medicinal products – medicinal products which contain the same molar amount of the same active substance (s) in the same dosage form and meet the same or comparable standards. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution rate and/or absorption;

{Subitem 58 of item 1 of section II in wording of MoH Ukraine Order № 1528 of 27.06.2019}

59) Quality of medicinal product – a set of properties, which make a medicinal product appropriate for its intended use to meet consumer needs and comply with the legal requirements.

2. Other terms used in this Procedure are applied based on definitions specified in the legislation.

III. Types of medicinal products submitted for state registration and related materials of registration dossier

Below are the types of medicinal products and requirements to compilation of registration dossier for their state registration according to each type.

1. For registration of medicinal products an applicant should substantiate the selected type of medicinal product to which a set of available registration documents corresponds. The applicant should submit a registration form of medicinal product for one of the following types:

Medicinal product with complete dossier (stand alone dossier);

Generic, hybrid, medicinal product or biosimilar;

Medicinal product with well established medicinal use;

Fixed-combination medicinal product;

Informed consent;

Other types as specified in item 2 of this section.

Registration dossier for all types of medicinal products specified above irrespectively of their nature and other peculiarities should comply with the general requirements to materials of registration dossier (in format of Common Technical Document (hereinafter – CTD) taking into account the provisions of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (formerly - The International Conference on Harmonization of

Technical Requirements for Registration of Pharmaceuticals for Human Use, hereinafter- ICH) and information given in this section below. At the same time the specific requirements stated in annexes to the Procedure shall be applied to registration dossiers of the following types of medicinal products: medicinal products derived from plasma, vaccines, radiopharmaceutical medicinal products and precursors, homeopathic medicinal products, herbal medicinal products, gene therapy medicinal products and somatic cell therapy, and tissue engineered medicinal products, products of limited use (orphan products).

{Paragraph eight of item 1 of section III amended according to the MoH Ukraine Order № 1345 of 09.06.2020}

1.1. Medicinal product with complete dossier (stand alone dossier)

Medicinal product with complete registration dossier – a medicinal product containing the new or known active substance (s) which is (are) an ingredient of another registered medicinal product;

Registration dossiers for these medicinal products should include: complete modules 1 and 2, results of own pharmaceutical tests (physico-chemical, biological or microbiological) in module 3, either results of own preclinical tests (pharmacological and toxicological), and clinical trials, and detailed bibliographic data or only detailed bibliographic preclinical and/or clinical data in modules 4 and/or 5.

Justification of any deviations from the general requirements to registration dossier, in particular a lack of reports on specific studies/trials shall be provided.

Justifications should be given in appropriate preclinical and clinical overviews in module 2 of the registration dossier. The general justification of missing one or more study reports is allowed provided there is an indication that justification covers several reports.

1.2. Medicinal product with complete dossier of mixed type

Module 4 and/or 5 of mixed registration dossiers consists of reports on limited preclinical and/or clinical studies carried out by the applicant and of detailed bibliographical references. All other modules shall be submitted according to the general requirements to registration dossier (in CTD format).

The Center shall accept for expert evaluation the proposed format of dossier presented by the applicant on a case by case basis.

An absence of reports on own tests/trials and submission of bibliographic references instead should be justified in respect to why bibliographic references may substitute study reports and how the materials submitted ensure compliance of the registration dossier with general requirements.

Bibliographic references which substitute necessary study reports shall be given in appropriate items of module 4 and/or 5 of the registration dossier and summarized in module 2.

Bibliographic references submitted in addition to study reports shall be included in sections of CTD concerning references and not summarized in module 2 of the registration dossier.

Risk management plan shall be submitted for advanced therapy medicinal products.

For any item of module 4.1 and 5.1 of the registration dossier an applicant shall specify whether results of preclinical studies or clinical trials are presented in a form of detailed reports on studies performed and/or bibliographic references or such information is missing;

If reports on studies performed are submitted and they comply with all requirements to a specific section, no further justifications shall be required from the applicant;

If bibliographic references to a specific item are given a justification shall be made why they may substitute study reports and how the results presented ensure compliance of the registration dossier with general requirements to registration dossier (in CTD format);

If no reports on specific trial or study is submitted, reasons should be justified why such reports have not been submitted and whether the general requirements to registration dossier (in CTD format) are considered fulfilled. The formulation “not applicable” shall not be an acceptable justification.

To justify an absence of reports on own studies performed the following principles shall be used in each section:

Specific derogation foreseen in current legislation;

Proper care for animals (Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes) and ethical issues (WMA Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”) accompanied by expert conclusions that further trials or studies are unlikely to broaden scientific knowledge in the sphere investigated;

Expert conclusion that repeated studies are unlikely to generate new information in the sphere investigated (for example, clinical experience with the use of active substance at the time of development substitute some preclinical studies);

Scientific justification of acceptability of certain trials or studies;

Failure to provide comprehensive data as specified in item 8 of section IV of the Procedure (exceptional cases);

Other proofs to be provided for justification of missing data on some trials and studies.

1.3. Generic, hybrid or similar biological medicinal products:

1) generic medicinal product

Generic medicinal product – a medicinal product which is proved to be generic to the reference product according to the provisions of Guideline on the investigation of bioequivalence of the European Medicines Agency (hereinafter – EMA) (CPMP/QWP/EWP/1401/98 Rev.1) or current version of MoH Ukraine document 42-7.2:2018.

This type of medicinal product envisages that registration dossier should contain references to the registration information included in the dossier for reference product provided their bioequivalence has been established.

{Paragraph 3 of subitem 1 of subitem 1.3 of item 1 of section III as amended by MoH Ukraine Order № 1528 of 27.06.2019}

Generic is defined as a medicinal product which has the same qualitative and quantitative composition of active substances and the same pharmaceutical form as the reference medicinal product, and bioequivalence of which to the reference medicinal product is demonstrated by relevant bioavailability studies. Different salts, esters and esters, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance,

unless they differ significantly with regard to safety and efficacy. The various immediate-release oral pharmaceutical forms are considered to be one and the same pharmaceutical form.

Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

(Paragraph 4 of subitem 1 of subitem 1.3 of item 1 of section III in wording of MoH Ukraine Order of 27.06.2019 № 1528)

If the active substance of the generic contains the same active moiety of molecule as the registered original medicinal product but in the form of different salt, ester and ester, isomer, mixture of isomers, complex or derivative, an evidence is needed that there is no change in the pharmacokinetics, pharmacodynamics and/or toxicity of that moiety, which is responsible for these properties and could change safety/efficacy profile. If there is no such evidence, this substance is to be considered as a new active substance;

2) hybrid medicinal product

If medicinal product does not fall within definition of “generic medicinal product” or its bioequivalence cannot be demonstrated through bioavailability studies, or it has the following differences compared to the reference product: changes in active substance(s), therapeutic indications, strength, pharmaceutical form or administration route, the applicant shall provide the results of the appropriate toxicological and pharmacological studies and/or clinical trials.

(Paragraph 2 of subitem 2 of subitem 1.3 of item 1 of section III in wording of MoH Ukraine Order of 27.06.2019 № 1528)

Hybrid medicinal products differ from generic ones in a sense that results of own preclinical studies and clinical trials are required for them in the following cases:

strict definition of a ‘generic medicinal product’ is not met;

bioavailability studies cannot be used to demonstrate bioequivalence;

there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration compared to the reference product.

At the same time results of trials and studies should comply with general requirements to materials of registration dossier (in CTD format).

Registration dossiers for hybrid medicinal products shall include references to the results of preclinical studies and clinical trials of the reference product and partly the new data.

(Paragraph 9 of subitem 2 of subitem 1.3 of item 1 of section III in wording of MoH Ukraine Order № 1528 of 27.06.2019)

Registration dossiers for the generic and hybrid medicinal products shall follow the CTD structure.

Specific requirements to these dossiers are as follows:

registration dossier for medicinal products submitted without any own preclinical and clinical data shall include data described in modules 1-3 provided the applicant has a consent of registration certificate holder of the reference medicinal product to make cross-references to content of modules 4 and 5 of his registration dossier,

or

registration dossier shall contain data described in modules 1-3 of CTD, and data proving bioavailability and bioequivalence to the original medicinal product provided the latter is not a biological medicinal product.

Module 1

In section 1.5.2. of module 1 of the registration dossier a brief overview (not more than 5 pages) which summarizes all justifications and evidence used to demonstrate that the medicinal product concerned is:

A generic to the reference medicinal product. This brief overview shall contain information on the medicinal product: qualitative and quantitative composition of active substance(s), pharmaceutical form; safety-efficacy profile of its active substance(s) compared to active substance(s) of the reference medicinal product, and issues related to bioavailability and bioequivalence as this applies to the generic medicinal product;

A hybrid to the reference medicinal product. This brief overview shall contain information on medicinal product: qualitative and quantitative composition of active substances, pharmaceutical form; strength, therapeutic indications, route of administration, if applicable, compared to the reference medicinal product, and issues related to bioavailability and bioequivalence as this applies to the hybrid medicinal product.

A table “Overview of selection of reference medicinal product” is given in section 1.5.2 of module 1. The selected reference medicinal product should be at least the medicinal product with established safety and efficacy, registered based on complete dossier.

All other requirements of the CTD module 1 shall apply to generic and hybrid medicinal products.

If some information is missing, the applicant shall provide a justification why a lack of this information in the registration dossier is acceptable.

Module 2

Module 2 of the registration dossier shall include: quality overall summary, preclinical overview and clinical overview. Preclinical summary and clinical summary may be submitted but these summaries are obligatory when there are data available in the documentation on the new additional studies performed.

For these medicinal products the preclinical/clinical overviews/summaries shall include the following elements:

the grounds that the medicinal product is a generic;

a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the medicinal product to be marketed together with an evaluation of these impurities;

an evaluation of the bioequivalence studies or a justification why studies were not performed in compliance with Guideline on the investigation of bioequivalence of the European Medicines Agency (hereinafter – EMA) (CPMP/QWP/EWP/1401/98 Rev.1) or current version of MoH Ukraine document 42-7.2:2018;

the published literature relevant to the API or medicinal product. It may be acceptable for articles in ‘peer review’ journals to be annotated for expert evaluation;

every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the preclinical/clinical overviews/summaries and substantiated by published literature and/or additional studies. In addition, instructions for medical use for a generic medicinal product shall contain information identical to that given in the formally approved instructions for medical use for a reference medicinal product. Any differences of the instructions for medical use for a generic medicinal product shall be substantiated by the results received during multicenter clinical trials;

when the medicinal product is claimed to be generic, and if there are differences in active substance, additional data shall be provided in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives of the registered active substance.

Module 3

The applicant shall submit a complete module 3 as specified in general requirements to registration dossier (in CTD format).

Modules 4 and 5

The applicant shall submit modules 4 and 5 as specified in general requirements to registration dossier (in CTD format) taking into consideration the following:

For generic products no results of own toxicological or pharmacological studies or clinical trials shall be provided. Results of generic/hybrid bioequivalence studies shall be included in section 5.2.1 of module 5. Additional data to demonstrate equivalence of safety/efficacy profile of different salts, esters and esters, isomers, mixtures of isomers, complexes or derivatives of an active substance of the reference medicinal product shall be provided in compliance with a dossier structure in CTD format;

For hybrid medicinal products the results of relevant preclinical studies and clinical trials shall be provided.

For registration of generics, hybrids and for changes which require a new registration the additional data shall be provided in cases of:

a) different salts/ester, complex/derivative of an active substance (with the same active moiety of molecule).

Evidence that there is no change in the pharmacokinetics, pharmacodynamics and/or in toxicity of the active moiety of molecule which could change the safety/efficacy profile shall be demonstrated (otherwise a new active substance shall be considered).

b) other route of administration/dosage form (for parenteral dosage forms intraarterial, intravenous, intramuscular, subcutaneous routes are different routes of administration)

a new route of administration;

a new dosage form (the same route of administration).

Clinical data (safety/efficacy), pharmacokinetics, preclinical data (for example, local tolerance) shall be provided depending on the available modifications;

c) different strengths at the same route of administration/dosage form and posology.

Results of bioavailability studies shall be submitted.

d) suprabioavailability of medicinal product: same dosage intervals but reduced doses intended to achieve same plasma/blood concentrations as a function of time.

Results of the bioavailability studies may suffice (paragraph 5 of the EMA Guideline on the investigation of bioequivalence (CPMP/QWP/EWP/1401/98 Rev.1) or current version of MoH Ukraine document 42-7.2:2018);

e) active substances associated in a different proportion/different posology or if one or more is intended for modified release.

Results of clinical studies comparing existing/new proportion or dosage regimen, including bioavailability studies, shall be provided;

3) similar biological medicinal product (biosimilar)

Where a biological medicinal product which is similar to a reference biological product, does not meet the conditions in the definition of generic medicinal product, the results of relevant preclinical tests or clinical trials must be provided.

The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in the related detailed EMA guidelines or MoH recommendations on biosimilars.

For a biosimilar, after the expiry of data protection period for the earlier registered original biological medicinal product, the following approach shall apply:

Information to be supplied shall not be limited to Modules 1-3 (pharmaceutical, chemical and biological data), supplemented with bioequivalence and bioavailability data. The type and amount of additional data (i.e. toxicological and other non-clinical and relevant clinical data) shall be determined on a case by case basis in accordance with relevant requirements stated in EMA Guidelines or MoH recommendations on biosimilars;

Due to the diversity of biological medicinal products, the identified studies foreseen in Modules 4 and 5 of registration dossier may be required taking into account the specific characteristic of each individual medicinal product.

The main principles to be applied are addressed in EMA Guidelines or MoH recommendations on biosimilars developed for a specific type of biotechnological products.

If the originally registered biological medicinal product has more than one indication to use, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

(Paragraph nine of subitem 3 of subitem 1.3 of item 1 of section III excluded according to on the MoH Ukraine Order № 711 of 13.04.2018)

Registration dossier for a biosimilar shall meet the general requirements to materials of registration dossier (in CTD format) taking into account the following.

Module 1

In section 1.5.2. of module 1 a brief overview (not more than 5 pages) which summarizes all justifications and evidences used to demonstrate that the medicinal product concerned is a similar biological medicinal product (biosimilar).

This overview should contain detailed information on a similar biological medicinal product, its active substance, starting material and manufacturing process. In addition, also included shall be the information on all differences with regard to the relevant characteristics of the reference product and any other changes introduced by manufacturer during the development, which may have impact on the comparability of the product.

The comparability of the biosimilar and the reference product in terms of quality, safety and efficacy shall be described, and the reference product used in the development with respect to quality, safety and efficacy shall be specified.

A table “Overview of selection of reference medicinal product for comparability studies” is given in section 1.5.2 of module 1. The selected reference medicinal product compared to which the biosimilar comparability is studied should be a medicinal product first registered in the world based on the complete dossier (an innovator product). A single source of the reference product for all comparability studies should be used, preferably registered in a country with stringent regulatory system. In case the reference product from another country is used, an additional information is required (for example, maintaining the cold chain during transportation, etc.).

Risk management plan shall be provided for biosimilars.

All other requirements of Module 1 shall apply to biosimilars.

If some information is missing, a justification why a lack of this information in registration dossier is acceptable shall be provided in the appropriate section.

Module 2

Module 2 of the registration dossier shall include: quality overall summary, preclinical overview and clinical overview. Preclinical summary and clinical summary shall be submitted when there are data on the new additional studies included in the documentation.

Issues on comparability of the biosimilar and the reference medicinal product shall be highlighted in separate sections of preclinical summary and clinical summary using references to appropriate sections of the registration dossier containing results of the comparability studies.

Module 3

The applicant shall submit a complete module 3 as required for the registration dossier in CTD format.

Besides, added to complete module 3 shall be the results of comparability studies of biosimilar and reference product performed according to the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMA/CHMP/BWP/247713/2012) or MoH document 42-8.0:2013. Comparison data for a biosimilar and a reference medicinal product is an additional element of general requirements to a dossier on quality and shall be reviewed separately from data provided in module 3. This information shall be given in module 3.2.R (Regional Information) of registration dossier in CTD format.

Modules 4 and 5

Results of preclinical studies and clinical trials shall be submitted for biosimilars according to CTD format.

Studies of safety and efficacy of biosimilars shall be performed in compliance with appropriate EMA guidelines or MoH recommendations on biosimilars.

General and specific approaches to comparison studies for a specific pharmacotherapeutic group of biotechnological products are stated in the EMA scientific guidelines. If there is no appropriate EMA guideline for products of a specific pharmacotherapeutic group, the applicant shall contact MoH and the Center for a scientific advice.

1.4. Medicinal product with well-established medicinal use

Medicinal product with well-established medicinal use – a medicinal product for which the applicant can demonstrate that active substance(s) of the medicinal product with well-established therapeutic properties within the European Union (hereinafter – EU) and/or Ukraine has (have) a recognised efficacy and an acceptable level of safety in any dosage forms, at least for the 10-year period. In such case the relevant data of the published scientific literature (public information) shall substitute the results of preclinical studies and clinical trials contained in modules 4 and 5 of registration dossier.

The following rules should apply to prove a well-established medicinal use:

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

- the time over which an active substance has been used in medical practice in any dosage form;
- quantitative aspects of the use of the active substance, taking into account the extent of its use in medical practice, the extent of use on a geographical basis;
- the degree of scientific interest in the use of the active substance (reflected in the published scientific sources);
- the coherence of scientific assessments;
- the extent of the substance monitoring exerted by pharmacovigilance or other methods.

Different periods of time are used for establishing a well established use of different active substances. In any case, the period of time required for establishing a well established medicinal use must not be less than 10 years from the first systematic and documented use of that active substance as a medicinal product in any dosage form;

b) the documentation submitted by the applicant should cover all aspects of the safety and efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and postregistration studies and published scientific literature concerning experience of use in the form of epidemiological studies and, in particular, of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be provided. For demonstrating ‘well established medicinal use’ bibliographic references to other sources of evidence (postregistration studies, epidemiological studies, etc.) and not just data related to methods of control and trials may serve as a valid proof of safety and efficacy of a medicinal product if registration materials explain and justify the use of these sources of information satisfactorily;

c) If any information is missing justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking;

d) The preclinical and/or clinical overviews must explain the relevance of any data submitted which concern a medicinal product different from the product intended for marketing. A judgement must be made whether the medicinal product in question can be considered as similar to the registered medicinal product, in any dosage form, in spite of the existing differences.

e) Data on postregistration experience with other medicinal products containing the same constituents should be provided for proving safety and efficacy of the active substance.

A structure of registration dossier for medicinal products with well-established medicinal use should be in CTD format. Such registration dossiers shall be reviewed as mixed complete dossiers (own development studies, own and/or bibliographic data on safety and efficacy).

Module 1

In section 1.5.1. of module 1 a brief overview (not more than 5 pages) which summarizes all justifications and evidences used to demonstrate that active substance of the medicinal product has been in well established medicinal use.

This overview shall contain detailed information on medicinal product: qualitative and quantitative composition of active substances, pharmaceutical form, strength, indications for use, route of administration; issues related to scientific interest in the use of the active substance in any dosage form in medical practice and time periods of its systematic use.

All other requirements to module 1 shall be used to medicinal products with well-established medicinal use.

If some information is missing, a justification why a lack of this information in registration dossier is acceptable shall be provided in the appropriate section.

Module 2

Module 2 shall include: quality overall summary, preclinical and clinical overviews and summaries.

Module 3

A complete module 3 as required for registration dossier in CTD format shall be submitted taking into account the following:

Pharmaceutical form and excipients have no impact on safety and/or efficacy of the finished medicinal product;

Pharmacokinetics and pharmacodynamics of the active substance and its stability remain unchanged;

There is no problem related to bioavailability of the active substance or its forms.

Modules 4 and 5

Modules 4 and 5 shall contain detailed scientific bibliographic data on preclinical and clinical characteristics but their summaries shall be included in module 2. If some information is missing in the dossier, particular attention must be paid to justification of its absence in preclinical/clinical overviews.

References should be made to published scientific literature. The published literature means that the text may be for general use and be published in a scientific source preferably specialized scientific publications.

Copies of full text from a literature source shall be provided including their translations if applicable.

The EMA assessment report on registration dossier for medicinal product shall not be considered as a source of sufficient scientific information for proving a well-established medicinal use.

Well-established medicinal use refers to a specific therapeutic indication.

If well-known active substances are used for entirely new therapeutic indications, it is not possible to solely refer to a well-established use. In such cases, additional data on the new therapeutic indication together with appropriate pre-clinical and human safety data should be provided.

1.5. Fixed combination medicinal product

The combination of more than one active substances in a single pharmaceutical form for therapeutic purposes is a fixed combination. Active substances contained in separate pharmaceutical forms and presented in a combination pack cannot be considered as fixed combination.

A structure of registration dossier for fixed combination medicinal products should be in CTD format.

Registration dossier for a medicinal product with fixed combination of active substances shall contain all information related to this combination of modules 1-5. If some information on fixed combination is missing in the dossier, particular attention must be paid to justification of its absence in preclinical/clinical overviews. Where applicable, information regarding the manufacturing sites, the adventitious agents and safety evaluation shall be provided.

Modules 4 and 5

Scope and design of preclinical studies and clinical trials required for fixed combination depend on available data on individual active substances to be combined, and on the intended clinical use.

During the development of a fixed combination medicinal product the provisions of EMA Guideline on the non-clinical development of fixed combinations of medicinal products (EMA/CHMP/SWP/258498/2005) and EMA Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1) should be followed.

In the case of medicinal products containing active substances used in the composition of separate registered medicinal products but not hitherto used in combination for therapeutic purposes, the results of new preclinical tests or new clinical trials relating to that combination must be provided, but it is not necessary to provide scientific references relating to each individual active substance.

For combination medicinal products containing known active substances used earlier in the medical practice as separate medicinal products in the same pharmaceutical forms, doses and appropriate ratio for the same therapeutic purpose, the results of studies evidencing that there is no interaction between constituents which may affect the efficacy and safety of the medicinal product either during the manufacture or during the shelf life of the combination medicinal product should be provided.

For medicinal products containing only one or more new active substances in a combination with known active substance(s) the results of preclinical and clinical studies of the new active substance(s) should be provided together with preclinical and clinical data on the combination.

1.6. Informed consent

Following the obtaining of a registration certificate, its holder may allow another applicant to use his own pharmaceutical, preclinical and clinical documentation contained in the registration dossier for the registered medicinal product, with a view to examining other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

A prerequisite for registration of such medicinal product is the consent granted by the holder of the registration certificate for the registered medicinal product to use all information of modules 3-5 containing pharmaceutical data, data of pre-clinical studies and clinical trials, and the applicant who submits another medicinal product for registration shall have permanent access to this documentation or have the above information at his disposal.

For medicinal products registered based on the informed consent provided should only be a full module 1 including a registration form with appropriate annexes, and modules 2-5 with a letter of access from the registration certificate holder for the registered medicinal product who grants a consent to access to his registration dossier and to any further documentation.

If a dossier of the registered medicinal product includes an API master file, a new letter of access to it shall be included in module 1 of the registration dossier.

2. In addition to the main types of the medicinal products mentioned in item 1 of this section there are other types of medicinal products with other format of the registration dossier. Registration dossiers of other formats shall contain full modules 1-3, but modules 4 and/or 5 shall include instead of full data on the own preclinical studies and clinical trials either cross-references to other registration dossiers or the bibliographic data, or data on limited studies conducted by the applicant/the manufacturer for this medicinal product. A format of modules 4 and/or 5 depends on types of medicinal products.

Other types of medicinal products

2.1. Traditional medicinal product

Registration dossier of another format shall be submitted for traditional medicinal products in particular herbal ones, which fulfil the following criteria:

- a) Medicinal products have indications exclusively appropriate to traditional medicinal products which, by virtue of their composition and purpose, are developed and designed for use without the supervision of a doctor for diagnostic or therapeutic purpose;
- b) Medicinal products are designed exclusively for administration in accordance with a specified strength and posology (in doses and in compliance with dosage regimen as specified in instructions for medical use);
- c) Medicinal products are intended for oral, external or inhalation use;
- d) The period of traditional use (more than 30 years in the world and more than 15 years in EU and/or Ukraine) has elapsed;

e) The data on the traditional use of the medicinal product are sufficient, in particular the product proves not to be harmful under normal conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience.

The presence in the herbal medicinal product of vitamins or minerals the safety of which is well-documented, provided that their action is ancillary or capable of potentiating action of active ingredients regarding the claimed indication(s) shall not prevent the registration of such medicinal products.

These requirements shall not apply when MoH or the Center decide that a traditional medicinal product meets the criteria applied to the medicinal product with a complete dossier or to the homeopathic medicinal product without therapeutic indications.

Registration dossier for traditional medicinal products submitted for state registration shall include the particulars specified in modules 1-3, and:

The results of pharmaceutical (physicochemical, biological or microbiological) tests without results of preclinical (toxicological or pharmacological) studies and clinical trials;

The summary of product characteristics and/or instructions for medical use without clinical particulars;

In case of combinations of herbal substances with vitamins and minerals, the information referred to in item e); if the individual active ingredients are not sufficiently known, the data shall also relate to the individual active ingredients;

Bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the submission of the traditional medicinal product for registration, including at least 15 years in EU and/or Ukraine.

A corresponding product is characterised by having the same active ingredients, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the medicinal product in question;

A bibliographic review of safety data together with an expert report, and where required by the competent authority, upon additional request, data necessary for assessing the safety of the medicinal product.

The evidence of medicinal use over 30 years should also be provided in case of no registration of the medicinal product in Ukraine. The medicinal product is also considered as one, which fulfils this requirement even if a quantity of ingredients in the medicinal product has been reduced during this period.

2.2. Medicinal product from “in bulk” product

Medicinal products from “in bulk” product shall be submitted for registration when the corresponding medicinal product in packaging “in bulk” is registered in Ukraine or submitted for registration together with a medicinal product from “in bulk” product. During registration of medicinal products from “in bulk” product a confirmation of compliance of the manufacturing conditions of the medicinal product with requirements to the manufacture of medicinal products in Ukraine (good manufacturing practice) should not be provided for product “in bulk”, if such confirmation is available for this medicinal product in a consumer package in a manufacturer’s and/or applicant’s country, and in case of no such confirmation for the consumer packaging a

confirmation of compliance of the manufacturing conditions of the medicinal product with requirements to the manufacture of medicinal products in Ukraine (good manufacturing practice) should be provided for “in bulk” product.

For finished medicinal products produced through such stages of the manufacturing process as final packaging and/or labelling the following approaches shall be used during submission of the registration dossier.

The applicant shall submit module 1 according to the general requirements to the registration dossier in CTD format.

For modules 2-5 pharmaceutical, preclinical and clinical characteristics of the medicinal product shall be fully specified based on the registration dossier of the “in bulk” product manufacturer. The corresponding sections of module 3 shall contain additional data and documentation of the applicant (who submits the medicinal product for registration) concerning stages and manufacturing processes performed by him.

Name and location of the “in bulk” product manufacturer (responsible for quality control) and the manufacturer responsible for batch release should be specified in the corresponding sections of the registration dossier. Information on the manufacturer responsible for batch release should be specified on the package of medicinal product.

IV. Procedure for Conducting Expert Evaluation of Registration Materials for Medicinal Product Submitted for State Registration and Re-Registration

1. Before conducting expert evaluation the Center can give free consultations regarding state registration of medicinal products at the applicant’s request.

When the Center receives a MoH’s letter of referral the applicant shall submit to the Center a registration form of medicinal product submitted for state registration (annex 1), for homeopathic medicinal product – a registration form of homeopathic medicinal product submitted for state registration (annex 2), and for medicinal products produced according to the approved specifications – a registration form of medicinal product produced according to the approved specification which is submitted for state registration (annex 3) with the purpose of expert evaluation;

For API a registration form of active pharmaceutical ingredient which is submitted for state registration (re-registration) (annex 4) shall be provided.

If at the applicant’s request a simultaneous registration of the finished medicinal product and the API as part of this medicinal product is conducted separate registration certificates for the API and the finished medicinal product can be granted. The applicant shall submit one registration dossier for the finished medicinal product, and separate a registration form of medicinal product submitted for state registration (annex 1) and a registration form of active pharmaceutical ingredient submitted for registration (re-registration) (annex 4).

If medicinal product submitted for state registration is not registered in a manufacturer’s and/or applicant’s country or other countries its registration in Ukraine is allowed provided there are registration documents in volume envisaged by this Procedure, including cases of registration of medicinal products by applicants/manufacturers who are residents and use manufacturing sites located outside Ukraine on contract basis.

Applicant shall submit to the Center the registration form both in paper and electronic formats.

(Item 1 of section IV amended by new paragraph six according to the MoH Ukraine Order № 711 of 13.04.2018)

Information on the registration form submitted to the Center shall be entered into the e-database.

Collection and processing of personal data shall be performed in compliance with requirements of the Law of Ukraine “On Protection of Personal Data”.

2. Expert evaluation of a medicinal product, which is submitted for state registration, includes the following stages:

Preliminary expert evaluation for completeness of the registration dossier of a medicinal product according to the type of application and requirements specified in item 4 of this section;

Specialized expert evaluation of the registration dossier of a medicinal product in order to make a motivated conclusion concerning efficacy, safety, and quality of a medicinal product.

3. After receipt of the registration form the Center shall issue an invoice for payment of cost of expert evaluation under the contract concluded between the applicant and the Center within 7 working days.

4. After an invoice is paid by the applicant materials of the registration dossier, including preclinical study report and clinical trial report, shall be submitted to the Center depending on type of the medicinal product and requirements of:

(Paragraph 1 of item 4 of section IV in wording of MoH Ukraine Order № 1528 of 27.06.2019)

Section III of the Procedure and annexes 5, 6, 9, 10, 11 (depending on type of the medicinal product) and 28;

(Paragraph 2 of item 4 of section IV in wording of MoH Ukraine Order № 1528 of 27.06.2019)

Annex 7 – for registration of specific homeopathic medicinal products;

Annex 8 – for medicinal products produced according to the approved specification;

Annex 12 – for registration of API.

Preclinical study report and clinical trial report shall be structured according to the templates given in annexes 29, 30 of this Procedure and written pursuant to Information on completing the preclinical study (PS) report and Information on completing the clinical trial (CT) report according to Annexes 31, 32 of this Procedure.

(New paragraph 6 is added to item 4 of section IV according to MoH Ukraine Order № 1528 of 27.06.2019. Therefore, paragraphs 6 - 23 shall be considered as subparagraphs 7 - 24 respectively)

The Center shall accept registration materials within 7 working days of the date of their submission by the applicant.

The registration dossier shall be submitted according to the requirements of section V of the Procedure.

In case of state registration of medicinal products pertaining to a group “Medical gases”, submitted shall be registration form according to annex 3, materials of registration dossier according to annex 12 and instructions for medical use drawn up according to requirements of instructions for medical use of medicinal product.

In case of registration by the same applicant of a medicinal product under the name different from that under which this medicinal product has been registered the registration form shall be submitted according to annex 1 or annex 2 (depending on type of the medicinal product). The applicant shall submit the updated information included in module 1 of CTD in paper format and the updated registration materials for this medicinal product included in modules 2-5 of CTD which may be submitted in e-format. During specialized expert evaluation a compliance of registration materials with those submitted at the primary registration of this medicinal product shall be established taking into account all changes introduced by the applicant during the validity period of registration certificate. No laboratory testing of the medicinal product according to annex 13 shall be conducted.

If the applicant submits the medicinal product for registration to the regulatory authority(ies) of another country for the first time in the world he may submit an application for registration of this medicinal product in Ukraine and registration materials only after publication of final report on expert assessment of registration dossier on the official site of regulatory authority. Nevertheless, MoH shall make a decision as to registration of this medicinal product in Ukraine only after the approval of corresponding decision of regulatory body(ies) of the country(ies) where this medicinal product has been submitted for registration.

The applicant and/or his representative shall guarantee reliability of the information provided in materials of registration dossier.

If the applicant fails to submit to the Center the registration materials or a letter (singly) with substantiation of delay (not more than 20 working days) in their submission within 3 months after receipt of a MoH's letter of referral by the Center, the Center shall inform the applicant in writing within 3 working days on withdrawal of the medicinal product from the review.

Further on, the registration materials for this medicinal product may be repeatedly submitted to the Center for expert evaluation as foreseen by the Procedure.

Preliminary expert evaluation of registration dossier for the medicinal product submitted for state registration shall start upon receipt of the registration dossier compiled according to the type of the medicinal product. Related information shall be entered into the e-database.

During preliminary expert evaluation the registration dossier for a medicinal product shall be checked for completeness according to the type of medicinal product and requirements of the Procedure and its annexes specified in paragraph 2-5 of this item without evaluating the contents. In case of positive results of the preliminary expert evaluation the registration dossier shall be sent for the specialized expert evaluation, and the Center shall notify the applicant thereof in writing and enter the corresponding information into the e-database.

The period of delay in submitting an attested copy of the document confirming compliance of the manufacturing conditions of the medicinal product with requirements for the manufacture of medicinal products in Ukraine (good manufacturing practice) shall not be included in the timeframe for conducting expert evaluation of the registration materials established by the legislation. The preliminary expert evaluation shall be performed within 14 working days. Based on the results of preliminary expert evaluation the Center shall notify the applicant in writing and enter the corresponding information into the e-database.

If the results of preliminary expert evaluation are negative, the Center shall inform the applicant in writing that the registration materials could not be sent for the specialized expert evaluation indicating detailed grounds with reference to numbers of sections, subsections, items, subitems, paragraphs of the Procedure, or singly request the applicant to provide additional data and/or information necessary to ensure compliance of the registration dossier with requirements set by this Procedure.

The applicant shall provide additional data and/or information in accordance with the Center's remarks within 90 working days, or a letter with substantiated timeframe necessary for their finishing-off (not more than 20 working days). This information shall be entered into the e-database within 3 working days.

The time necessary for preparing and submitting additional data and/or information shall not be included in the time period for conducting expert evaluation.

The Center shall accept materials of the registration dossier finished-off by the applicant within 3 working days after their submission by the applicant and enter the obtained information into the e-database.

If the applicant fails to provide additional data and/or information or the latter is incomplete, and if the additional data and/or information submitted by the applicant do not ensure the compliance of the registration materials with the established requirements (except for a notarized copy of the document confirming compliance of the manufacturing conditions of the medicinal products with requirements to the manufacture of medicinal products in Ukraine (good manufacturing practice)) the registration materials shall be withdrawn from the evaluation, and the Center shall notify the applicant thereof within 3 working days.

The Center's decision on withdrawal of the registration materials from the evaluation may be contested according to the procedure established by the legislation.

Further on, at applicant's request the materials, taking into account the Center's remarks, may be submitted for state registration of medicinal products following the requirements of the Procedure.

5. Specialized expert evaluation of materials of the registration dossier for a medicinal product shall be performed by the Center's registration experts with an involvement of freelance experts and consultants. The aim of a specialized expert evaluation is to make a motivated conclusion on efficacy, safety, and quality of a medicinal product, including a confirmation of the correspondence between the preclinical study reports and clinical trial reports submitted by the applicant and the registration dossier materials, with recommendations to publish them on the MoH official website and recommendations to approve the instructions for medical use, text of packaging labelling of the finished medicinal product and methods of quality control of the medicinal product (hereinafter – MQC), and in addition, for the medicinal products to be purchased by a person authorized to make health care procurement, a confirmation of the correspondence between translations of the text of packaging labelling of the medicinal product, instructions for use of the medicinal product or summary of the product characteristics of the medicinal product and the registration dossier materials. The MQC recommended for approval shall be drawn up as a separate document based on the specifications/methods of control of the medicinal product developed and substantiated by results of the studies performed by the applicant (the manufacturer). Information given in MQC shall fully agree with the information included in the corresponding sections of the registration dossier submitted by the applicant (the manufacturer).

*{Paragraph 1 of item 5 of section IV in wording of
MoH Ukraine Orders № 1528 of 27.06.2019, № 1948 of 21.08.2020}*

During state registration of medicinal products to be purchased by a person authorized to make health care procurement specified in subitem 10.4 of item 10 of section V of the Procedure the conclusion shall include information on referring a medicinal product to the medicinal products to be procured using the funds under the state budget based on the procurement results to execute programmes and take centralized health care measures.

*{New paragraph 2 is added to item 5 of section IV according to
MoH Ukraine Order № 1948 of 21.08.2020}*

During state registration of medicinal products to be purchased by a person authorized to make health care procurement specified in subitem 10.5 of item 10 of section V of the Procedure the conclusion shall include information on referring a medicinal product to the medicinal products to be procured using the funds under the state budget based on the procurement results solely for the purpose of free supply to the health care units of the regional state administrations, the state administrations of the city of Kyiv and the city of Sebastopol, or entities licensed to conduct economic activity relating to medical practice.

{New paragraph 3 is added to item 5 of section IV according to MoH Ukraine Order № 1948 of 21.08.2020}

During specialized expert evaluation of the registration dossier aimed at receiving complete data on efficacy, safety and quality of the medicinal product each Center's expert commission may request twice the necessary additional data on efficacy, safety and quality of the medicinal product with references to numbers of sections, subsections, items, subitems, paragraphs of the Procedure, with no new requests of the materials already reviewed by an expert except for cases when additional materials submitted are incomplete. Information contained in the Center's requests addressed to the applicant shall be entered into the e-database.

If within 90 days after the Center's request for additional materials the applicant fails to provide these materials or fails to substantiate other timelines for submission of the materials, or they are incomplete except for a notarized copy of the document confirming compliance of the manufacturing conditions of the medicinal products with requirements to the manufacture of medicinal products in Ukraine (good manufacturing practice)), the registration materials shall be withdrawn from the evaluation, and the Center shall notify the applicant thereof in writing within 3 working days.

Further on, at the applicant's request the registration materials with due account of the Center's remarks may be submitted for expert evaluation as foreseen by the Procedure.

During registration of the medicinal products centrally authorized by the EMA (item 9 of section V of the Procedure), the original medicinal products specified in subitem 10.1 of item 10 of section V of the Procedure and the WHO-prequalified medicinal products specified in subitem 10.2 of item 10 of section V of the Procedure the correspondence of the registration dossier submitted for registration in Ukraine and the assessment report for the medicinal product drawn up by a drug regulatory authority (EMA and/or WHO and/or regulatory authority of any other country) shall be verified. In addition, the correspondence of the instructions for medical use, summary of product characteristic (if any), text of packaging labelling of the finished medicinal product and MQC submitted by the applicant and materials of the registration dossier shall be verified with no laboratory testing of the medicinal product according to annex 13. The applicant shall not receive remarks concerning the introduction of changes and amendments to the registration materials for these groups of medicinal products.

If state registration of the medicinal product to be purchased by a person authorized to make health care procurement (regardless of the country of manufacture) is conducted with the labelling, instructions for use of the medicinal product, and summary product characteristics of the medicinal product in the original language (in a language other than the state language) the correspondence between the instructions for medical use, summary of product characteristics, text of the labeling of the immediate and outer (if any) packaging, their translations submitted by the applicant and the materials of registration dossier shall be verified.

{Paragraph 8 is added to item 5 of section IV according to MoH Ukraine Order № 1948 of 21.08.2020}

During specialized expert evaluation of materials of the registration dossier the Center may refer the medicinal product submitted for registration to the authorised laboratory(-ies) according to the

sphere of accreditation in order to perform laboratory testing. Laboratory testing shall be performed in compliance with provisions of annex 13 for ensuring the reproducibility of the methods of control proposed by the applicant and specified in materials of the registration dossier.

During specialized expert evaluation the Center shall ensure a communication of independent expert representing the applicant's interests with the corresponding expert of the Center concerning particulars of the expert conclusions.

6. Medicinal product shall not be recommended for state registration if the results of specialized expert evaluation have not proved the conclusions concerning its efficacy, safety and quality namely:

Medicinal product is health harmful in humans (risk of using medicinal product outweighs an expected benefit);

Composition of the medicinal product is not as specified in the registration materials;

Registration materials do not comply with the requirements of the Procedure and its annexes;

If during the specialized expert evaluation of the registration materials for medicinal product containing the same active substance as the reference/original medicinal product, the efficacy and safety information for this reference/original medicinal product originally registered in Ukraine based on complete registration information is revealed to have been used or referenced earlier than 5 years since the day of first registration of the reference/original product in Ukraine. This requirement shall not apply to situations when the applicant has obtained according to the legislation a right to refer and/or use the registration information for the reference/original medicinal product, or has submitted his own full registration information which complies with requirements to the registration information for the reference/original medicinal product, or in other situations, envisaged by article 9 of the Law of Ukraine "On Medicines";

If a court decision comes into force that such registration has caused violation of intellectual property rights protected by the patent of Ukraine including those pertinent to manufacturing process, use, marketing of medicinal products. Copies of the court decision shall be submitted to the MoH and the Center;

In the case of a lack of correspondence revealed between translations of the text of packaging labelling of the medicinal product, instructions for use of the medicinal product or summary of product characteristics for the medicinal product and the registration dossier materials.

{New paragraph is added to item 6 of section IV according to MoH Ukraine Order № 1948 of 21.08.2020}

7. If the applicant can prove that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective reasons and refers to one of such grounds:

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

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

it would be contrary to generally accepted principles of medical ethics to collect such information,

the registration certificate may be granted subject to certain specific obligations.

These obligations may include:

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

the medicinal product submitted for registration may be supplied on doctor's prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radiopharmaceutical, by qualified specialist;

the instructions for medical use and any medical information shall draw attention of the doctor to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects;

the applicant shall report on adverse reactions to the medicinal product.

Based on the results of the expert evaluation of the registration dossier prepared shall be an expert report according to which the motivated conclusions on efficacy, safety and quality of the medicinal product, including a confirmation of the correspondence between the preclinical study reports and clinical trial reports submitted by the applicant and the registration dossier materials shall be granted. Registration experts of the Center's appropriate divisions shall be responsible for results of the expert evaluation performed by them.

{Paragraph 11 of item 7 of section IV in wording of MoH Ukraine Order № 1528 of 27.06.2019}

Results of the expert evaluations performed shall be examined at meetings of the Center's advisory body with participation of chairmen and deputy chairmen of the specialized expert working groups.

Based on the meeting results advice shall be given on drawing up Center's recommendations for MoH concerning state registration of medicinal products.

8. Registration certificate for medicinal product shall be granted according to the provisions of section VIII of the Procedure.

After obtaining the registration certificate for the finished medicinal product an applicant shall:

Include all obligations specified in item 7 of this section into the Risk Management Plan;

Introduce on timely basis any changes into the registration dossier for the registered medicinal product according to provisions of section VI of the Procedure;

Introduce changes into the instructions for medical use of any medicinal product in case of obtaining new data including conformation of the instructions for medical use of a generic medicinal product with the approved instructions for medical use of the original (reference) medicinal product;

Ensure that information on the medicinal product complies with the state of the art;

Submit periodic safety update report on the medicinal product (periodic report) at the Center's request or with the following frequency:

According to the frequency specified in the registration certificate at its issue, or

For the medicinal product registered in Ukraine, as the first country of the world, or for the first time in any other country – every 6 months during first 2 years after the date of registration of the

medicinal product (irrespective of the availability of the medicinal product in the circulation), annually during subsequent 2 years and thereafter at three-yearly intervals.

9. After expiration of the validity period of registration certificate the finished medicinal product may be re-registered according to the legislation unless MoH decides, on justified grounds relating to pharmacovigilance, to proceed with additional re-registration after 5 years.

Recommendations for re-registration of the medicinal product shall be provided based on expert evaluation of the updated benefit-risk balance conducted by the Center as foreseen by provisions of this section of the Procedure.

At re-registration of the finished medicinal product from “in bulk” product the validity period of registration certificate for “in bulk” product, from which this medicinal product is produced, shall also be renewed provided they are re-registered simultaneously.

At re-registration of any finished medicinal product prolonged shall be a validity period of approval to use the API as part of the medicinal product and the particulars on which are specified in the registration certificate for the finished medicinal product.

At re-registration of MIP reclassified as a medicinal product the expert evaluation of registration materials shall be conducted in the same way as for the medicinal product submitted for registration following provisions of this section of the Procedure, and the recommendation for registration of the medicinal product is provided. For this group of medicinal products the registration dossier shall be submitted in an available format (either in format of four parts, or in CTD format). If MIP meets the criteria of non-comparable biotechnological medicinal product the expert evaluation of registration materials shall be conducted according to the procedure envisaged for medicinal products submitted for registration based on the expert evaluation of updated risk/benefit data conducted by the Center according to the provisions of this section resulted in the issuance of registration certificate for the term of 5 years taking in account obligations to provide results of comprehensive comparability quality, safety and efficacy studies confirming its similarity to the reference (biotechnological) medicinal product.

{Paragraph 5 of item 9 of section IV as amended by the MoH Ukraine Order № 711 of 13.04.2018}

During re-registration procedure of the medicinal product the applicant may introduce changes into the registration dossier as required by provisions of section VI of the Procedure. These procedures shall be conducted simultaneously and independently of each other.

After entry of a MoH's letter of referral to the Center the applicant shall submit to the Center for expert evaluation:

A registration form of a medicinal product which is submitted for re-registration (annex 14),

A registration form of API which is submitted for registration (re-registration) (annex 4) together with a list of all approved changes in the form of the comparison table including date of submission, date of approval and short description of changes; MQC approved in Ukraine; certificate of analysis for one API batch.

Applicant shall submit to the Center the registration form both in paper and electronic formats.

{Item 9 of section IV amended by new paragraph ten according to the MoH Ukraine Order № 711 of 13.04.2018 }

Information on the submitted registration form shall be entered into the e-database.

10. The expert evaluation of documents at the re-registration includes the following stages:

Expert evaluation of particulars contained in the registration form in order to check them for compliance with information of the State register of medicinal products of Ukraine and with requirements of this Procedure;

Preliminary expert evaluation is conducted in order to check documents submitted by the applicant for completeness as required by the Procedure;

Expert evaluation of the risk-benefit balance of the finished medicinal product which is performed in order to draw up a motivated conclusion confirming favorable balance of expected benefits in relation to potential risk at use of the medicinal product.

11. After the entry of registration form the Center shall issue an invoice for making payment of cost of expert evaluation under the contract concluded between the applicant and the Center within 7 working days. After payment of an invoice the applicant shall submit a set of documents for finished medicinal products according to annex 15; for medicinal products produced according to the approved specification – according to annex 16.

If the applicant fails to submit the corresponding documentation or a letter (singly) with substantiated timeframe necessary for their submission (not more than 20 working days) to the Center within 3 months after receipt of a MoH's letter of referral at the Center, the Center shall inform the applicant in writing on the withdrawal of the medicinal product from the review within 3 working days.

Further on, materials for this medicinal product may be repeatedly submitted to the Center for expert evaluation as foreseen by the Procedure.

12. Preliminary expert evaluation shall start upon receipt of a set of documents and be performed within 14 days. Based on results of preliminary expert evaluation the Center shall inform the applicant in writing and enter the corresponding information into the e-database.

If the results of preliminary expert evaluation are negative, the Center shall inform the applicant in writing that the documents submitted could not be sent for specialized expert evaluation indicating detailed grounds with reference to numbers of sections, subsections, items, subitems, paragraphs of the Procedure, or singly request the applicant to provide additional data and/or information necessary to ensure compliance of the documents submitted with the Procedure.

The applicant shall provide additional data and/or information in accordance with the Center's remarks within 60 working days, or a letter with substantiated timeframe necessary for their finishing-off (not more than 20 working days). This information shall be entered into the e-database within 3 working days.

The time necessary for preparing and submitting additional data and/or information shall not be included in the timeframe for conducting expert evaluation.

If the applicant within 60 working days after the Center's request for additional materials fails to provide these materials or to substantiate another timeframe for providing them (not more than 20 working days), or the these are incomplete the materials shall be withdrawn from the evaluation, and the Center shall notify the applicant thereof in writing within 3 working days.

If a set of documents is verified to comply with requirements of the Procedure and annex 15 or annex 16 based on results of preliminary expert evaluation the corresponding documents shall be sent for the expert evaluation of the benefit-risk balance, instructions for medical use, labelling text

for the finished medicinal product, and the Center shall notify the applicant thereof in writing and enter the appropriate information into the e-database.

13. Expert evaluation of the benefit-risk balance shall be performed by postregistration surveillance experts involving, if necessary, freelance experts and consultants (with their consent).

Expert evaluation of the benefit/risk ratio of the medicinal products centrally authorised by the EMA (item 9 of section V of the Procedure), the original medicinal products specified in subitem 10.1 of item 10 of section V of the Procedure, the WHO-prequalified medicinal products specified in subitem 10.2 of item 10 of section V of the Procedure, the WHO prequalified vaccines and toxoids specified in subitem 10.3 of item 10 of section V of the Procedure, and the medicinal products to be purchased by a person authorized to make health care procurement that are specified in subitem 10.4 of item 10 of section V of the Procedure shall be conducted out of turn.

{Paragraph 2 of item 13 of section IV in wording of MoH Ukraine Order № 1948 of 21.08.2020}

During expert evaluation aimed at receiving the comprehensive data confirming the positive balance of expected benefits in relation to potential risk at use of the medicinal product, and data contained in the instructions for medical use each Center's expert commission may request twice the necessary materials supplementing data with references to numbers of sections, subsections, items, subitems, paragraphs of the Procedure. Information contained in the Center's requests addressed to the applicant shall be entered into the electronic database.

If within 60 days after the Center's request for additional materials the applicant fails to provide these materials or fails to substantiate another timeframe for submission of the materials, or they are incomplete, the registration materials shall be withdrawn from the evaluation, and the Center shall notify the applicant thereof in writing within three working days.

Further on, at applicant's request a set of documents with due account of the Center's remarks may be repeatedly submitted for expert evaluation as foreseen by the Procedure.

In case of the Center's remarks concerning the update of safety information in the instructions for medical use for the medicinal product submitted for re-registration, including conformation of the instructions for medical use of the generic medicinal product with the instructions/officially approved information for medical use of the original (reference) medicinal product the update of such information is admissible during the re-registration without interrupting expert works through submission of additional materials with no variation procedure.

{Paragraph 6 of item 13 of section IV in wording of MoH Ukraine Order № 1528 of 27.06.2019}

In case of the Center's remarks concerning introduction of efficacy-related changes (pharmacovigilance) into the appropriate documents for the medicinal product submitted for re-registration, these changes shall be introduced according to provisions of section VI of the Procedure after the end of the re-registration procedure.

(Paragraph of item 13 of section IV in wording of MoH Ukraine Order of 27.06.2019 № 1528)

Based on results of expert evaluation the motivated conclusions on benefit-risk balance of the medicinal product, compliance of the instructions for medical use and labelling text for the finished medicinal product shall be made. Registration experts of the Center's appropriate divisions shall be responsible for results of expert evaluation performed by them.

Results of expert evaluations performed shall be examined at meetings of the relevant Center's advisory body with a participation of chairmen and deputy chairmen of the specialized expert working groups, as applicable.

Based on results of the above meetings advice shall be given on drawing up the Center's recommendations for MoH concerning re-registration of medicinal products.

14. The medicinal product shall not be recommended for re-registration if during expert evaluation of documents pertinent to postregistration surveillance results the medicinal product has been proved to be harmful to human health (risk of using of medicinal product outweighs the expected benefit).

15. The controversial issues that occurred during expert works pertinent to registration (re-registration) and/or introduction of changes into registration materials, and other issues pertinent to circulation of medicinal products within the Center's competence shall be examined at meetings of the Center's advisory body with a participation of chairmen and deputy chairmen of the specialized expert working groups.

If positive conclusions are made based on results of expert evaluation of the registration materials concerning the registration (re-registration) and/or introduction of changes into the registration materials the Center shall weekly compile materials according to item 1 of section VIII of the Procedure.

16. If the applicant doesn't agree with results of expert evaluations performed during the state registration and/or re-registration, he may contest the Center's decision according to the procedure established by MoH within 30 working days of its receipt. The Applicant shall present to the Center the relevant materials substantiating his position within 30 working days after submission of such appeal.

The Center shall perform specialized expert evaluation of the additional materials submitted by the applicant within 60 working days after their receipt and provide relevant motivated recommendations to MoH.

At the applicant's request an independent expert representing him may take part in discussion of the results of the expert evaluation of registration materials performed by the Center.

17. At the applicant's request the Center shall arrange for applicant's access to certain sections of the e-database in terms of medicinal product submitted to the Center for expert evaluation. The conditions of applicant's access to certain sections of the e-database shall be stipulated under a contract for conducting expert evaluation concluded between the applicant and the Center.

V. Main registration dossier requirements

1. Materials of registration dossier submitted for an expert evaluation shall include the following:

1) For state registration – information structured according to annex 5, preclinical study report and clinical trial report for their publication on the official MoH website according to the templates (annexes 29, 30). During preparation of registration materials for finished medicinal products the applicant shall follow general registration dossier requirements stated in annex 6, taking into account requirements of section III of the Procedure and annexes 7 - 11 (depending on type of the medicinal product); for API – the documents specified in annex 12 and structured according to annex 5 as regards API;

{Subitem 1 of item 1 of section V in wording of MoH Ukraine Order № 1528 of 27.06.2019}

2) For re-registration – particulars specified in annex 15 or annex 16 (for medicinal products produced according to the approved specifications);

3) For introduction of changes into the registration materials – information specified in annex 17, or information required for expert evaluation of the Type II variations taking into account

requirements of item 6 of section VI of the Procedure, and changes requiring a new registration – information necessary for expert evaluation of these changes.

2. Registration materials shall be drawn up taking into account the information stated in annexes 18-24.

3. For state registration of medicinal products for which the patent has been issued according to the current legislation of Ukraine, the applicant shall submit a copy of patent or authorization (license) to manufacture and sale the registered medicinal product, and a document confirming the patent validity in Ukraine. The applicant shall submit a letter in a format given in annex 25, specifying that rights of the third party being patent-protected or transferred according to the authorization (license) are not violated because of registration of the medicinal product.

4. For registration of APIs the possibility of their use as medicinal products in packaging “in bulk” and quantity of additional materials in such situations shall be specified.

5. For registration of API undergone in part the technological stages of their reprocessing into finished dosage form (in particular, as granulated material, pellets, other presentations) specified shall be the quantity of additional materials in the CTD format (annex 5) for confirming properties given to active substance due to the above partial technological reprocessing (extended or sustained action, resistance to gastric juice, etc.).

6. For registration of the finished medicinal product the specifications for active substance (sections of the registration dossier 3.2.S.4 of CTD) may contain additional indices of technological parameters of active substance substantiated at the pharmaceutical development (parts of the registration dossier 3.2.P.2 of CTD), and supplement indices of the specifications contained in MQC for active substance and/or in a certificate of quality issued by the manufacturer.

7. Amount of registration materials related to medicinal products submitted for state registration shall be determined by type of the medicinal product (section III of the Procedure). List of documents for expert evaluation of materials submitted for state registration of API and medicinal products pertaining to a group “Medical gases” is specified in annex 12.

8. For homeopathic medicinal products which are registered in compliance with annex 7, or for medicinal products produced according to the MoH-approved specifications (annex 8), the applicant shall submit a registration dossier as complete as specified in the above annexes to the Procedure. If the information is insufficient for expert evaluation of safety of the medicinal product the Center may request additional safety data.

9. If medicinal product is centrally authorized by the EMA the applicant may submit information contained in module 1 of the CTD (with translation into Ukrainian) and in module 2 of the CTD (with translation into Ukrainian if applicable) in paper format. The applicant may submit Modules 3-5 of CTD in electronic format, submitted also are MQC, labelling text for immediate and outer (if any) packaging of the finished medicinal product, instructions for medical use of the medicinal product, and at applicant’s request – a summary of product characteristics for the medicinal product. The EMA public assessment report for medicinal product shall be submitted together with the registration dossier.

{Item 9 of section V as amended by MoH Ukraine Order № 1528 of 27.06.2019}

10. Specific requirements can be applied to the materials of registration dossier in the case of registration of the original medicinal products and WHO-prequalified medicinal products included in the WHO List of Prequalified Medicinal Products in order to provide the necessary medical aid to population for treating socially dangerous diseases (TB, HIV/AIDS, viral hepatitis), rare and oncological diseases, and to provide the population with the necessary **preventive** healthcare aimed

at immunoprophylaxis in case of the risk of unsafe infectious disease or mass spread of unsafe infectious disease. The applicant may submit information included in module 1 of the CTD (with translation into Ukrainian) and module 2 of the CTD (with translation into Ukrainian, if applicable) in paper format. The applicant may submit Modules 3 - 5 of the CTD in electronic format, submitted also are: MQC, text of the labeling of the immediate and outer (if any) packaging of the finished medicinal product, instructions for medical use of the medicinal product, and at applicant's request – summary of product characteristics for medicinal products specified in subitems 10.1 – 10.3 of item 10 of this section.

{Item 10 of section V as amended by MoH Ukraine Order № 1528 of 27.06.2019}

During registration of medicinal products to be purchased by a person authorized to make health care procurement according to the list approved by the Cabinet of Ministers of Ukraine to execute programmes and take centralized health care measures specific requirements to materials of the registration dossier can be applied. The applicant may submit information contained in Module 1 of the CTD (with translation into Ukrainian) and Module 2 of the CTD (with translation into Ukrainian, if applicable) in paper format. The applicant may submit Modules 3-5 of the CTD in electronic format, submitted also are MQC, labeling of the immediate and outer (if any) packaging of the medicinal products, instructions for medical use of the medicinal product, summary of product characteristics of the medicinal product, and certified copy of a document confirming the compliance of manufacturing conditions for the medicinal product submitted for the registration with the requirements to manufacture of medicinal products in Ukraine (for domestic manufacturers – a copy of valid license to manufacture medicinal products certified according to the established procedure) for the medicinal products specified in subitems 10.4, 10.5 of item 10 of this section.

{New paragraph is added to item 10 of section V according to MoH Ukraine Order № 1948 of 21.08.2020}

10.1. In addition, the following documents shall be submitted during registration of original (innovator) medicinal product (molecule is not placed on the market of Ukraine) for treating socially dangerous diseases (TB, HIV/AIDs, viral hepatitis) and medicinal product with original molecule for treating rare and oncological diseases, which were registered in countries where regulatory authorities use high quality standards complying with the WHO standards, in particular: the US Food and Drug Administration (FDA); the European Medicines Agency (EMA) (centrally authorized); the Swiss Agency for Therapeutic Products (Swissmedic); the Pharmaceuticals and Medical Devices Agency of Japan (PMDA); the Medicine and Healthcare Products Regulatory Agency of UK (MHRA); the Therapeutic Goods Administration of Australia (TGA):

- a) An official assessment report for a medicinal product drawn up by a regulatory authority, attested by an applicant's/an applicant's representative stamp (if any);
- b) An applicant's written confirmation that the medicinal product submitted for registration corresponds to the medicinal product registered in a country the regulatory authority of which applies high quality standards complying with the WHO-recommended standards.

10.2. During registration of medicinal products for treating TB or HIV/AIDs or viral hepatitis, prequalified by the WHO and included in the WHO List of Prequalified Medicinal Products (hereinafter – the WHO List) the medicinal product submitted for registration shall be produced at the manufacturing site inspected within the framework of WHO Prequalification Programme and included in the WHO List; the pack type and size for product submitted for registration shall be specified in the WHO List. In addition, the following shall be submitted:

{Paragraph 1 of subitem 10.2 of item 10 of section V amended by the MoH Ukraine Order № 711 of 13.04.2018}

- 1) WHO Public Assessment Report (WHOPAR(s)), sealed by the applicant/applicant's representative (if applicable);

- 2) WHO Public Inspection Report for manufacturers and clinical study divisions (WHOPIR(s)), sealed by the applicant/applicant's representative;
- 3) Official letter from the applicant (using the WHO approved template) about the start of product state registration procedure in Ukraine when access code to the official WHO Prequalification Programme site has been received;
- 4) The applicant's written confirmation that the medicinal product submitted for registration corresponds to that prequalified and included in the WHO List based on the documents mentioned in subitems 1 and 2 of this item. In this case the medicinal product may be registered in Ukraine under the name different from that under which this medicinal product has been registered in another country or specified in the WHO List.

Registration dossier for such medicinal products shall be submitted to the Center in the same format as per WHO prequalification procedure.

10.3. During registration of vaccines, toxoids prequalified by WHO and included in the list of WHO-prequalified vaccines the vaccine and/or toxoid submitted for registration shall be produced at the manufacturing site inspected within the framework of WHO Prequalification Programme and included in the WHO List; pack type and size for product submitted for registration shall be specified in the WHO List. In addition, the following shall be submitted:

- 1) Batch control certificate issued by the national control authority of the country-manufacturer of vaccine and/or toxoid;
- 2) Protocol of manufacturer for three consecutive final batches produced from three consecutive bulk batches of vaccine and/or toxoid;
- 3) Information about Vaccine Vial Monitor (VVM) or other control methods of maintaining cold chain (in particular, temperature indicators);

{Subitem 4 of subitem 10.3 of item 10 of section V is deleted. Therefore, subitem 5 should be considered as subitem 4 according to MoH Ukraine Order № 1528 of 27.06.2019}

- 4) Applicant's written confirmation that the vaccine and/or toxoid submitted for registration corresponds to that prequalified and put on the official WHO List.

Registration dossier for such vaccines and toxoids shall be submitted to the Center in the same format as one submitted to WHO for prequalification procedure.

{Paragraph 7 of subitem 10.3 of item 10 of section V is deleted. Therefore, paragraph 8 should be considered as subitem 7 according to MoH Ukraine Order № 1528 of 27.06.2019}

{Paragraph 7 of subitem 10.3 of item 10 of section V is deleted. Therefore, paragraph 8 should be considered as subitem 7 according to MoH Ukraine Order № 1948 of 21.08.2020}

10.4. If state registration of the medicinal product to be purchased by a person authorized to make health care procurement (regardless of the country of manufacture) is conducted with the labelling and instructions for use of the medicinal product, which meet the requirements of parts 1, 2, 3 and 5 of article 12 of the Law of Ukraine "On Medicines", on the submission date of an application for state registration the medicinal product shall be put on the List of medicinal

products, medical devices and accessories to them, procured using the funds under the state budget to execute programmes and take centralized health care measures approved by the Cabinet of Ministers of Ukraine, and the applicant shall be determined as the winner of the procurement/simplified procurement procedure announced by a person authorized to make health care procurement.

{New subitem 10.4 is added to item 10 of section V according to MoH Ukraine Order № 1948 of 21.08.2020}

10.5. If state registration of the medicinal product to be purchased by a person authorized to make health care procurement (regardless of the country of manufacture) is conducted with the labelling, instructions for use of the medicinal product and summary product characteristics of the medicinal product in the original language (in a language other than the state language), on the submission date of an application for state registration the medicinal product shall be put on the List of medicinal products, medical devices and accessories to them, procured using the funds under the state budget to execute programmes and take centralized health care measures approved by the Cabinet of Ministers of Ukraine, and in addition, the following shall be submitted:

1) layout of the packaging mockup of the medicinal product;

2) translations of the text of the labeling of the immediate and outer (if any) packaging, the instructions for use and the summary of product characteristics of the medicinal product in the language meeting the language requirements as foreseen by legislation, formed according to the requirements for labeling of immediate and outer (if any) packaging, instructions for use of the medicinal product and summary of characteristics established by this Procedure, which are certified by the signature of the applicant or his authorized representative.

In the case of registration of the medicinal products specified in items 9 and 10 (subitems 10.1-10.5) of this section the registration materials shall be reviewed out of turn.

{New subitem 10.5 is added to item 10 of section V according to MoH Ukraine Order № 1948 of 21.08.2020}

11. The registration dossier materials shall be submitted to the Center according to the type of medicinal product in triplicate.

The registration dossier materials and additional data and/or information necessary for ensuring compliance of the registration dossier materials shall be submitted as compiled volumes. Each volume should be limited to 250 sheets, the sheets should be numbered. The applicant shall gross number all dossier sheets by Arabic numerals in the upper right corner with an ordinary soft pencil or electronically or with a mechanical numerator.

The applicant may also submit the e-registration dossier in a format corresponding to the e-CTD format recommended by ICH if technically possible.

The registration dossier materials shall be submitted in Ukrainian or English.

{Item 11 of section V in wording of the MoH Ukraine Order № 1345 of 09.06.2020}

VI. Procedure for expert evaluation of materials on introduction of changes in registration materials related to medicinal product

1. Before conducting expert evaluation at applicant's request the Center may give free consultations on issues pertinent to introduction of changes in registration materials for the medicinal product.

2. The Applicant shall inform the MoH of any changes (listed in annex 17 to this Procedure and in subitems 2.2 - 2.4 of this item) associated with the registered medicinal product providing information on reasons for these changes and their potential effect on efficacy, safety, quality of a

medicinal product, and introduce appropriate changes in the registration materials. The applicant shall not stop introducing changes in the registration dossier materials according to the provisions of this section when the medicinal product undergoes re-registration procedure. Both procedures shall be conducted simultaneously and separately from each other.

If the introduction of safety-related changes into instructions for medical use of the medicinal product is necessary the applicant shall notify the Center thereof in whatever way, and submit an application for introduction of changes within 60 calendar days after receipt of information necessitating introduction of such changes.

At the applicant's request the registration materials pertinent to the registered medicinal products may be supplemented via the procedure for introducing changes into the registration materials by the preclinical study report and the clinical trial report to be published on the official MoH website according to the Law of Ukraine "On Medicines".

{New paragraph is added to item 2 of section VI of MoH Ukraine Order № 1528 of 27.06.2019}

2.1. As regards their nature, the variations are classified as follows:

Type IA – minor variations having a minimal impact or no impact at all, on the quality, safety or efficacy of the medicinal product, which pertain to introduction of changes into the content of the registration materials submitted by the time of making a decision about registration of medicinal product, and do not require its new registration;

Type IB - minor variations which are neither a Type IA variation nor a Type II variation nor a variation requiring new registration;

Type II– any variations in the registration materials, which do not require new registration of medicinal product, and may have a significant impact on its quality, safety or efficacy but should not be considered as Type IA or Type IB variation.

2.2. Urgent safety-related variations pertinent to a medicinal product – urgent safety restrictions associated with safety of the use of the medicinal product, which are to be implemented by the applicant in case of detection of a risk to human health at the use of registered medicinal product. The applicant shall immediately inform the Center about any reason, nature and date of an expected implementation of urgent restrictions. If within 24 hours after receipt of such information the Center has not raised objections the applicant shall impose these urgent restrictions and at the same time (but not later than within 48 hours after making a decision on implementation of urgent variations) shall announce introduction of changes (according to legislation) and submit supporting documents to the Center as required by the Procedure.

If the applicant has become aware of detected unsafe properties of medicinal product for human health or life which are a reason for making decision by the applicant to implement restrictions of its use, the applicant shall inform the Center in any format and announce (according to legislation) introduction of changes pertinent to detected safety issues, and submit to the Center appropriate documentation pertinent to the detected safety issues immediately, but not later than 15 calendar days after receipt of this information. The proposed changes shall be approved by the respective MoH order, and then the medicinal product shall be used according to the revised instructions for medical use.

If the Center receives a substantiated information on the detected unsafe properties of the medicinal product for human health or life, which are a reason for making an appropriate decision on implementation of restrictions of use of the medicinal product as required by the legislation the Center shall inform the applicant about this in any format immediately, but not later than 15 calendar days of the date when such decision is made.

If the applicant agrees with the decision made he shall announce introduction of such changes according legislation immediately, but not later than 15 calendar days of receipt of this information, and submit to the Center documentation substantiating them according to the Procedure. The proposed changes shall be approved by the respective MoH Order, thereafter the medicinal product shall be used according to the revised instructions for medical use.

In case of the applicant's disagreement with the decision made and his refusal to introduce changes pertinent to safety of medicinal product to the registration materials with no substantiation or feedback given concerning this decision, MoH shall make a decision on annulment or temporary suspension of validity of registration certificate according to the procedure envisaged by current legislation.

If the 15th calendar day is a day-off or holiday the information should be submitted on the next working day.

2.3. Change of applicant (holder of registration certificate) refers to the procedure for transfer of ownership of the registered medicinal product from the approved applicant (the holder of registration certificate) to another legal entity/natural person as a new applicant (an assignee). Change of the applicant's name and/or location is not classified as a change of the applicant if the applicant is the same legal entity/natural person. In case of a change of holder of registration certificate the registration certificate insert specifying the new applicant shall be issued but with no prolongation of its validity.

If change of the applicant (the holder of registration certificate) applies to several registered medicinal products a separate application shall be submitted for each registration certificate.

2.4. Technical mistake – an error made in the documents approved at the registration. It does not require an expert evaluation by the Center's registration experts, and is detected when comparing the documents approved at the registration with the applicant's registration materials. Technical mistakes include:

- 1) Mistakes pertinent to spelling and/or grammatical mistakes including those associated with transliteration;
- 2) Mistakes caused by incorrect translation into Ukrainian of the administrative data, such as form of property, name, location of applicant/manufacturer of the medicinal product;
- 3) Discrepancy in MQC, labelling text of immediate and outer (if any) packaging of the medicinal product, summary of product characteristics, instructions for medical use of the medicinal product;
- 4) Errors in MQC pertinent to translation or transfer of information concerning:

Name, quantitative and qualitative composition of the medicinal product and/or packaging materials, shelf life, storage conditions, name and location of manufacturer/applicant, etc;

Errors in specifications and/or methods of quality control in particular digital and those caused by translation; errors in design equations occurred at reducing expanded equations;

Mistakes at referencing to general pharmacopoeial articles and monographs, normative documents if the basic information of the section contains the above references;

- 5) Discrepancies in information (variant reading) within one document;

- 6) Spelling and/or grammatical mistakes in summary product characteristics for a medicinal product and instructions for medical use of the medicinal product provided they do not have impact on the contents;
- 7) Discrepancies in the presentation of information on medical use of the medicinal product in the summary of product characteristics and instruction for medical use for the medicinal product which have been approved simultaneously; specifying doses of the product in units of the pharmaceutical form, more detailed presentation of the information in one of the documents;
- 8) Entering name or INN of the medicinal product into the documents approved during the registration of the medicinal product provided this information is available, at least, in one of such documents;
- 9) Spelling and/or grammatical mistakes in the registration certificate for a medicinal product; discrepancies in the presentation of information given in the registration certificate for a medicinal product and in approved summary of product characteristics, and/or instructions for medical use and/or MQC.

Correction of technical mistakes, except for those specified in subitem 9 of this subitem, shall be approved by the MoH Order. For mistakes specified in subitem 9 of this subitem the corrected registration certificate shall be submitted to MoH for endorsement.

{Subitem 2.4 of item 2 of section VI as amended by MoH Ukraine Order № 1528 of 27.06.2019}

3. Variations requiring new registration of the medicinal product:

3.1. Changes to the active substance(s):

- 1) Replacement of an active substance by a different salt, ester, derivative, where characteristics specifying a benefit-risk ratio do not significantly differ from the registered ones or use of other isomers, or replacement of isomer composition, or slight changes in molecular structure of biological active substances, except for changes to active substance of an influenza vaccine;
- 2) Modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where characteristics specifying a benefit-risk ratio do not significantly differ from the registered ones;
- 3) New ligand or coupling mechanism for a radiopharmaceutical medicinal product, where characteristics specifying a benefit-risk ratio do not significantly differ from the registered ones;
- 4) Change to the extraction solvent or the ratio of herbal drug to herbal drug preparation for the herbal medicinal product where characteristics specifying a benefit-risk ratio do not significantly differ from the registered ones;

3.2. Changes to strength, pharmaceutical form and method of use:

- 1) Change of bioavailability;
- 2) Change of pharmacokinetics;
- 3) Change or introduction of an additional strength of the medicinal product (additional strength);
- 4) Change or addition of a new pharmaceutical form;
- 5) Change or addition of a new route of administration (for parenterals because of differences in efficacy and safety of the medicinal product at intraarterial, intravenous, intramuscular and other routes of administration).

When introducing such changes, the applicant shall submit appropriate parts of registration materials with reasons for the need of changes which would substantiate the above mentioned changes and are sufficient for the expert evaluation of the medicinal product. Expert evaluation of registration materials in support of introduction of changes requiring a new registration shall be performed according to provisions of section IV of the Procedure like for the primary registration of medicinal product. A separate registration certificate or an insert into the valid registration certificate depending on type of the changes introduced shall be granted to the applicant upon the approval of changes requiring a new registration.

4. Subject to expert evaluation shall be each certain change, even if introduced simultaneously.

After receipt of a MoH's letter of referral by the Center the applicant shall submit materials pertinent to the introduction of changes to the Center for expert evaluation as follows:

For Type IA, IB or II changes – a registration form according to annex 26;

For change of applicant (holder of registration certificate) – a registration form according to annex 26 with a cover letter concerning transfer of ownership of the registered medicinal product (signed by the approved applicant who transfers the ownership);

For variations requiring a new registration – a registration form according to annex 1;

For correcting technical mistake – a letter (optional format) where a mistake and grounds for its correction are indicated.

Attached to the registration form should be:

A copy of the valid registration certificate (if changes related to safety of the use of a medicinal product submitted for re-registration need to be introduced, a copy of the valid registration certificate shall be submitted, if any).

{Paragraph 8 of item 4 of section VI in wording of MoH Ukraine Order № 1528 of 27.06.2019}

A confirmation of the approval of proposed changes by the competent authority of a manufacturer's/applicant's country or another country on which market this medicinal product is placed, otherwise a justification of a lack of the corresponding document.

Applicant shall submit to the Center the registration form both in paper and electronic formats.

{New paragraph 10 is added to item 4 of section VI according to the MoH Ukraine Order № 711 of 13.04.2018}

Information on the registration form submitted shall be entered into the e-database.

After receipt of the registration form the Center shall issue within 7 working days an invoice for payment under the contract concluded between the applicant and the Center. The applicant shall make the payment and submit to the Center the registration materials in support of the proposed changes. The Center shall accept the registration materials within 7 working days of the date of applicant's request.

If the applicant fails to submit the materials of registration dossier or a letter (singly) with substantiated period of delay in their submission (not more than 20 working days) to the Center within 3 months after receipt of a MoH's letter of referral by the Center, the Center shall withdraw the variations from the review and inform the applicant in writing thereof within three working days.

Further on, documents in support of introduction of changes into the registration materials for this medicinal product may be submitted for expert evaluation as foreseen by the Procedure. An appropriate information shall be entered into the e-database.

5. In case of introduction of Type IA or IB changes to the registration dossier of one medicinal product the registration form shall deal with only one Type IA or IB variation. In case of simultaneous introduction of several Type IA or IB variations a separate registration form shall be submitted for every variation, which shall refer to other registration forms for introduction of changes.

If Type IA change causes other successive Type IA changes, one registration form may include all successive changes together with description of correlations between these successive Type IA changes.

If Type IB change causes other successive Type IA or IB changes, one registration form may include all successive changes together with description of correlations between these successive Type IA or IB changes.

If changes require successive review of summary of product characteristics, instructions for medical use of the medicinal product, MQC, labelling text of immediate, outer (if any) packaging for the finished medicinal product, they are considered as a part of changes.

6. In case of introduction of major Type II changes, the application may apply to only one Type II change. If several Type II changes are necessary to be introduced, a separate registration form shall be submitted for every change; every such application shall refer to other registration form.

If Type II change causes other successive Type II changes, one registration form may include all successive changes together with description of correlations between these successive Type II changes.

If changes require successive review of summary for product characteristics, instructions for medical use, MQC, labelling text of immediate, outer (if any) packaging they are considered as a part of changes.

7. If a proposed change isn't covered by the classification given in annex 17 this change is indicated as a subitem "Other variations" in the respective item of registration form (annex 26).

8. The changes concerned including "Other changes" may be either IA or IB Type changes or II Type changes.

8.1. IA Type variations include:

1) Administrative variations only:

Changes in the name and/or location of the applicant (registration certificate holder);

Changes in the name and/or location of the manufacturer of finished medicinal product;

Changes in the name and/or location of the manufacturer of API;

2) Deletion of any manufacturing site for the following manufacturing stages of finished medicinal product: manufacture of API, manufacture of intermediate product or finished medicinal product, packaging, batch release, batch control;

- 3) Variations related to changes to an approved physico-chemical method of analysis provided the method of analysis remains the same (for example, a change in column length but not a different type of column), the updated method of quality control which shows compliance with the previous method has been validated, and the specification limits remain the same;
- 4) Variations related to changes made to the specifications of API or of an excipient in order to comply with an update of the SPhU or the European Pharmacopoeia or another pharmacopoeia, where the change is made exclusively to comply with these pharmacopoeias;
- 5) Variations related to changes in the packaging material not in contact with the medicinal product, which do not affect the delivery, use, safety or stability of the medicinal product;
- 6) Changes in specifications for the medicinal product, API or active substance, starting materials, intermediates, excipients which result in the tightening of specification limits, provided the new updated parameters remain within the currently approved range, and do not result from unexpected events arising during manufacture.

8.2. Type II variations include:

- 1) Variations related to introduction of a new indication to use or to the modification of an existing one;
- 2) Significant modifications of the summary of product characteristics due, in particular, to new quality findings, results of preclinical studies and clinical trials, new safety reports of a medicinal product including urgent safety-related changes;
- 3) Variations related to changes outside the range of approved specifications, limits or acceptance criteria if this is not because of bringing into compliance with the SPhU or the European Pharmacopoeia;
- 4) Variations related to substantial changes to the manufacturing process, formulation, specifications or impurity profile of API or active substance, or finished medicinal product which may have a significant impact on its quality, safety or efficacy;
- 5) Variations related to modifications in the manufacturing process or sites of the biological API or active substance;
- 6) Variations related to introduction of a new design space or the extension of an approved one, where the design space has been developed in accordance with the relevant European and international scientific guidelines;
- 7) Variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza.

8.3. Type IB changes include minor variations which are neither a Type IA variation nor a Type II variation nor a variation requiring new registration.

9. Expert evaluation of proposals for an introduction of changes to materials of the registration dossier shall be performed by the Center after receipt of the registration materials in support of the proposed variations and payment of its cost specified by the contract concluded between the applicant and the Center.

Expert evaluation of proposals for an introduction of changes to the registration dossier materials of the medicinal products centrally authorised by the EMA (see item 9 of section V of the Procedure),

the original medicinal products specified in subitem 10.1 of item 10 of section V of the Procedure, the WHO-prequalified medicinal products specified in subitem 10.2 of item 10 of section V of the Procedure, and the WHO-prequalified vaccines and toxoids specified in subitem 10.3 of item 10 of section V of the Procedure, and the medicinal products to be purchased by a person authorized to make health care procurement and specified in subitems 10.4, 10.5 of item 10 of section V of the Procedure shall be conducted out of turn.

{Paragraph 2 of item 9 of section VI in wording of MoH Ukraine Order № 1948 of 21.08.2020}

10. In case of introduction of Type IA, IB variations, the materials shall be submitted to the Center for an expert evaluation according to annex 17.

If the applicant introduces Type IA variations to the registration dossier the applicant may optionally notify of their introduction according to the legislation within 12 months after the implementation of these variations by the applicant. This does not apply to Type IA_{IN} (Type IA variations with immediate notification). According to the legislation the applicant shall submit a notification of such changes immediately after their implementation specifying its date.

For Type IB variations the applicant shall submit a notification of introduction of such changes before their implementation as required by the legislation.

For introduction of Type II variations the applicant shall submit to the Center:

Materials which substantiate introduction of changes;

Appropriate materials with changes introduced;

Revised or updated existing expert reports (reviews, conclusions) where the changes are taken into account (if necessary);

If variations result in changes to MQC, labelling text of immediate, outer (if any) packaging of the finished medicinal product, instructions for medical use, copies of these documents shall be provided for approval according to requirements of annex 23 and annex 20 respectively.

In case of changes in the instructions for medical use which are not associated with and do not affect the clinical information (name of medicinal product, composition, dosage form, main physical and chemical properties, manufacturer, location, storage conditions, shelf life, etc.), the applicant shall submit, as part of other registration dossier, a registration form together with changes to the instructions for medical use for a medicinal product according to a form given in annex 27.

At applicant's request the registration dossier may be submitted in the form of changes introduced into certain sections of the registration dossier in CTD format.

11. For introduction of Type II variations into registration materials for a seasonal, pre-pandemic or pandemic vaccine for preventing influenza the applicant shall submit to the Center:

Completed registration form;

Update or addendum to sections for quality, preclinical overviews and clinical overviews (if any);

Supporting data to the proposed variation(s);

Revised information on vaccine which is presented in the appropriate sections of registration dossier;

Copies of the revised MQC, labelling text of immediate, outer (if any) packaging of the finished medicinal product, instructions for medical use shall be presented for approval according to requirements of annex 23 and annex 20, respectively.

12. In case of change of applicant (holder of registration certificate) a new applicant (a transferee) shall submit to the Center documents listed in annex 28.

13. Expert evaluation of materials pertinent to introduction of changes includes the following stages:

Preliminary expert evaluation of the registration materials to verify their compliance with the appropriate type of changes applied for, which lasts 14 working days of their receipt by the Center;

Specialized expert evaluation of the registration materials pertinent to introduction of changes.

Review of technical mistakes to be corrected shall be performed within the preliminary expert evaluation (within 20 days after the submission by the applicant of a letter-application with necessary documents which substantiate them) through comparison of the corrected registration materials with the applicant's original registration materials. In the situations specified in items 3 - 7 of subitem 2.4 of item 2 of this section the specialized expert evaluation of the materials submitted shall be performed.

14. If the registration materials for a medicinal product have been demonstrated to comply with the type of changes based on results of preliminary expert evaluation of the registration materials, they shall be subject to specialized expert evaluation, and in case of correction of technical mistakes the Center shall recommend MoH their approval and inform the applicant thereof in writing and enter the appropriate information into the electronic database.

15. If the registration materials for a medicinal product have been demonstrated not to comply with the type of changes applied based on results of preliminary expert evaluation of the registration materials, the Center shall inform the applicant thereof in writing with the appropriate grounds referring to numbers of sections, subsections, items, subitems, paragraphs of the Procedure and singly request the applicant to provide additional data and/or information necessary to ensure the compliance of the submitted registration materials with the requirements. Appropriate information shall be entered in the e-database.

The applicant shall provide additional data and/or information in accordance with the Center's remarks or a letter with substantiated timeframe necessary for their finishing-off within 30 working days. The time necessary for their finishing-off shall not be included in the time period for conducting the expert evaluation. The Center shall accept the finished-off materials within 3 working days after their submission by the applicant. An appropriate information shall be entered in the e-database.

If the applicant fails to provide additional data and/or information to the Center, or the additional data and/or information submitted by the applicant do not ensure compliance of the registration materials with the established requirements the registration materials shall be withdrawn from the evaluation, and the Center shall notify the applicant thereof within three working days.

Further on, at the applicant's request the materials pertinent to introduction of changes into the registration materials during the validity period of registration certificate, taking into account the Center's remarks, may be submitted for expert evaluation following the requirements of the Procedure.

16. During specialized expert evaluation of the registration materials in support of introduction of changes in order to receive additional data on the impact of the changes on efficacy, safety and

quality of the medicinal product each Center's expert commission may singly request the applicant for additional data and/or information with references to numbers of sections, subsections, items, subitems, paragraphs of the Procedure. The time necessary for their finishing-off shall not be included in the time period for conducting expert works.

In case of non-compliance of the submitted materials to the established requirements the registration materials shall be withdrawn from the evaluation, and the Center shall notify the applicant in writing thereof within three working days. An appropriate information shall be entered in the e-database.

If during expert evaluation of registration materials in support of introduction of changes the need for introduction of additional changes arises the delay may be possible in payment of cost of the expert evaluation of these changes without interrupting expert works through submission of a letter of guarantee to make payment of the appropriate invoices before the end of expert evaluation.

If the applicant fails to provide within 60 working days the requested additional data and/or information or a letter with substantiated timeframe necessary for their preparation, or they are incomplete, the registration materials shall be withdrawn from the evaluation, and the Center shall notify the applicant thereof within 3 working days. An appropriate information shall be entered in the e-database.

Further on, at the applicant's request the materials pertinent to introduction of changes may be submitted to the Center for expert evaluation according to the requirements of the Procedure.

17. Based on results of expert evaluation the Center shall draw a conclusion on introduction of changes into the registration materials or changes requiring new registration of the medicinal product taking into account the timelines indicated by the applicant in the registration form within which the changes applied for shall be implemented (the implementation period).

Results of expert evaluations performed shall be examined at meetings of the relevant Center's advisory body with a participation of experts and employees of relevant divisions of the Center.

Based on the results of such meetings the advice shall be given on drawing up the Center's recommendations to MoH concerning introduction of changes in the registration materials.

An appropriate information shall be entered in the e-database.

If variations affect the instructions for medical use of the medicinal product, MQC, labelling text of immediate, outer (if any) packaging of the finished medicinal product, the Center shall also recommend MoH approval of the revised instructions for medical use, or changes to the instructions, changes to the MQC, changes to the labelling text of immediate, outer (if any) packaging of the finished medicinal product (if applicable).

18. In case of disagreement with the Center's recommendations based on results of the expert evaluation of changes requiring a new registration, the applicant may contest this decision within 30 working days of its receipt according to the procedure established by MoH. The applicant shall present relevant materials with grounds for contestation to the Center within 30 working days after the contestation submission.

The Center shall perform expert evaluation of the materials submitted by the applicant within 60 working days after their receipt and give appropriate substantiated recommendations to MoH.

19. The term for introduction of changes (implementation period) shall not be more than 6 months of the date of approval of changes by the MoH Order unless otherwise substantiated. This does not apply to urgent safety related variations pertinent to a medicinal product.

VII. Timeframe for conducting expert evaluation

1. Expert evaluation of materials for a medicinal product submitted for state registration with complete (stand-alone dossier), or a MIP submitted for state registration, or a biosimilar shall take not more than 210 working days after formal receipt of registration dossier by the Center for state registration.

Expert evaluation of materials pertinent to the medicinal products specified in item 9 and subitems 10.1 – 10.3 of item 10 of section V of the Procedure shall take not more than 45 working days after the formal receipt of registration dossier by the Center.

Expert evaluation of materials pertinent to the medicinal products specified in subitems 10.4, 10.5 of item 10 of section V of the Procedure shall not exceed 30 working days after formal receipt of materials of the registration dossier by the Center.

(New paragraph is added to item 1 of section VII according to MoH Ukraine Order № 1948 of 21.08.2020)

2. Expert evaluation of registration dossier shall take not more than 90 working days after its formal receipt by the Center and shall pertain to:

Other types of medicinal products specified in section III of the Procedure submitted for state registration;

Medicinal products submitted for re-registration;

API submitted for registration;

Medicinal products produced according to the approved specification;

Changes requiring new registration;

MIP reclassified as a medicinal product during their registration as medicinal products.

3. Expert evaluation of materials in support of introduction of changes into the registration dossier shall take not more than 60 calendar days after receipt of appropriate materials by the Center.

This period may be reduced for the urgency if changes pertain to the safe use of the medicinal product.

Expert evaluation shall take not more than 45 working days after receipt of the appropriate registration materials by the Center in support of introduction of changes to a seasonal, pre-pandemic or pandemic vaccine against human influenza.

The expert evaluation according to the procedures for:

Correction of technical mistake;

API re-registration

shall take not more than 20 working days after receipt of the appropriate materials by the Center.

4. The date of completion of expert evaluation of registration materials specified in items 1-3 of this section shall be considered a date of signing the registration expert's conclusions based on results of the expert evaluation by the Center's head, specifically:

Motivated conclusions on efficacy, safety and quality of a medicinal product and recommendations of the latter for state registration;

Recommendations for rejection in state registration;

Motivated conclusions on evaluation of the benefit-risk balance of the medicinal product and recommendations to re-register it;

Recommendations for rejection in re-registration;

Conclusions concerning introduction of changes into the registration materials or new registration of a medicinal product in due order;

Recommendations for rejection of introduction of changes into the registration materials during the validity period of registration certificate of a medicinal product.

5. The timeframe for expert works indicated in items 1 - 3 of this section shall not include the time period when the materials are finished-off by the applicant, the time necessary for receiving answers from third parties (including authorized bodies of Ukraine and/or other countries) to the Center's requests pertinent to expert evaluation, as well as the time for conducting laboratory tests.

VIII. Procedure for preparation of lists of medicinal products and registration certificate (registration certificate insert) for medicinal product

1. At drawing motivated conclusions on efficacy, safety and quality of the medicinal product (hereinafter – the conclusions) the Center shall prepare and pass (within 10 working days) to the applicant the following draft documents for editing and agreeing upon:

For state registration of the medicinal product: registration certificate, instructions for medical use and summary of product characteristics (if any) for the medicinal product, MQC, labelling text of immediate, outer (if any) package of the finished medicinal product;

For re-registration of the medicinal product: registration certificate, instructions for medical use and summary of product characteristics (if any) for the medicinal product, labelling text of immediate, outer (if any) package of the finished medicinal product;

For introduction of changes into the registration dossier during the validity period of registration certificate of medicinal product: registration certificate insert or new registration certificate (for changes requiring a new registration), revised instructions for medical use for medicinal product and summary of product characteristics (if any), revised MQC, revised labelling text of immediate, outer (if any) package of the finished medicinal product.

Information on issuing draft documents to the applicant for editing and agreeing upon shall be entered into the integrated e-database.

If the applicant fails to edit and agree upon the draft documents within 15 working days or submit a letter with substantiation of delay of editing and agreeing upon (not more than 30 working days) the Center shall submit these documents to MoH.

The time needed for editing and agreeing upon the draft documents by the applicant shall not be included in the timeframe of expert evaluation of the registration dossier.

Information on returning the draft documents after editing and agreeing upon by the applicant shall be entered into the integrated e-database.

2. After agreeing upon the draft registration documents with the applicant the Center shall make, within 5 working days, lists of medicinal products proposed for state registration (re-registration) or introduction of changes into the registration materials (hereinafter – the Lists), supplement the conclusions (if any, according to the procedure) with specimen copies (with the Center's stamp "Specimen copy") of documents specified in paragraphs 2-4 of item 1 of this section, preclinical study reports and clinical trial reports which are recommended for publication on the MoH official website and pass them together with the Lists (both in paper and electronic formats) and a cover letter on to MoH.

Information about passing the Lists with conclusions on efficacy, safety and quality of the medicinal product confirming the correspondence between the preclinical study reports and clinical trial reports submitted by the applicant to materials of the registration dossier on to MoH shall be entered by the Center into the integrated e-database.

(Item 2 of section VIII in wording of MoH Ukraine Order of 27.06.2019 № 1528)

3. If there are reasons for giving recommendations for rejection of state registration (re-registration) of the medicinal product or introduction of changes into the registration documents the Center shall draw an appropriate conclusion and include the medicinal product into a separate List.

4. The date of transfer of positive or negative conclusions together with the Lists to MoH shall be placed on the Center's official website on the day of their transfer.

5. MQC for the medicinal product, labelling text of immediate and outer (if any) packaging of the finished medicinal product, instructions for medical use for the medicinal product, summary product characteristics (if any) shall be approved by the decision on state registration. At formalizing the above documents the Center shall specify the number and date of the decision on state registration.

6. Labelling text of immediate and outer (if any) packaging of the finished medicinal product, instructions for medical use for the medicinal product, summary product characteristics (if any) shall be approved by the decision on state re-registration. At formalizing the above documents the Center shall specify the number and date of the decision on state re-registration.

7. Revised MQC, revised instructions for medical use for the medicinal product, revised labelling text of immediate and outer (if any) packaging of the finished medicinal product shall be approved by the decision on introduction of changes into the registration materials. At formalizing the above documents the Center shall specify the number and date of the decision on introduction of changes into the registration materials.

8. After receipt of the MoH order on state registration (re-registration) of medicinal products and introduction of changes into registration certificate the Center shall inform the applicant within 3 working days in writing on the MoH's decision, prepare the original registration certificates (registration certificate inserts), letters on introduction of changes into registration certificates (if

changes do not apply to registration certificate) or letters on rejection in the latter and transfer them to MoH.

9. The Center shall transfer the signed registration certificate (registration certificate insert), letters on introduction of changes into registration materials (if changes do not apply to registration certificate) or letters on rejection in the latter to MoH with a cover letter on availability of properly formalized documents and confirmation of applicant's powers. The registration documents (instructions for medical use of the medicinal product, summary of product characteristics (at applicant's request), MQC, labelling text of immediate, outer (if any) packaging of the finished medicinal product) shall be attached to the formalized registration certificate (registration certificate insert), letters on introduction of changes into registration materials (if changes do not apply to registration certificate).

IX. Procedure of payment

1. Subject to payment is the preliminary expert evaluation and specialized expert evaluation of registration dossier for state registration, re-registration, introduction of changes into the registration dossier during the validity period of registration certificate of the medicinal product.

2. Payment of the above works shall be made according to the terms of contract concluded between the applicant and the Center.

X. Protection of confidential information

1. During expert evaluation of materials pertinent to medicinal products submitted for state registration, re-registration, and expert evaluation of materials on introduction of changes into registration materials during the validity period of registration certificate the Center must ensure protection of the confidential registration-related information against disclosure and unfair commercial use.

2. The examination by third parties of confidential registration information, making hard, electronic and other copies is not allowed without written consent of the holder of such information or in other cases specified by acting legislation.

3. Turnover of documents, containing confidential registration information, shall be performed at the Center.

4. Persons who might have conflict of interests with the applicant must not be allowed to work with documents with confidential registration information.

{The Procedure in wording of MoH Ukraine Order № 3 of 04.01.2013, № 460 of 23.07.2015}

L.V. Konoshevykh
Chief, the Administration of Medicinal Products
and Health Care Products MoH Ukraine