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CURRENT TRENDS AND LEGAL ASPECTS OF COUNTERACTING DRUG COUNTERFEITING AROUND THE WORLD

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Резюме. Проблема фальсифікації ліків відома людству не менше двох тисяч років. Проте лише наприкінці XX століття підробка ліків стала глобальною проблемою. Вперше на проблему підроблених ліків звернула увагу медична спільнота в особі ВООЗ у 1987 році, коли підроблені ліки стали з'являтися в загрозливих масштабах спочатку в розвинених країнах, а потім і в Європі. На теперішній час проблема підроблених ліків є загальносвітовою проблемою. За даними Асоціації міжнародних фармацевтичних виробників, частку підробок припадає 5-7% фармацевтичного ринку в розвинених країнах. За загальної річної вартості світового фармацевтичного ринку 200-300 мільярдів доларів, на частку підроблених ліків припадає 14-21 мільярд доларів. Фармацевтичне виробництво стає одним із найприбутковіших видів бізнесу після торгівлі зброєю, наркотиками, алкоголем та бензином. За даними ВООЗ, підроблені ліки були виявлені щонайменше у 28 країнах. З 951 випадку 25% підробок надійшло з промислово розвинених країн, 65 – з країн, що розвиваються, і 10% – з невідомих джерел. Використання таких ліків може спричинити серйозні негативні наслідки для здоров'я людини, оскільки підроблені препарати під час виробництва та продажу не проходять контроль, передбачений для легальної продукції.

ВООЗ у другій половині XX ст. активно розробляла рекомендації для таких країн, для створення і посилення ефективності їх НРО і забезпечення населення якісними лікарськими засобами. Перші спеціальні рекомендації ВООЗ щодо боротьби з фальсифікованими ліками були викладені у 1999 р. у документі «Counterfeit drugs: guidelines for the development of measures to combat counterfeit drugs». У 2013 р. ВООЗ впровадила Систему глобального епіднагляду та моніторингу (Global Surveillance and

Monitoring System – GSMS), яка стала основним міжнародним інструментом у боротьбі з субстандартними та фальсифікованими лікарськими засобами. Ще одним з елементів GSMS стала програма навчання для співробітників НРО щодо визначення та повідомлення про лікарські засоби, що не відповідають стандартам. Зі збільшенням числа фахівців, що пройшли це навчання, спостерігалося зростання кількості повідомлень, наданих через GSMS. У 2017 р., Всесвітня асамблея охорони здоров'я своїм рішенням у документі WHA70.23, на основі аналізу та узагальнення інформації у повідомленнях, отриманих ВООЗ, рекомендувала використовувати об'єднане визначення – «субстандартні та фальсифіковані лікарські засоби» («Substandard and falsified medical products» – SFMP), поставивши на перше місце субстандартні лікарські засоби як найбільш небезпечні. Ще однією важливою публікацією ВООЗ 2017 р. щодо субстандартних та фальсифікованих лікарських засобів стали рекомендації ВООЗ до GSMS. У цих оновлених у порівнянні з WHO/EDM/QSM/99.1 рекомендаціях були враховані рішення щодо об'єднання в одну категорію субстандартних і фальсифікованих лікарських засобів, нові статистичні дані ВООЗ і оцінка нових сучасних факторів, що спричиняють розповсюдження таких ліків. У 2016 р. в ЄС було опубліковано настанову з вимогами до нанесення елементів безпеки на пакувальні матеріали деяких лікарських засобів (Regulation (EU) 2016/161). Нею було передбачено, що маркування 2D-кодами буде обов'язковим тільки для рецептурних лікарських засобів. З 09.02.2019 р. в ЄС почала працювати система серіалізації та контролю першого розкриття упаковки як додатковий до існуючої в ЄС жорсткої регуляторної системи метод боротьби з фальсифікацією ліків. У ЄС була створена Європейська організація з верифікації лікарських засобів (European Medicines Verification Organisation – EMVO), яка відповідає за збір та зберігання інформації щодо продуктів та елементів безпеки, а також містить платформи для перевірки автентичності лікарських засобів кінцевими та проміжними операторами ланцюга поставки – лікарнями, аптеками, дистриб'юторами тощо.

Ключові слова: *фальсифіковані ліки, керівництва та рекомендації ВООЗ і ЄС, національні регулюючі органи, активні фармацевтичні інгредієнти*

Introduction. Falsification of medicines is a global problem, particularly in low- and middle-income countries. The relevance of this topic for the population sometimes leads to attempts to manipulate politicians (to attract attention and raise the rating of voters) and officials (to obtain additional financial resources and powers). This article provides an overview of the development of the WHO guidelines on fighting against falsified medicines and the process of creation, development and weakening of the national system of fighting against counterfeit medicines in Ukraine. Thanks to the creation of this system, the scale of falsification of medicines in Ukraine is relatively insignificant and is much less than 1% of their quantity in the market. Therefore, it is recommended to support and improve the system against falsification of drugs as it exists today, and not to spend limited resources on modern and costly drugs, in terms of feasibility of the expected results, new large-scale and high-cost projects on the scale of 2D package production. In our view, nowadays the Ukrainian health care system and its pharmaceutical sector have a number of more important and urgent problems that require political will and attention, The pharmaceutical sector has a number of more important and urgent unresolved issues that require the attention and efforts of policy makers and regulators (improving affordability and rational use of medicines, renewing the prescription system, reducing the number of medication errors, etc.) [1, 2, 3].

Counterfeit medicines are illegal and unsafe products because they may not meet the basic requirements for medicines in terms of their efficacy, safety and quality. They can be ineffective (don’t contain active ingredients or contain them in inadequately, or not bioequivalent), be contaminated (containing an unacceptable quantity of toxic chemicals or undeclared active pharmaceutical ingredients (with other harmful effects) and/or defective (as long as they are not produced in line with Good Manufacturing Practice (GMP), there is no certainty about the stability of their composition and properties), even if the samples of falsified medicinal products formally comply with pharmacopoeia requirements [4, 5, 6].

The Aim of the study was to examine the regulations of international organisations that regulate the fight against the manufacture, distribution and sale of counterfeit medicines.

Materials and Methods. The legal instruments (directives and laws) of the World Health Organisation and the European Medicines Regulatory Agencies were used in the study. Literature on distribution and sale statistics of counterfeit medicines was reviewed [7, 8, 9].

Results of the Research. Counterfeit medicines are less widespread in developed, high-income countries, where a strong regulatory system is in place to monitor the pharmaceutical market and national regulatory authorities (NRAs) apply an effective set of measures to deter and combat counterfeit medicines, taking into account the market situation, their own experience and significant available resources. As a result, the number of detections of counterfeit medicines in these countries is very low, estimated by NRAs themselves, at well under 1%.

In developing countries (middle- and low-income), the problem of falsified medicines is more severe due to the lack of stringent regulatory requirements and the weak capacity of NRAs. Consequently, the WHO in the second half of the twentieth century actively developed recommendations for such countries, to establish and strengthen the effectiveness of their NRAs and provide quality medicines to the population. The first WHO specific recommendations for combating counterfeit drugs were published in 1999 in "Counterfeit drugs: guidelines for the development of the development of measures to combat counterfeit drugs" (WHO/EDM/QSM/99.1). The guidelines provided an overview of the problems and factors contributing to the emergence of counterfeit medicines and suggested approaches to developing national strategies and a set of specific actions to combat counterfeit medicines (including the organization of surveys). This document provides for the establishment of an inspection of suspected counterfeit products, screening of potentially counterfeit products, training of practitioners, etc.). This document first recommended the use of the term "Counterfeit medicines" which means medicines that are inherently mislabelled for their identity

and/or the name of the manufacturer. Falsified preparations may be both original and manufactured; they may contain ingredients in the correct or incorrect composition, be without active ingredients, in insufficient quantities or in defective packaging.

The importance of this definition was due to the fact that the legislation of different countries had used very different definitions of counterfeit medicines, which often obscured the real picture of the availability of these products in different countries. For example, the regulatory documents of some African countries also included substandard, unregistered and contraband drugs in the list of counterfeit medicines, this allowed officials of these countries to manipulate the figures of 30-50-70% of counterfeit medicines on the market and demand additional powers and resources from their governments and financial and technical support from international organizations. But in the 2000s, the international expert consensus on counterfeit medicines as the most serious threat to the lives and health of patients in developing countries began to change. Based on a wide range of information, experts have concluded that the number of substandard medicines in developing countries is significantly (by an order of magnitude) higher and the harm from such medicines is no less than that from counterfeit medicines. Moreover, the most high-profile and widespread cases of death and hospitalization in 1990-2015 in developing countries were not caused by counterfeit medicines but by substandard registered products produced by legitimate manufacturers with deviations from GMP requirements:

- 1995-1996 – about 80 children die in Haiti from acute renal and hepatic failure after cough syrup used to produce glycerol contaminated with diethylene glycol;
- 2011 p. – over 200 patients died and 850 were hospitalized in Pakistan after taking a cardiac drug contaminated with antimalarial active pharmaceutical ingredients which was inadvertently produced by the manufacturer instead of an inert adjuvant;
- 2012-2013 – nearly 60 adult drug users died in Pakistan after consuming large quantities of cough syrup with active pharmaceutical ingredients

dextromethorphan which was improperly replaced by another stereoisomer – levomethorphane with the same chemical formula but with twice as much active substance;

- 2013 in Paraguay, 44 children were hospitalized following the use of cough syrup with levomethorphane instead of dextromethorphan (the same series of active pharmaceutical ingredients that caused the death of drug addicts in Pakistan);
- in the Democratic Republic of the Congo in 2014, dozens of people died after taking paracetamol tablets laced with large quantities of phenobarbital.

Due to the seriousness of the problem in 2013. The WHO introduced the Global Surveillance and Monitoring System (GSMS), which has become the main international tool in the fight against substandard and adulterated medicines. The WHO lists of notifications of falsified medicines can be found on a dedicated resource. Another element of the GSMS is a training programme for NRAs staff to identify and report medicines that do not comply with standards. As the number of practitioners who attended the training increased, the number of notifications made through GSMS increased. Five years later, in early 2017, The World Health Assembly issued its decision in document WHA70. 23, based on the analysis and consolidation of information in the notifications received by the WHO, recommended the use of a generic term "Substandard and falsified medical products" (SFMP), The WHA has ranked Substandard and Falsified Medical Products as the most dangerous. Document WHA70.23 also established new definitions for 3 categories of high risk medicines:

- substandard medical products (also referred to as "those not in compliance with specifications") – licensed medicinal products which do not comply with the quality standards and/or specifications;
- unregistered/unlicensed medical products – medicines that have not been evaluated and/or not authorized by NRAs for the markets in which they are sold/distributed or used, in accordance with the regulatory requirements of national or regional legislation;

- falsified medical products – medical products in which the name, stock or manufacturer is incorrectly stated in writing.

However, this categorisation of sub-standard and adulterated medicinal products has created a degree of confusion. Substandard drugs are registered products whose production and use can be reduced by the introduction of GMP, increased registration and licensing requirements. Counterfeit medicines are illegal products that are manufactured and distributed outside the legal field, and mechanisms other than substandard medicines should be used to combat them.

In order to plan an adequate response to these two groups of unsafe products, it is important for NRAs to understand their quantities and the balance in the markets. This will determine which areas of work by NRAs should be prioritized and which resources should be used to reduce threats to patients. Also, NRAs should decide on target quantification indicators – what might be an acceptable level of sub-standard. The level of the treatment of sub-standard and adulterated medicines in terms of the balance between the risk to patients and the resources required to reduce the number of patients.

The WHO has repeatedly stressed that the real magnitude and scope of the problem of substandard and adulterated medicines in different countries and regions is difficult to assess due to highly fragmented and disparate data. The WHO supplementary report published in July 2017, "Study on public health and socioeconomic impacts of substandard and adulterated health products", for the first time presented the combined results of a metanalysis of 100 publications from reliable sources over a 10-year period (2007-2016) on the results of laboratory controls by various methods, mainly high-performance rinse chromatography and MiniLabTM, more than 48,000 samples of medicinal products. More than 48,000 samples of medicines originating from 88 countries at different income levels. Of these, only 178 samples were selected from 13 high-income countries. Therefore, it was statistically impossible to use these data for extrapolation to estimate the number of substandard and counterfeit medicines in these markets. But the review also included publications with the control results of over 11 thousand units selected in 19 low-income countries and

close to 37 thousand units in 56 countries. The number of cases from 56 middle-income countries. For these groups of countries, the percentage of tested samples that did not meet the specification requirements (were substandard and falsified) was 10.6 and 10.5% respectively. To assess the situation with substandard and falsified medicines in selected countries, the WHO recommends that other sources of information be taken into account, above all the statistical data from the NRAs of these countries.

Another important publication of the 2017 edition of the WHO Global Surveillance and Monitoring System for Substandard and Adulterated Medicines was the WHO Global System of Surveillance and Monitoring of Substandard and Adulterated Medicinal Products recommendations. These updated guidelines as per WHO/EDM/QSM/99.1 recommendation were based on the decision to lump substandard and counterfeit medicines into a single category, new WHO statistics and an assessment of new current factors that lead to the spread of such medicines.

This publication noted that sub-standard and adulterated medicines were most often found in the presence of a combination of 3 main conditions in the countries: limited access to affordable, quality, safe and effective medicines, including the need for patients to buy the medicines themselves at their own cost; low standards of oversight of the pharmaceutical market - from poor ethical practices in health facilities and outlets to corruption in the public and private sectors; limited resources and technical capacity of NRAs to ensure good practices in the production, quality control and distribution of medicines.

Among other problems in low- and middle-income countries, publication authors highlighted the low level of awareness of the threat of substandard and counterfeit medicines in many countries, even among health professionals; Lack of strong regulatory systems or failure to comply with regulatory requirements, which creates a vacuum in legislation and is exploited by perpetrators; increasing levels of online sales of medicines, creating a largely unregulated and invisible market. Authorities also note that the risks of sub-standard and adulterated medicines have increased significantly in crisis situations and regions (military conflicts, the use of medications in crisis situations

and regions (military conflicts, natural disasters, etc.) when government control of the drug delivery system is weakened or lost altogether. To counteract the spread of substandard and counterfeit medicines, the above recommendations suggest developing national strategies for action in three areas – "prevent, detect and respond":

- the consumption of substandard and adulterated medicines by patients should be discouraged by creating a system for the quick removal of these products from pharmacies and hospitals. It is also important to conduct an extensive information campaign to raise awareness and understanding among patients and medical staff of the dangers of substandard and counterfeit medicines. The integrity of supply channels must be ensured by closing off the possibility of such medicines entering the system. And finally, a strong regulatory system should be created so that police and police station officers also have the necessary information and tools to protect the population from substandard and counterfeit medicines;
- substandard and adulterated medicines should be detected. This requires investment in increased control at the borders, improved system of notification of such medicines, more intelligent inspection and increased access to laboratories and equipment for polyscreening of samples of medicines;
- should be reactivated. A system for alerting and declaring detected substandard and adulterated medicines should be established, the regulatory system should be strengthened and legal procedures should be made more transparent.

A strong political will to oppose substandard and adulterated medicines must be in place to enhance the effectiveness of these efforts and all stakeholders must work together. The issue of substandard and counterfeit medicines is not just a health system issue, it also requires the involvement of regulators, law enforcement officers, ministers of health, logisticians and other stakeholders. In the fight against substandard and adulterated medicines, the active involvement of political leaders is needed to translate policy into action by mobilising the necessary human and financial resources. These inputs aren’t costs, they should be seen as investments to protect business and the market, as well as the integrity of health systems.

In 2016, the EU published a regulation on requirements for safety features on packaging materials for certain pharmaceutical products (Regulation (EU) 2016/161) [10]. It stipulated that 2D code marking would be mandatory only for prescription medicinal products (with the exception of most infusion solutions, etc.) and one over-the-counter medicinal product. As of 09.02.2019, the EU began to operate a system of certification and control of the first disclosure of packaging as a complementary method to the current rigorous regulatory system in the EU to combat counterfeiting of medicines. This guideline sets forth strict requirements for unique identification numbers to be applied to package materials, for application and quality of 2D code files and for a system of verification of drug safety elements.

The European Medicines Verification Organization (EMVO) has also been established in the EU and is responsible for collecting and storing information on products and safety elements, It also includes platforms for verifying the authenticity of medicines by final and intermediate supply chain operators – hospitals, pharmacies, distributors and others. EMVO is a private non-profit organization founded by the European professional associations of pharmacies, pharmacies, distributors and pharmaceutical manufacturers. It is financed through membership fees from members of the system. The role of governments and EU regulatory bodies is to oversee the EMVO operation and approve relevant regulatory documents.

Implementation of the system and adherence to project terms in the EU has not been easy. In the first results of 2019, the number of technical failures of the verification system in the EU countries was close to 6%, and against this background, it was impossible to determine the number of detected falsified medicines. Also, no data has yet been published on the increase in the cost per package of medicines after implementation of this system in the EU, taking into account investments in additional manufacturing equipment and information infrastructure, EMVO membership fees, etc. Thus, leave it out that no opinion can be drawn as to whether the EU countries have achieved the objectives of this project and what the cost of such implementation was to the pharmaceutical manufacturers and other market operators.

A relatively successful project was the implementation of the 2D-encoding system for drug packaging in Turkey, which was launched in 2009. The nationwide implementation of the system required a major upgrade in IT infrastructure (availability of computers and Internet access points), the cost of the production (installation of additional equipment, modernization of packaging lines, installation of track trace systems) and the cost of distributors and pharmacy chains (software, scanners, staff training) was high.

European Council expert Francois-Xavier Lerle spoke about the problem of counterfeit medicines in Europe and how counterfeit medicines can be identified. François-Xavier Lerle, Head of the Department of Pharmaceutical Services, Consumer Health Protection and Anti-Counterfeiting, European Medicines Quality and Medical Services Directorate of the European Commission (EDQM), outlines how counterfeit medicines are fought in European countries. The expert said that the threat of counterfeit medicines is more than serious. By taking a drug, the patient expects a certain result, and if it does not come, the disease may not last. The case in point was a major incident in 2007 when a drug called heparin (manufactured with a substance that inhibits blood coagulation) was launched on the pharmaceutical market. At the time, over 60 human deaths were attributed to the manufacturers of the falsified batch of the drug. Separately, the European Council expert spoke about how the counterfeit drug can be detected. According to François-Xavier Lerle, an experienced pharmacist can easily identify counterfeiting through the appearance of packaging. In general, an adulterated drug can be quickly detected in a specially equipped laboratory, but if the counterfeiters use a certain concentration of the active ingredient, it is difficult to detect the adulteration. The expert also shared European experience of combating counterfeiting of medicines. A number of programs have been developed in Europe to discourage drug counterfeiting, particularly in the field of legal protection of the pharmaceutical industry. These include the Europe-wide eTACT project for the development of a drug monitoring and approval system. Through this system, for example, the relevant authorities can track the location and diversion of a particular medicine. At the stop of François-Xav'e Leri suggested how

Ukrainian consumers can save themselves from misused medicines. Firstly, you should only buy medicines from legitimate pharmacies. Don't buy drugs via the Internet, because such sales of medicines are forbidden in Ukraine. Also, the patient does not have to make any additional examinations of the drug. If you have any doubts about the quality of the medicine, contact your pharmacist and he or she will know exactly where the medicine has come to the pharmacy.

Conclusion

In 2017 the WHO updated the concept of recommendations to combat counterfeiting of medicines by combining substandard and counterfeit medicines into one category of two types of unsafe products – "substandard and counterfeit medicines".

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Summary. The problem of adulteration of medicines has been known to mankind for at least two thousand years. However, it was only at the end of the twentieth century that counterfeiting of medicines became a global problem. The problem of counterfeit medicines first came to the attention of the medical community, represented by the WHO in 1987, when counterfeit medicines began to appear on an alarming scale, first in developed countries and then in Europe. The problem of counterfeit medicines is a worldwide problem today. According to the Association of International Pharmaceutical Manufacturers, counterfeiting accounts for 5-7% of the pharmaceutical market in developed countries. With the total annual global pharmaceutical market value of $200-300 billion, counterfeit drugs account for $14-21 billion. Pharmaceutical production is becoming one of the most lucrative businesses after trafficking in arms, drugs, alcohol and gasoline.

According to the WHO, counterfeit medicines have been found in at least 28 countries. Of the 951 cases, 25% of the counterfeits came from industrialised countries, 65 from developing countries and 10% from unknown sources. The use of such drugs can cause serious negative consequences for human health, as counterfeit products do not pass the controls prescribed for legal products in their production and sale.

In the second half of the twentieth century, WHO actively developed recommendations for such countries to establish and strengthen the effectiveness of their

NDAs and provide quality medicines to their populations. The first specific WHO recommendations on counterfeit medicines were published in 1999 in Counterfeit Medicines: Guidelines for Developing Measures to Combat Counterfeit Medicines. In 2013. WHO launched the Global Surveillance and Monitoring System (GSMS) as the main international tool in the fight against substandard and counterfeit medicines. Another element of GSMS was a training programme for National Regulatory Authorities on identifying and reporting substandard medicines. As the number of practitioners trained increased, so did the number of notifications send through the global system of surveillance and monitoring of substandard and counterfeit medicines.

As the number of practitioners who attended the training increased, the number of notifications made through GSMS increased. In 2017, The World Health Assembly issued its decision in document WHA70. 23, based on the analysis and consolidation of information in the notifications received by the WHO, recommended the use of a generic term "Substandard and falsified medical products" (SFMP), The definition of "substandard and falsified medical products" – SFMP – is the first one. The WHO Global Surveillance and Monitoring System for substandard and falsified medical products was another important publication in 2017. This updated guideline, in line with WHO/EDM/QSM/99.1 recommendation took into account the decision to consolidate substandard and falsified medicines into a single category, new WHO statistics, and an assessment of the new current factors contributing to the spread of such medicines. In 2016, the EU published a regulation on requirements for safety features on packaging materials for certain medicinal products (Regulation (EU) 2016/161). It stipulated that the labelling of 2D codes would be mandatory only for prescription medicinal products. From 09.02.2019. The EU has launched a system for certification and control of first package disclosure as a complementary method to the EU's rigorous regulatory system to combat drug counterfeiting. The European Medicines Verification Organization (EMVO) has been established in the EU and is responsible for collecting and storing information on products and safety elements, It also includes platforms for verifying the authenticity of medicines by final and intermediate supply chain operators – hospitals, pharmacies, distributors, etc.

Key words: *adulterated medicines, WHO and EU guidelines and recommendations, national regulatory authorities, active pharmaceutical ingredients*