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LEGAL STATUS OF THE DATA EXCLUSIVITY FOR ORIGINAL MEDICINAL PRODUCTS AND PROTECTION OF INTELLECTUAL PROPERTY RIGHTS TO PRECLINICAL AND CLINICAL TRIALS

This research deals with the legal nature and functions of the legal status of the data exclusivity for medicinal products and analyses specifics of granting the data exclusivity legal status for medicinal products in Ukraine, subject to the relevant obligations of Ukraine under the EU Association Agreement. Also, the article presents some examples of functioning of the legal status of the data exclusivity for medicinal products in foreign countries. In the article, the authors give their own definition of the concept of Data Exclusivity. The authors analyze the essence of preclinical and clinical trial data. Moreover, the article reveals the specifics of protecting intellectual property rights to preclinical and clinical trial data in Ukraine.
Keywords: the data exclusivity for medicinal products, original medicinal product, generic medicinal product.

Problem statement. It may take from several years to several decades of years to develop an original medicinal product and to carry out its preclinical and clinical trials and, accordingly, it comes at a high price to a pharmaceutical company. In view of this, before putting an original medicinal product on the market of such or the other country, a pharmaceutical company must consider two factors: 1. whether the country's laws provide for the status of the data exclusivity being available to such company with respect to its original medicinal product and 2. whether the country guarantees to such company the protection of intellectual property rights to preclinical and clinical trials.

The research issue is of current interests in view that Ukraine lacks comprehensive research relating to the granting of the data exclusivity legal status for original medicinal products and protection of intellectual property rights to preclinical and clinical trials.

Research progress. There has been no comprehensive research relating to the granting of the data exclusivity legal status for original medicinal products and protection of intellectual property rights to preclinical and clinical trials in Ukraine.

The purpose and tasks of the article are to analyze the data exclusivity legal status for medicinal products and its specifics in Ukraine, as well as the specifics related to the protection of intellectual property rights to preclinical and clinical trials in Ukraine.

Statement of basic materials. In order to enable Ukrainian citizens to exercise their rights to health, the state ensures that the most needed medicinal products are affordable and that citizens are protected whenever any harm is done to their health due to using medicinal products according to their medical indications, and grants benefits and guarantees to certain groups of population and categories of citizens relating to their provision with medicinal products if they become ill. Thus, the state regulates thoroughly the market access to medicinal products.

As provided in article 2 of Law of Ukraine on Medicinal Products No. 123/96-BP, dated 4 April 1996 (the "**Law**")[1], a medicinal product is any substance or combination of substances (one or more active pharmaceutical ingredients and excipients) capable of and intended for treating or preventing diseases in human beings, or any substance or combination of substances (one or more active pharmaceutical ingredients (API) and excipients) that may be administered for preventing a pregnancy, restoring, correcting

[1] *Закон про лікарські засоби 1996* (Верховна Рада України). *Офіційний сайт Верховної Ради України*. <https://zakon.rada.gov.ua/laws/show/123/96-%D0%B2%D1%80>. (2019, April, 15).

or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

The medicinal products intended for treating or preventing diseases undergo thorough control by the state at all stages while they are marketed. State registration of a medicinal product is the key instrument available to the state to regulate this process. Thus, pursuant to article 9(1) of the Law, medicinal products are permitted for application in Ukraine after their state registration thereof.

The state registration of medicinal products is conducted on the basis of an application submitted to the central body of executive power that implements the public policy relating to healthcare.

An application for the state registration of a medicinal product must contain the manufacturer's name and address; its registered address and address of its manufacturing facilities; the name of a medicinal product and its trade name; the name of an active substance (in Latin); synonyms; pharmaceutical form; full composition of a medicinal product; indications and contra-indications; dosage; dispensing conditions; modes of administration; shelf life and storage conditions; information on the packaging; information on the registration of the medicinal product in other countries, including name of the country, number and date of the registration (article 9(2) of the Law).

An application must be accompanied by materials of preclinical study, clinical trials and expert examination; pharmacopoeia article or materials related to methods of medicine quality control, draft process procedure or information on production process; samples of the medicinal product; its packing; document evidencing payment of the registration fee. An application for state registration of a medicinal product registered by a competent body in the United States, Switzerland, Japan, Australia, Canada or the European Union and medicinal product registered under a centralized procedure by a competent body of the European Union for use in the territory of such countries or member states of the European Union must be accompanied solely by materials related to methods of medicinal product quality control; registration dossier materials; samples of the packaging of a medicinal product with labelling written in the language for labelling of medicinal products as provided for by this Law, and medicinal product use instructions written in the language required by this Law, and document certifying that the registration fee has been paid.

Thus, preclinical and clinical studies precede the state registration of a medicinal product and, in particular, an original medicinal product.

The public policy related to creating, manufacturing, quality control of, and selling, medicinal products is aimed at supporting scientific research of, creating and implementing new technologies and at developing the manufacture of highly efficient and safe medicinal products, meeting public demands for medicinal products of proper quality.

In view that the development of an original (innovative) medicinal product and its preclinical and clinical trials take on average from 10 to 12 years and cost to an innovating pharmaceutical company from USD 0.8 to 1.2 billion[1], most countries, in addition to guaranteeing to such company that its intellectual property rights are protected, also grant the status of data exclusivity with respect to its original medicinal product.

The applicable laws of Ukraine lack the definition of the legal status of data exclusivity. We believe that it may be defined as follows: **the status of data exclusivity** is an exclusive right of an innovating pharmaceutical company as manufacture of an original medicinal product to use, within certain period set out in the domestic laws, data of its own studies summarized in the registration dossier for its own medicinal product for commercial purposes and, in the first place, for the medicinal product entering the relevant country's market.

As provided in clause 38, Section II of the Procedure for Examining Materials for Medicinal Products Filed for State Registration (Re-Registration) and Examining Materials for Changing the Registration Materials During the Effective Period of the Marketing Authorization as approved by Order No. 426 of the Ministry of Health of Ukraine, dated 26 August 2005 (the "**Procedure**")[2], an **original**

[1] Андрощук, Н. (2017). Режим ексклюзивності даних: зміни у підходах. *Юридична газета, 23 (573).*

[2] *Про затвердження Порядку проведення експертизи реєстраційних матеріалів на лікарські засоби, що подаються на державну реєстрацію (перереєстрацію), а також експертизи матеріалів про внесення змін до реєстраційних матеріалів протягом дії реєстраційного посвідчення 2005* (Міністерство охорони здоров'я України). *Офіційний сайт Верховної Ради України.* <https://zakon.rada.gov.ua/laws/show/z1069-05> (2019, April, 15).

(innovative) medicinal product means a medicinal product that has been first registered in the world based on a complete set of documents relating to its quality, safety and efficacy (complete registration information).

Ukraine started implementing the data exclusivity concept pursuant to the Association Agreement between Ukraine, on the one hand, and the European Union, the European Atomic Energy Community and their Member States, on the other hand, which agreement was ratified by Law of Ukraine No. 1678, dated 16/09/2014[1]. Thus, pursuant to article 222 of the mentioned Agreement, the Parties shall implement a comprehensive system to guarantee the confidentiality, non-disclosure and non-reliance of data submitted for the purpose of obtaining an authorization to put a medicinal product on the market. For that purpose, when a Party requires the submission of test data or studies concerning the safety and efficacy of a medicinal product prior to granting approval for the marketing of such product, the Party shall not, for a period of at least five years from the date of the first approval in that Party, permit other applicants to market the same or a similar product, on the basis of the marketing approval granted to the applicant which had provided the test data or studies, unless the applicant which had provided the test data or studies has given consent. During such period, the test data or studies submitted for the first approval will not be used for the benefit of any subsequent applicant aiming to obtain marketing approval for a medicinal product, except when the consent of the first applicant is given. Ukraine undertook to bring its laws on the data protection related to medicinal products in line with the EU laws in effect as of the date to be designated by the Trade Committee.

As provided in article 12(9) of the Law, if a medicinal product registered on the basis of the registration information submitted in full (the "**reference/original medicinal product**") is registered in Ukraine for the first time, the state registration of another medicinal product containing the same active substance as the reference/original medicinal product may be carried out at least five years after the date of the first registration of the reference/original medicinal product in Ukraine, unless otherwise provided for by this Article. This requirement does not apply when an applicant has obtained, in accordance with the laws, the right to refer and/or use the registration information of the reference/original medicinal product or has submitted its own the full registration information that meets the requirements established with respect to the registration information of the reference/original medicinal product.

The period referred to in article 9(11) of the Law may be extended up to six years if, during the first three years after the state registration of the reference/original medicinal product, the central body of executive power that implements the public policy relating to healthcare has permitted using it with respect to one or more indications which are considered as having a special advantage over the existing indications. The central body of executive power that ensures the formation of the public policy relating to healthcare shall establish the rules and criteria for determining which indications have a special advantage over the existing indications. The time period defined in article 9(11) of the Law shall be set if an application for registration of a reference/original medicinal product in Ukraine is submitted within two years after the date of its first registration in any country (article 9(11) of the Law).

As provide clause 37(1), Section II of the Procedure, **illegal use of the registration information on the safety and efficacy of a medicinal product** means a reference to or other use of information on the efficacy and safety of a medicinal product, as registered under a complete and independent application, earlier than 5 years from the date of the registration of such medicinal product in Ukraine for the state registration of the relevant generic medicinal product, except when the applicant has obtained, under the law, the right to refer to and/or use the registration information of the reference/original medicinal product or has submitted its own complete registration information that meets the requirements to the registration information on the reference/ original medicinal product.

These requirements should not preclude any entity from developing accordingly within this period a medicinal product, including bioequivalence studies of generic and original medicinal products, and submitting the registration dossier to the regulatory body in order to get the marketing authorization five years after the registration in Ukraine of the reference medicinal product specified in the previous sub-paragraph (clause 36(2) of the Procedure).

[1] *Про затвердження Порядку проведення експертизи реєстраційних матеріалів на лікарські засоби, що подаються на державну реєстрацію (перереєстрацію), а також експертизи матеріалів про внесення змін до реєстраційних матеріалів протягом дії реєстраційного посвідчення 2014* (Верховна Рада України). *Офіційний сайт Верховної Ради України*. <https://zakon.rada.gov.ua/laws/show/1678-18> (2019, April, 15).

Thus, the data exclusivity status does exist in Ukraine in relation to medicinal products, which status may be obtained by filing an application and all necessary supporting documents as required for the procedure for full registration of a medicinal product. Having obtained the data exclusivity status with respect to medicinal products, a pharmaceutical company will be guaranteed that its medicinal product will have exclusive access to the market for 5 years and, under exceptional circumstances, for 6 years.

Moreover, an innovating pharmaceutical company may permit another pharmaceutical company to use the active substance of its original medicinal product. A medicinal product derived based on such active substance is a generic medicinal product.

In accordance with clause 12, Section II of the Procedure, a **generic medicinal product (also "generic" or "interchangeable")** is a medicinal product with the same qualitative and quantitative active substance composition and pharmaceutical form as the reference product, which interchangeability with the reference product has been demonstrated based on appropriate studies.

As provided in sub-clause 1, clause 1.3, Section II of the Procedure, a generic medicinal product is a medicinal product for which it is proved, in accordance with provisions of the European Medicines Agency (the "EMA") Guidelines on Bioequivalence Study (CPMP/QWP/EWP/1401/98 Rev. 1), or the ST-N MOZU 42-7.1:2014 guideline, that it is a generic of a reference product.

A generic medicinal product is defined as a medicinal product that has the same qualitative and quantitative composition in API and the same pharmaceutical form as the reference medicinal product, and whose equivalence 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 the active substance will be considered to be the same active substance, unless they differ significantly by properties with regard to the safety and/or efficacy. If so, the applicant should submit additional information proving the safety and/or efficacy of different salts, ethers or derivatives of the active substance. Various immediate-release oral pharmaceutical forms will be treated as one and the same pharmaceutical form. A bioequivalence study will not be required from an applicant if the latter proves that the generic medicinal product meets the established criteria. If the active substance of a generic contains the same active component of the molecule as the original registered medicinal product but in the form of a different salt/ether/complex/derivative, it should be proved that in such case there is no change in the pharmacokinetics, pharmacodynamics and/or toxicity of the substance component that is responsible for such properties and can change the safety/ efficacy profile. If there is no such proof, then the substance is new active substance (sub-clause 1, clause 1.3, Section III of the Procedure).

Since recently, there has been an active discussion between scientists and practitioners whether it is appropriate to extend the data exclusivity period. The minimum data exclusivity period in Europe is 6 years or, for high technology products, 10 years[1]. Supporters of the idea to extend to the data exclusivity period refer particularly to figures.

We believe that it is not appropriate to increase the period of data exclusivity for medicinal products in Ukraine in view that the market entry of generics results in reducing prices of the relevant medicinal products, which is a more advantageous option in terms of the situation currently existing in Ukraine.

Thus, the data exclusivity does exist in Ukraine in relation to medicinal products, which status may be obtained by registration of an original medicinal product under the full procedure for registration of a medicinal product. Having obtained the data exclusivity status with respect to medicinal products, a pharmaceutical company will be guaranteed that its medicinal product will have access to the market for 5 years and, under exceptional circumstances, for 6 years. We believe it is not appropriate to increase this period.

In addition to the instruments intended for verifying the quality and safety of medicinal products, the legal protection of intellectual property rights used to create such products has a special place, so that protection of commercial interests of developers and investors is in place.

The intellectual property right to medicinal products is protected under the applicable laws of Ukraine. Moreover, data related to the composition of the active substance are not the only thing of value to pharmaceutical companies, but the data of preclinical and clinical trials as well, considering that a company may spend on them more time and money than on the development of a medicinal product as such.

[1] Ексклюзивність даних клінічних досліджень. *Pharmaceutical Encyclopaedia*. <https://www.pharmencyclopedia.com.ua/article/6878/eksklyuzivnist-danix-klinichnix-doslidzhen> (2019, April, 15).

Preclinical studies help to understand whether it is worth to examine further new substance, measure initial doses for investigating its effects on a human body, and evaluate the likelihood of adverse events and their nature. This stage involves such laboratory tests as in vitro (in labware) and in vivo (on laboratory animals). As required under the international laws, laboratory animals may be used if the ethics committee and competent healthcare body in the country, where the study is intended to be carried out, approves such use. Different doses of substances are tested during preclinical studies to obtain preliminary data on their pharmacological features; toxicological tests are carried out; pharmacokinetic properties (absorption, division, excretion (extraction) and metabolism) are examined.

Clinical studies are efforts aimed at examining the effects of medicinal products with direct involvement of human beings being healthy volunteers and carried out to evaluate the efficacy and safety of new medicines and potential expansion of indications for applying already known ones. Such studies may be initiated only after positive results are obtained from preclinical study of the product.

Clinical studies with involvement of human beings may be commenced only if findings of the preclinical studies prove that the product is rather safe and that such studies do not pose a risk to human beings and the new product as such has perspectives in terms of treating illnesses.

Article 39 of the Agreement on Trade-Related Aspects of Intellectual Property Rights (the "**TRIPS Agreement**")[1] states that "undisclosed information" shall be protected, so that to ensure effective protection of that pharmaceutical or of agricultural manufacturers against unfair competition (clause 1); natural and legal persons shall have the possibility of preventing information lawfully within their control from being disclosed to, acquired by, or used by others without their consent in a manner contrary to honest commercial practices (clause 2). Such information shall be secret (i.e., generally known among or readily accessible to persons within the circles that normally deal with the kind of information in question), have commercial value (because it is secret) and be subject to reasonable steps under the circumstances, by the person lawfully in control of the information, to keep it secret.

As far as medicinal products are concerned, such information shall be the outcome of preclinical and clinical trials, i.e., study data. As provided in article 39(3) of the TRIPS Agreement, members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use (clause 3).

Thus, the rights to findings of preclinical and clinical studies related to medicinal products may be categorized as a kind of intellectual property rights.

Pursuant to article 222 of the Association Agreement between Ukraine, on the one hand, and the European Union, the European Atomic Energy Community and their Member States, on the other hand, which agreement was ratified by Law of Ukraine No. 1678, dated 16/09/2014, the Parties shall implement a comprehensive system to guarantee the confidentiality, non-disclosure and non-reliance of data submitted for the purpose of obtaining an authorization to put a medicinal product on the market.

Article 9(14) of the Law states that, for the purpose of securing the public health and upon registering a medicinal product, the Cabinet of Ministers of Ukraine may, as a matter of the law, permit a person designated by it to use a patented invention (utility model) related to such medicinal product without consent of the patent owner.

Moreover, article 9(16) of the Law imposes liability for disclosing data of preclinical and clinical trials. Consequently, persons in fault shall be brought to disciplinary, administrative, civil and/or criminal responsibilities for disclosure and unlawful use of registration information in accordance with laws of Ukraine.

As provided in Section X of the Procedure for Examining Materials for Medicinal Products Filed for State Registration (Re-Registration) and Examining Materials for Changing the Registration Materials During the Effective Period of the Marketing Authorization as approved by Order No. 426 of the Ministry of Health of Ukraine, dated 26 August 2005, during the conduct of the expert examination of materials for medicinal products submitted for the state registration, re-registration, as well the expert examination of materials related to changes in the registration materials within the effective period of the marketing authorization, the Centre should ensure that the confidential registration information is protected from

[1] *Угода про торговельні аспекти прав інтелектуальної власності* (Світова організація торгівлі). *Офіційний сайт Верховної Ради України.* <https://zakon.rada.gov.ua/laws/show/981_018> (2019, April, 15).

disclosure and unfair commercial use. The confidential registration information should not be made available to any third parties and such materials should not be reproduced in a hard copy, electronic or any other media without written consent of the owner of such information or otherwise as provided by the applicable laws. The circulation of documents containing the confidential registration information should take place within the Centre. Persons who may have a conflict of interests with the applicant must not have access to documents containing the confidential registration information.

Thus, in order to register an original medicinal product and obtain a permit for its sales in Ukraine, an innovating pharmaceutical company must file with regulatory bodies its findings of preclinical and clinical trials to prove that the medicinal product submitted for registration is safe and efficient. Furthermore, both the EU laws approximated by Ukraine and the applicable laws of Ukraine guarantee that data of preclinical and clinical studies of medicinal product are protected. Persons at fault for disclosing such information shall bear disciplinary, administrative, civil and/or criminal liability.

CONCLUSIONS:

1. The data exclusivity does exist in Ukraine in relation to medicinal products, which status may be obtained by registration of an original medicinal product under the full procedure for registration of a medicinal product.

2. Having obtained the data exclusivity status with respect to medicinal products, a pharmaceutical company will be guaranteed that its medicinal product will have access to the market for 5 years and, under exceptional circumstances, for 6 years.

3. We believe that it is not possible for the time being to increase the period of data exclusivity for medicinal products in Ukraine.

4. The applicable laws of Ukraine guarantee that data of preclinical and clinical studies of medicinal product are protected.

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