The study of the current state of quality assurance of medicines in the pharmaceutical market of Ukraine

Abstact

The aime of our study was to investigate the current state of normative legal regulation and control over the quality assurance of medicines in the pharmaceutical market of Ukraine. The functions and activities of organizations that carry out state regulation and quality control of medicines in Ukraine were considered. The special relevance of solving the problem of drug falsification in Ukraine was determined, the main factors influencing the spread of falsified medicines (FM) in the pharmaceutical market of Ukraine are analyzed. The variety of causes that contribute to the appearance of FM requires effective comprehensive measures to detect and prevent their appearance. It is substantiated that only a complex of legal and organizational measures in combination with the use of modern technologies to combat the spread of FM will ensure that only high-quality, effective and safe medicines will be in the pharmaceutical market of Ukraine.

Keywords

drug falsification, falsified medicines, MEDICRIME Convention, regulatory system, State Service of Ukraine on Medicines and Drug Control

Introduction

The quality and safety assurance of medicines is an integral part of Ukraine's state policy in the field of health care. The current understanding of quality assurance approaches is based on a comprehensive concept that covers the quality assurance of drugs, from the stage of their pharmaceutical development, laboratory and clinical research, production, quality control, storage, realization and providing information to doctor and patient. According to this concept, reliable guarantees of quality and safety of drugs should be provided at all stages of the life cycle of the drug. According to the World Health Organization (WHO) recommendations, all activities to implement the concept of quality assurance of medicines should be aimed at meeting the needs of citizens (https://www.who.int/medicines/areas/quality_safety/quality_assurance/about/activities/).

The main task of the state, according to the Concept of development of the pharmaceutical sector of Ukraine for 2011-2020 years, approved by the order of the Ministry of Health of Ukraine (MOH), dated 13.09.2010 № 769 (https://zakon.rada.gov.ua/rada/show/v0769282-10), is to ensure the quality, effectiveness and safety of drugs that improve public health, increase the duration and quality of life of the entire population of Ukraine.

It was established that in different countries have already gained experience in creating and implementing mechanisms that ensure the effectiveness of quality assurance of medicines. To provide the population with quality medicines in Ukraine, there is a regulatory system for controlling the pharmaceutical market and national regulatory organizations. Today, drug falsification is a global problem that affects countries at different financial levels, from high-income countries to low-income countries, including Ukraine (Barry 2014; Venhuis et al. 2016; Ozava et al. 2018). FM - medical products that deliberately/fraudulently misrepresent their identity, composition or source (https://www.who.int/medicines/regulation/ssffc/definitions/en/).

FM are illegal and dangerous products because they may not meet the basic requirements for medicines - in terms of their effectiveness, safety and quality. They can be ineffective (do not contain active ingredients or contain them in inappropriate quantities, or not be bioequivalent), be dangerous (contain unacceptable amounts of toxic impurities or undeclared active pharmaceutical ingredients with other dangerous effects) and / or poor quality are not produced in accordance with the requirements of Good Manufacturing Practice (GMP), there is no certainty about the consistency of their composition and properties, even if the samples of FM formally meet the

pharmacopoeial requirements (https://www.who.int/medicines/services/counterfeit/faqs). FM are less common in developed countries with high incomes, where a strict regulatory system is in place to control the pharmaceutical market and national regulatory organizations use an effective complex of measures to prevent and combat againts FM, taking into account the market situation, their experience and the significant resources available. As a result, the number of cases of detection of FM in these countries is very small, much less than 1%. In developing countries, the problem of FM is more acute due to insufficiently stringent regulatory requirements (Koczwara and Dressman 2017; Rahman et al. 2018).

It is found that the scale of drug falsification in Ukraine is significantly affected by the average level of affluence, military conflicts, insufficient work of regulatory organizations, imperfect legal system, high level of corruption and limited public access to medicines due to their high cost (Demchenko and Soloviov, 2014). During the past 10 years, the State Service of Ukraine on Medicines and Drug Control has issued 440 orders banning the circulation of FM, including 19 orders issued in 2019. Besises, a serious danger is an increase in the level of falsification of pharmaceutical substances, 80% of which are imported in Ukraine by indirect contracts from China and India without proper customs control.

The circulation of FM is a direct threat to public health, but sometimes in people's lives and leads to significant financial losses for legal manufacturers. The 2006 estimate of falsified medicines by WHO indicated that the prevalence of falsified medicines ranged from less than 1% in developed countries to over 10% developing countries (http://www.who.int/medicines/services/counterfeit/impact/TheNewEstimatesCounterfeit.pdf).

About 50% of medicines for online sale are falsified, about 95% of the 50,000 online pharmacies do not meet the laws and standards (Nayyar et al. 2019; Nayyar et al. 2015; Mackey et al. 2015). That is, in the conditions of active development of the national pharmaceutical market the problem of quality assurance of medicines is especially actual (Kovalenko 2018). However, the issue of the comprehensive assessment of the problem of drug quality in the field of circulation, the effectiveness of measures to combat against FM and identify priority ways to improve the quality assurance of drugs in the pharmaceutical market of Ukraine was not given due attention.

Matherials and methods

The article aimed to conduct a study of the current state of normative legal regulation and control over quality assurance of medicines in the pharmaceutical market of Ukraine, to identify the main problems hindering the transition of the pharmaceutical sector to international and European quality standards of drugs and identify ways to solve them. The materials used in this article are the official websites of the authorized organizations on quality assurance of medicines and against the appearance of FM, regulatory documents and scientific publications on the subject. The study was conducted using the methods of statistical, logical, comparative analysis and generalization of information.

Results and discussion

Ensuring the regulatory quality of drugs is closely related to the trends that characterize the current state and development of the pharmaceutical market of Ukraine. According to the State Drug Register of Ukraine (SDRU) (http://www.drlz.com.ua), in October 2020 were registered 13664 drugs (Table 1). That is today the pharmaceutical market of Ukraine consist of the imported drugs, in the structure of the range of drugs foreign medicines are more than 70 %, and in some ATC classification groups up to 90%. The main importers of medicines to Ukraine are Germany, India, France, Italy, Slovenia and Hungary. Ukraine has virtually no own production of active pharmaceutical ingredients (API's), about 80% of API's are imported from China and India. Today the quality of API's is largely the responsibility of distributors and manufacturers of medicines.

Table 1. The number of medicines registered in the State Drug Register of Ukraine, 2020.

№	Group of medicines	Ukrainian medicines	Foreign medicines	Total
1	Medicines	3603	7090	10693
2	Active pharmaceutical ingredients	355	1815	2170
3	In bulk	190	422	612
4	Packing with in bulk	53	136	189
5	Total	4201	9463	13664

Given the high import dependence of the domestic pharmaceutical market, the real way to solve this problem is import substitution. Recently, despite the decline in real incomes and a significant increase in prices for imported drugs, there has been a tendency to increase sales of domestically produced drugs. Also, over the past 5 years, domestic drug manufacturers have been increasing exports to Belarus, Kazakhstan, Azerbaijan, Uzbekistan, Moldova and Georgia. Among the main trends in the pharmaceutical market of Ukraine is the increase in the share of Ukrainian enterprises in the structure of production of generic drugs, their share in the domestic market is over 70%, while in the USA - 12%, Japan - 30%, Germany - 35%, France - 50%. Despite the unstable social and economic situation in the country, the domestic pharmaceutical market is growing. The average annual growth of the national market over the past 5 years remains at 15-20%. The volume of the pharmaceutical market of Ukraine in 2019 amounted to 3.4 billion USD (http://www.ukrstat.gov.ua/). Experts predict further growth of the Ukrainian pharmaceutical market given the global trend to increase production and consumption of pharmaceutical products.

In 2020, 115 enterprises of various forms of ownership carried out industrial production of drugs in Ukraine. It should be noted that recently there has been a downward trend in the number of pharmaceutical manufacturers, which can be explained by fierce competition and production licensing under GMP rules. Domestic pharmaceutical companies are trying to change the range in order to meet the needs of customers, improving the quality and range of products every year. Given the financial constraints, the problem of supply of raw materials, domestic pharmaceutical production is directed mainly to the production of generics.

In 2020, 401 pharmaceutical wholesalers were engaged in Ukraine, 17485 pharmacies and 4399 pharmacy points were engaged in the retail trade of drugs. Over the past 15 years, there has been a 1,4 times decrease in the number of distributors and a 1,3 times steady increase in pharmacies. Significant potential for the development of the domestic pharmaceutical industry, increasing the volume of FM in circulation requires a reliable system of regulatory and control and constant improvement of mechanisms to ensure the quality of drugs at the stages of their entry into Ukraine, production, transportation, storage, wholesale and retail. At the same time, the role of the Ukrainian state system for drug quality control acquires special significance. The system of state control is built on the principle of centralization with administrative subordination and has three levels: national, regional and microeconomic. The national level includes the Ministry of Health of Ukraine, the State Service of Ukraine on Medicines and Drug Control (SMDC) and the State Expert Center of the Ministry of Health of Ukraine. To the regional level - territorial authorized regulatory organizations of the SMDC in the regions and in the city of Kyiv. The third level includes authorized persons for quality control of drugs of pharmaceutical manufacturers and pharmacy istitutions: pharmacies and wholesalers. The Ministry of Health of Ukraine is the main organization in the system of central executive authority for the implementation of state policy in the field of production, quality control and sale of drugs. Regulation in the field of drug quality assurance is carried out by the Law of Ukraine № 123/96 "On Medicines" dated 04.04.1996 , relevant legal documents was adopted by the Ministry of Health of Ukraine. According to the current legislation, the main regulatory functions in the field of pharmacy are: licensing of production, wholesale and retail trade of drugs, import, implementation of good GXP practices, inspecting manufacturers and

wholesalers companies for compliance with good manufacturing/ distribution practice standards, state quality control of drugs, pharmacovigilance of drug safety. The SMDC performs the following tasks: compliance with legislation on quality and safety of drugs, compliance by licensees with licensing conditions for economic activity of drug production, import, wholesale and retail sale of drugs, import of drugs into the customs territory of Ukraine, compliance with the requirements of standards and technical conditions for transportation, storage and use of drugs. Specialists of the SMDC take samples of drugs from pharmacies for laboratory testing of their quality in authorized laboratories of the Ministry of Health and decides to withdraw from circulation and prohibit the production, sale and use of drugs that do not meet the requirements of regulations and issues licenses for the production of drugs, wholesale and retail trade. First of all, drugs that are stored, transported and sold in violation of current norms and rules on consumer complaints and in case of doubt about the quality of the results of preliminary visual inspection conducted by the state inspector are subject to selection for state quality control. If the inspection reveals FM, the SMDC prohibits the production, sale, storage, transportation and use of such medicines, as well as in addition to laboratory tests conducts investigations into the origin and distribution. The SMDC and its territorial authorized organizations have established work programs to prevent the import, production and distribution of FM, there are permanent groups with spesialists of the SMDC, law and customs organizations to track the distribution channels of FM.

According to the results of the work of SMDC in 2019 (https://www.dls.gov.ua/), the territorial authority regulatory organizations conducted scheduled inspections: 1215 pharmacy itstitutions (manufacturers, wholesalers and pharmacies) regarding their compliance with the requirements and norms of the legislation at all stages of drug circulation. During the inspections 2453 violations of the requirements of the current legislation were established. According to the results of scheduled inspections of pharmacy institutions, 1034 orders were issued to eliminate violations, 1917 samples of drugs were selected for laboratory analysis, 432 administrative protocols were drawn up for violations of current legislation. Typical violations are improper storage conditions of medicines in the process of their sale, trade in FM, wich are prohibited by the orders of the SMDC, the sale of medicines that are not confirmed by the manufacturer's quality certificate. The analysis of violations of the requirements of the legislation on the quality of medicines, which were detected during inspections of pharmacies, shows that their quantity and nature has remained unchanged over the past 5 years. As before, the problem of ensuring the quality of drugs in the process of their circulation remains acute. During 2019, pharmacy institutions imported 22026 series of medicines in Ukraine, of which 5230 (23,7 %) series of medicines were subjected to laboratory analysis, 34 negative conclusions were issued on the quality of medicines (0.65%). The territorial authority regulatory organizations of the SMDC analyzed 2511 series of 1565 of medicines during inspections of pharmacies. According to the results of analyzes, the SMDC issued 66 orders prohibiting the circulation of 78 unregistered medicines (4.9%) and 19 orders prohibiting the circulation of 57 series of 18 FM (2, 3%). The results of the analysis of the number of violations identified by the regulatory autorithy during the planned measures of state control over compliance with the legislation on drug quality at the stages of circulation, allows concluding poor compliance with regulatory requirements and ineffective system of state control of drugs.

Along with the dynamic development of the pharmaceutical industry, the functioning of the shadow economy in the field of drug circulation and a steady tendency to increase the number of FM in the domestic pharmaceutical market. According to the results of the state quality control of medicines in 2009 in Ukraine 230 packages of FM with a total value of 2 million UAH were found, in 2012 - 1.500 million packages of FM worth 55 million UAH, and during 2013 - 2016 about 9 million packages of FM with a total value of 270 million UAH. The SMDC together with law enforcement agencies for the period 2010 - 2016 identified 30 underground manufacturers of FM in the Ukrainian market. According to the data of SMDC, in Ukraine the circulation of FM is not more than 2% - 2.5%. However, the official data showed only the number of FM detected in circulation, and not the number of available FM, which is due to the lack of a unified system for monitoring drug circulation. Also does not take into account the online sales of FM, which has now become

large-scale and poses a serious threat to public health. False data on the presence of FM in circulation, both overestimated and underestimated, interfere control and regulatory and law enforcement agencies from adequately counteracting this shameful phenomenon.

We analyzed the reporting data of SMDC during 2008-2019 (Table 2). The analysis showed, that SMDC found in circulation 578 series 305 of FM, which 52% are domestic medicines, 48% are foreign medicines, the medicines of domestic manufacturers are falsified more often.

Table 2. Dinamics of number of detected and seized FM in Ukraine during 2008-2019.

Year	Series of FM	Quantity of FM
2008	21	12
2009	46	28
2010	69	27
2011	34	15
2012	62	39
2013	66	40
2014	117	63
2015	29	20
2016	59	22
2017	16	14
2018	9	7
2019	57	18
Total	578	305

At present medicines of almost all pharmacotherapeutic groups are falsified. However, antibacterials for systemic use are the leader in the structure of medicines (Table 3).

Table 3. The distribution of detected FM according to the ATC classification during 2008-2019.

№	ATC code of FM	ATC code name of FM	Number (%)
1	J01	Antibacterials for systemic use	28
2	C01	Cardiac therapy	18,5
3	M01	Anti-inflammatory and antirheumatic products	10,9
4	N02	Analgetics	8,1
5	D01	Antifungals for dermatological use	7,8
6	A	Alimentary tract and metabolism	6,6
7	H	Systemic hormonal preparations, excluding sex hormones and insulins	5,2
8	V	Various	7,6
9	R05	Cough and cold preparations	3,8
10	L01	Antineoplastic agents	3,5

It was investigated, a bigger quantity of FM was detected by indicators "Description", "Packaging", "Labeling" (48%) and "Identification of active pharmaceutical ingredient" (31%), prescription drugs (60%) were falsified more often than OTC drugs. According to the dosage form, FM for external use, solid dosage forms and injectable drugs were the most detected.

The main factors influencing the appearance of FM in circulation are identified, the most significant factors are: developed system of online sales of medicines, which does not allow regulatory authorities organizations to check their quality, unstable economic situation in Ukraine, high drug prices in line with the average solvency of the population, as well as a large difference in

market prices, which stimulates the sale of cheaper FM, as well as access to high-performance equipment and modern pharmaceutical technologies, which causes a high level of falsification of drugs. Also non-compliance with international norms of the existing legal framework governing the import, production, sale of drugs, lack of human, financial and information resources to combat drug trafficking of improper quality, ineffective activities of the regulatory autorities implementing state policy in the field of prevention of FM, insufficient or no sanctions for illegal actions in the field of drug quality, inconsistencies between various government agencies to prevent the circulation of FM, a significant number of agents in the pharmaceutical market, which contributes to interference in the chain of illegal sales channels, insufficient implementation of manufacturers and pharmacies standarts of good practices: GMP, Good Distribution Practice and Good Pharmaceutical Practice. The moratorium on inspections of pharmacies, introduced by the Government of Ukraine during 2014 - 2018, was a factor that recently contributed to the increase in cases of falsification in the field of drug trafficking. For more than 3 years, pharmacies were virtually out of state supervision, which made it impossible to use effective measures to prevent the circulation of FM in the domestic pharmaceutical market. The main ways of entering into the market of FM are: illegal supply of medicines abroad under the guise of other goods, repackaging of expired medicines in Ukraine for further sale and release of FM at unlicensed domestic enterprises using high-technology equipment and attracting qualified specialists. The variety of reasons that contribute to the falsification of drugs requires the application of comprehensive measures to prevent, detect and prompt withdrawal from circulation of drugs. But, today, measures to counter the spread of FM in the domestic pharmaceutical market are not effective enough and need to be improved. According to the WHO recommendations, the nature, extent and causes of counterfeiting vary from country to country, which is why there is no single strategy to address the problem (https://www.who.int/medicines/services/counterfeit/faqs). Therefore, each country must independently develop its own strategy to combat against FM, the appropriate regulatory framework, taking into account its capabilities.

To counteract the spread of FM on the Ukrainian pharmaceutical market, it is necessary to develop a national strategy of action in 3 areas - "prevent, detect and respond":

- FM should be prevented from reaching patients by creating a system for the rapid removal of these products from pharmacies and hospitals. It is also important to conduct a broad information campaign to increase the level of knowledge and understanding of the threats of FM by both patients and medical staff. It is necessary to ensure the integrity of supply channels, closing the possibility of entering the system of such drugs. Finally, a strong regulatory system should be in place so that police and customs officers also have the necessary information and tools to protect the public from FM;
- FM should be detected. This requires investment in strengthening border controls, improving the notification system for such drugs, smarter inspections and increasing access to laboratories and equipment for field screening of drug samples;
- should respond. A system for notifying and recalling detected FM should be established, the regulatory system should be strengthened, and legal procedures should become more transparent. To enhance the effectiveness of these actions, there must be a strong political will to counter FM, and all interested partners must work together. The problem FM is not only a problem of the health care system, it requires the involvement of regulators, law enforcement, customs, logisticians and other interested partners.

The fight against FM requires the active participation of political leaders who would translate policy into concrete action by attracting the necessary human and financial resources. Such involvement is not a cost, it should be seen as an investment to protect business and the market, as well as the integrity of health systems. The Council of Europe Convention on the counterfeiting medical products and similar crimes involving threats to public health MEDICRIME Convention was signed in December 2010 and entered into force in Ukraine in January 2016. The introduction of criminal liability for crimes related to the counterfeiting of medicines mainly in all countries of the world indicates an awareness of their big danger. According to the Law of Ukraine № 5065-VI

dated 05.07.2012 (https://zakon.rada.gov.ua/laws/show/5065-17), introduced criminal liability for falsification into the Criminal Code of Ukraine, namely Article 305 "Smuggling of narcotic drugs, psychotropic substances, their analogues or precursors or falsified medicines" and Article 321-1 "Falsification of medicinal products or circulation of falsified medicinal products", which for the manufacture, purchase, transportation, shipment, storage for the purpose of selling or selling scienter FM for imprisonment for a term from 3 years to life imprisonment with confiscation of FM, raw materials and equipment for their manufacture. According to the statistics from the General Prosecutor's Office of Ukraine (https://www.gp.gov.ua/ua/index.html), the year dynamics are as follows (Table 4).

Table 4. Criminal liability for the spread of FM, the Article 321-1 (2017-2019).

Year	Registered	Notified about the suspicion	Filed to the Court whit indictment	Terminated proceedings	No decision taken
2017	23	3	3	9	20
2018	40	2	1	7	39
2019	9	0	0	0	9

From 2017-2019 the Unified State Register of Court Decisions revealed 7 sentences under the Article 321-1 of the Criminal Code of Ukraine (Table 5).

Table 5. Sentences under Article 321-1 of the Criminal Code of Ukraine.

Year	2017	2018	2019
Number	3	2	2

First of all, it showed the high latency of this crime and the difficulties in establishing the factual circumstances of this crime, secondly, the need to clarify the methods for identifying, preventing and investigating this crime, thirdly, the actual lack of studying the experience of low enforcement organizations from another countries. According to the Law of Ukraine № 5038 dated 04.07.2012 (https://zakon.rada.gov.ua/laws/show/5038-17), economic activity on import of medicinal products subject to licensing from 01.03.2013. Therefore, this law obliges all importers of foreign drugs in Ukraine to obtain an additional license to sell their drugs in Ukraine. In addition, the government has introduced a mandatory inspection of GMP production for compliance with GMP requirements before their registration and re-registration in Ukraine. Those manufacturers who already have GMP certificates only need to document their existence. Import of drugs into the territory of Ukraine, the production of which does not meet these requirements, is prohibited from 15.02.2013. It should be noted that Ukraine has been a full member of The International Pharmaceutical Inspection Cooperation Scheme (PIC/S) since 2011 and implements a regulatory policy in the field of pharmaceutical market control in accordance with legislation similar to that in force in European countries. The patients can trust drugs that are manufactured in 42 PIC/S member countries, as well as those manufacturers whose companies are located in countries with a non-rigid regulatory system, but in which the regulatory authorities of the PIC/S member countries have carried out appropriate inspections for compliance with GMP requirements, and confirmed a high level of guarantee of the quality and effectiveness of drugs.

Thus, Ukraine carried out some positive changes in the system of state supervision and quality control of medicines. However, despite a significant number of positive changes, state regulation and control in the field of drug circulation still remains difficult, insufficiently effective and needs to accelerate the implementation of modern regulatory changes. To build an effective quality assurance system in Ukraine, an effective system must be created not only to detect and promptly withdraw from the circulation of FM, but also to track the channels of their appearance and

distribution in the pharmaceutical market and prosecute those involved or facilitating illegal circulation of FM. Also, it is necessary to establish active cooperation with the relevant international organizations dealing with the problem of combating FM. Transformation processes in Ukraine related to European integration, dynamic development of the domestic pharmaceutical sector, the establishment of additional requirements for the quality and safety of medicines determine the need of realization of state policy aimed at implementing modern methods against FM. Today, one of the effective means of preventing the spread of FM in the global and national pharmaceutical markets is the development and implementation of modern technologie for drug packaging protection 2D barcode system, which allow tracking and obtaining the necessary information at all stages of drug circulation (Mackey and Nayyar 2017; Kovacs at al. 2014). Thus, 2D barcode system make it possible to organize effective control of medicines throughout the supply chain from producer to consumer and prevent the emergence of FM in the legal supply system. Today the use of 2D barcode system is a large-scale and promising tool to prevent drug falsification at all stages of circulation, which is being introduced by more and more pharmaceutical manufacturers around the world.

Conclusion

The studies showed that the Ukrainian pharmaceutical sector is in the process of creating an effective system of drug quality assurance, which is based on international principles, innovative approaches, proper regulatory support and rational application of regulatory functions. It is proved that the problem of falsification of medicines is one of the most relevant in the pharmaceutical industry and requires improvement of mechanisms for regulating the quality and safety of medicines in the pharmaceutical market. To increase the effectiveness of drug quality control and reliable resistance to the spread of FM in Ukraine should be comprehensive measures to combine information and human resources, to establish active cooperation with the relevant international organizations dealing with the problem of combating FM. It is substantiated that the most important priorities of state policy, which allow to raise the quality and safety of medicines, are to improve the system of state regulation and quality control of medicines, strengthening criminal liability for falsification of drugs and harmonization of pharmaceutical legislation of Ukraine with European legislation, optimization of the system of detection and operative withdrawal from circulation of FM and also tracking of channels of their receipt and distribution by means of implementation of the mechanism of introduction in practice of effective system of obligatory 2D barcode system of drug packaging and carrying out constant monitoring at all stages of drug circulation.

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