Annex 18
to the Procedure for Conducting Expert Evaluation of Registration Materials Pertinent to Medicinal Products Submitted for the State Registration (Re-registration) and for Expert Evaluation of Materials about Introduction of Changes to Registration Materials during the Validity Period of Registration Certificate
(item 2 of section V)

ESTABLISHING
equivalence of generic medicinal products

1. General

During registration of the generic medicinal product its equivalence to the reference product should be demonstrated. If an equivalence is established, the instructions for medical use of the generic medicinal product should correspond to the instructions for medical use of the reference product which has been drawn up based on data obtained during preclinical studies and clinical trials. Approaches to establishing equivalence shall be determined based on the comprehensive analysis of factors including characteristics of active substance, pharmaceutical form, time period of action of active substance(s), possibility of statistical demonstration of reliability of study results and other factors affecting bioavailability.

2. Selection of reference product

The applicant shall specify selected reference medicinal product in the registration form; grounds for its selection shall be given in section 1.5.2 of module 1 of the registration dossier. While selecting the reference product the following condition should primarily be met: the reference medicinal product will normally be the original (innovator) medicinal product for which efficacy, safety and quality have been established.

In case of absence of original medicinal product and/or impossibility to determine it the applicant shall substantiate the selection of the reference product in detail.

3. Methods of establishing equivalence

3.1. For medicinal product an active substance of which is taken by the patient in a dissolved form, a pharmaceutical equivalence or pharmaceutical alternativeness of the generic and reference medicinal products shall be demonstrated.

3.1.1. Depending on pharmaceutical form the following requirements are set for:

1) medicinal products which are to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same active substance in the same molar concentration as the reference product and the same or similar excipients in comparable concentrations as in the reference product. Certain excipients (e.g., buffer, preservative and antioxidant) may be different provided it can be shown that in the given concentrations these excipients would not affect the safety and/or efficacy of the medicinal product;

2) medicinal products which are solutions for oral use (including syrups, elixirs and tinctures), contain the same active substance in the same molar concentration as the reference product, and contain essentially the same excipients in comparable concentrations. If excipient(s) are known to affect gastrointestinal (GI) transit, GI permeability and hence absorption and/or stability of the active substance in the GI tract, provided should be the relevant data on the effect of these substances in selected concentrations on safety and/or efficacy of the medicinal product;

3) medicinal products in the form of powders for reconstitution as a solution and the resultant solution meets either sub-item 1 or 2 of this sub-item;

4) medicinal products which are gases;

5) otic or ophthalmic medicinal products prepared as aqueous solutions and contain the same active substance(s) in the same molar concentration and essentially the same excipients in

comparable concentrations as in the reference product. Excipients in composition (e.g., buffer, preservative, substance to adjust tonicity or thickening agent) may be different provided in the given concentrations they are proved by the applicant in any way not to affect safety and/or efficacy of the medicinal product;

6) topical medicinal products which are prepared as aqueous solutions and contain the same active substance(s) in the same molar concentration and essentially the same excipients in comparable concentrations as in the reference product;

7) medicinal products which are aqueous solutions for nebulizer inhalation products or nasal sprays, intended to be administered with essentially the same device, and contain the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations as in the reference product. Excipients in composition may be different provided in the given concentrations they are proved by the applicant in any way not to affect safety and/or efficacy of the medicinal product;

8) medicinal products with systemic action in the form of aqueous solutions for rectal administration which contain the same active substance(s) in the same molar concentration and essentially the same excipients in comparable concentrations as in the reference product. Excipients in composition may be different provided in the given concentrations they are proved by the applicant in any way not to affect safety and/or efficacy of the medicinal product.

For situations specified in sub-items 2, 3, 5, 6, 7 and 8 of this item, where there are differences in composition of the excipients, if the applicant cannot provide evidence that in the given concentrations they do not affect safety and/or efficacy of the medicinal product and there is no access to the relevant data he shall perform the relevant studies for evidencing a lack of effect of these excipients and auxiliary devices on safety and/or efficacy of the medicinal product.

3.1.2. Results of the demonstration of pharmaceutical equivalence or pharmaceutical alternativeness of the generic and reference medicinal products shall be given in module 3 of the registration dossier. Materials shall contain a comparison of properties of the generic and reference medicinal products.

3.2. For medicinal product an active substance of which is taken by the patient in a non-dissolved form *in vivo* and/or *in vitro* studies shall be performed for demonstrating equivalence.

3.2.1. For oral immediate release dosage forms with systemic action *in vitro* studies according to BCS (a biowaiver procedure) shall be performed for establishing equivalence.

3.2.1.1. Application of a biowaiver procedure based on BCS for demonstrating equivalence of generic medicinal products is limited to the rapidly dissolving active substances with known absorption in humans, without narrow therapeutic index, and are not intended for critical use. The medicinal products for sublingual, buccal route of administration and modified release dosage forms are not eligible for a BCS-based biowaiver. For orally dispersible medicinal products, a BCS-based biowaiver may be used only when an oral absorption may be excluded. A BCS-based biowaiver shall be applied to medicinal products which contain an active substance pertaining to BCS class 1 or 3.

3.2.1.2. Materials pertinent to demonstration of equivalence using a biowaiver procedure shall be given in module 5 of the registration dossier. Materials shall include data of *in vitro* comparative studies. Provided should be: evidence of the active substance belonging to an appropriate BCS class, assessment of excipients in composition of the generic and reference medicinal products and their influence on bioavailability, comparison of kinetics of the active substance release from the generic and reference medicinal products, the primary data obtained and the expected results, analytical and validation reports with the primary results, data on assessing the results obtained.

3.2.2. For medicinal products, for which there is a risk that possible differences in bioavailability may result in significant pharmacological differences at clinical use of the generic medicinal product compared to the reference one, the *in vivo* studies shall be performed for establishing equivalence.

3.2.2.1. Risks which may result in significant pharmacological differences at clinical use of the generic medicinal product compared to the reference one include:

1) Oral immediate release medicinal products with systemic action when one or more of the following criteria apply:

critical use medicinal product;

narrow therapeutic range (efficacy/safety margins), steep dose–response curve (difference in bioavailability could lead to toxicity due to inadequate suprabioavailability or low efficacy, or high speed of elimination from the body in case of low bioavailability);

there are official data that other methods of the equivalence study are not permissible for active substances of the generic medicinal products;

either the polymorphs of active substance, the excipients or the processes used in manufacturing are known to affect *in vitro* dissolution tests of the generic medicinal product;

2) Non-oral, non-parenteral medicinal products with systemic action (such as transdermal patches, suppositories, nicotine chewing gum, testosterone gel and transdermal contraceptives);

3) Modified-release medicinal products with systemic action;

4) Fixed-combination medicinal products with systemic action, where at least one of the active substances requires an *in vivo* study;

5) Non-solution medicinal products, which are for non-systemic use, in particular for oral, nasal, ocular, dermal, rectal or vaginal application and intended to act without systemic absorption. In these cases, the equivalence is established through comparative clinical or pharmacodynamic, dermatopharmacokinetic studies and/or *in vitro* studies.

3.2.2.2. The following approaches shall be used while selecting a method for proving an equivalence through *in vivo* studies:

Where an active substance produces measurable concentrations in a biological fluid, comparative pharmacokinetic studies shall be performed in humans;

Where an active substance does not produce measurable concentrations in a biological fluid, comparative pharmacodynamic studies shall be performed in humans;

When it is not possible to determine the pharmacokinetic profile and to find suitable pharmacodynamic endpoints, comparative clinical trials shall be performed.

3.2.2.3. Results of proving an equivalence via *in vivo* studies shall be given in module 5 of the registration dossier. Materials shall include data of comparative *in vivo* studies. Provided should be detailed information on the study protocol and report, primary data obtained and derived parameters, study products, bioanalytical and validation reports with primary data, data on statistical assessment of the results obtained.

{Annex 18 in wording of MoH Ukraine Order №460 as of 23.07.2015}