Pharmaceutical Analytics: Methods of Analysis of Medicinal Products and their Quality Control

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Abstract: The importance of evaluating the quality of medicinal products is determined by their impact on public health, therefore there are many analytical methods for controlling the chemical composition and bioequivalence of medicines. Falsification of medicines and determining the composition of generics also remain a serious problem, therefore the search and systematization of modern methods of identifying the quality of medicines and methods of combating illegal medicines are relevant and timely. The purpose of the study is to determine effective methods of assessing the quality of medicines and methods of combating falsified medicines, which would meet the country's demands in conditions of war and economic crisis. The research used methods of analysis, synthesis, systematization, statistical comparison of groups using Student's t-test, survey and generalization of results. The obtained results revealed alternative methods of quality control of medicinal products in the conditions of economic and war crisis. We identified the prospect of introducing drug marking and assisting pharmaceutical manufacturers and distributors in drug marking. A low level of awareness of the population regarding the methods of assessing the quality of medicinal products and the algorithm of actions in case of detection of low-quality medicinal products was revealed. Among the doctors, there was also an insufficient level of knowledge regarding the assessment of the quality of medicines, which requires the introduction of training of doctors in this field and educational work among the population.

Keywords: Analytics, Falsification of medicines, Medicinal products, Pharmacy, Quality control, 2-D marking drugs.

INTRODUCTION

The relevance of the study of methods of evaluating the quality of medicines is demonstrated by numerous works related to this topic. Sardella *et al*. [2], emphasize that the problem has gained new importance due to the prevalence of generics and biosimilars. In this way, medicines that have existed for a long time can cause side effects that were not observed before, which is often caused by a violation of the production technology or the use of raw materials of inappropriate quality. Another aspect is the economic expediency of prescribing generics, which do not always take into account possible changes in the bioavailability of medicines, which can lead to the absence of the effect of medicines [3]. In countries that provide patients with medicines, doctors, based on experience, prescribe either generics or original drugs, depending on the effectiveness of analogues. In Italy, in the absence of a cheap generic, the patient independently pays the cost of the original drug, unless the original drug was prescribed by the doctor as mandatory. Such a system leads to an increase in the burden on doctors and requires improvement of their knowledge in the field of pharmacology.

Organizations and working groups have been created to control medicinal products, which are guided in their activities by regulatory documents that provide a list of unified requirements at the stage of production and distribution. In the European Union, it is Community Code 2001/83/EC Art. 49, which requires a qualified person responsible for the production and distribution of medicines. However, the authors emphasize the shortcomings of the current reactive approach to identifying low-quality drugs and recommend the introduction of preventive controls [2, 4]. Salvador *et al*. [5] and Koliadenko *et al*. [6] analyzed the effectiveness of spontaneous reporting of adverse drug reactions as a primary method of pharmacovigilance and found little documentation of spontaneous reports sent to competent authorities, requiring training for more informative reporting of adverse drug reactions.

At the production stage, the chemical compatibility of substances, their concentration, percentage and qualitative composition of impurities, transparency, density, etc. are determined. However, a more

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important stage is the determination of bioequivalence, which requires conducting clinical studies already after approval of the release of the drug. It is quite easy to use various high-precision and inexpensive methods to determine the chemical structure of medicines. Instead, bioequivalence requires studies of analyzes with the detected content of drugs and their effects on the body. Wu *et al*. [7] describe the definition of bioequivalence using the physiologically based biopharmaceutics model, which predicts the mechanisms of bioavailability by comparing the mechanistic relationships in vitro and in vivo. Zhang *et al*. [8] explored the possibilities of an innovative virtual method for determining bioequivalence by comparing bioavailability in vitro, in silico, and in vivo bioavailability and determining potential similarities in clinical action between originator medicines and generics. Ilić *et al*. [9] investigated the problem of evaluating dermatological medicines for external use in the form of ointments and creams, and found that the complexity of the structure and the state of aggregation complicate the validity of classical methods, which is manifested by lower efficiency compared to the evaluation of the quality of solid or liquid forms of medicines. Another aspect is the determination of the biological action, which is not revealed by the results of the analyses, but requires a long-term biological study. An example of a definition of biological action is our previous study of the drug "Quertulin" in the form of a gel, which is used for the treatment of periodontal diseases. The effectiveness of this dosage form has been proven to eliminate the symptoms of inflammation, reduce the depth of periodontal pockets and periodontal indices. At the same time, this drug showed effectiveness in the treatment and prevention of initial and I forms of acute pancreatitis against the background of non-alcoholic steatohepatitis, which was confirmed by the results of clinical studies based on shortening the terms and dynamics of treatment. In this way, the definition of the clinical effect allows to expand the areas of application of medical drugs [10-14].

Van Wyk and Prinsloo [15] describe the importance of assessing the quality of traditional medicines that are produced from plant raw materials, because wuality of plants depends of the environment in which they are grown, so in different areas the quality of plant raw materials can differ and even become dangerous due to the composition of the soil and atmosphere. For traditional Chinese medicine, it has become a challenge that quality assessment is carried out through the determination of the chemical composition of substances, without the possibility of determining biological activity, which is extremely important for Chinese medicine preparations that contain a large number of herbs [16, 17].

The evolution of methods for evaluating the quality of medicines was explained by the improvement of drug production technology and the emergence of appropriate methods in the search for the most valid one. Validity includes characteristics such as accuracy, specificity, reproducibility, reliability, and quantitative and qualitative limits [18, 19]. Analytical methods include chromatographic, electrochemical, electrophoretic, spectroscopic, titrimetric and their types [20]. A brief comparative description of the most used methods is presented in Table **1**.

Table 1: Methods of Determining the Quality of Medicinal Products

Method	Type	Features (Advantages and Disadvantages)
Chromatography	gas, thin-layer, highly effective liquid	Determination of impurities, volatile oils, solvent residues, analysis of volatile components (gas); determination of the amount of active substance based on the difference between absorbency.
Electrophoresis	capillary, microchip	Fast analytical time, economy, versatility, quality control of therapeutic proteins, determination of low molecular weight ions, small inorganic ions, chirality of large biomolecules. The possibility of modeling the cellular reaction (microchip).
Spectroscopy	infrared, near infrared, Raman spectroscopy, nuclear magnetic resonance (NMR) and mass spectrometry	Determination of the identity and content of active ingredients, the structure of proteins in pharmaceutical products, high resolution, expensive quipment and highly qualified personnel.
Electrochemical	electrochemical fingerprint-based data mining, electrochemical sensors	Fast and convenient technique, determination of electroactive components, including impurities, possibility of analysis of multicomponent medicines.
Titrametric		Determination of the minimum dose that has a clinical effect with the least side effect.

Source: created by the author based on [16, 21-25].

In practice, various methods are chosen according to the aggregate state, chemical structure, and pharmacological class of the drug. Also methods of drug analysis are combined to increase their efficiency. Chemometric methods are used more often and consist of the combination of chemical and mathematical methods which bring positive results, since they can be applied directly to the samples taken without extractions and additional stability studies. Chemometric methods are mostly cost-effective, allow pharmacists to choose non-destructive methods and are easy to repeat.

A combination of high-performance chromatography with mass spectrometry is often used and brings positive results for evaluating the composition of medicines at the production stage, determining metabolism in vivo and in vitro, and identifying impurities and degradation products. Liquid chromatography techniques are also combined with ultraviolet and mass spectrometric detectors [26]. For better validity, methods are constantly being improved, for example, innovations in liquid chromatography devices have led to its significant use as the "gold standard" of drug quality control, although it is characterized by high cost [27]. On the other hand, the use of liquid chromatography is limited for non-chromophoric molecules. For these cases, the use of aerosol universal detectors is provided, namely the evaporative light scattering detector, the condensation nucleation light scattering detector and the charged aerosol detector [28]. However, cheaper analogues such as quadrupole mass spectroscopy and high-resolution mass spectrometry have been developed, which can be recommended for use in countries with a low economic level.

Capillary electrophoresis is also economically beneficial, which can solve many analytical problems compared with chromatographic and spectroscopic analogues. Modern NMR spectroscopy is a highly accurate method, but due to the high cost of consumables (liquid gel), hardware and operation, it is inaccessible to small and medium-sized manufacturers, controlling and medical institutions. On the other hand benchtop NMR spectroscopy and low-frequency spectrometers (NMR) (40–100 MHz) are easy to operate and are more affordable [22]. Low-frequency NMR spectrometry devices are smaller in size, 5-20 times cheaper, do not require consumables, but are characterized by low resolution, so they are not used to determine new chemical structures, but only to control known compositions of substances. Compared to the instruments of the 60s, the new generation is capable of recording 2D spectra [29].

At the same time, if it is possible to achieve success in quality control at the production stage, it is increasingly difficult to trace the pharmaceutical chain, where falsification, substitution of the drug, disruption of the transportation or storage process may occur [30, 31]. Both national and international structures are involved in the fight against falsified medicines, because falsified medicines are dangerous, but this problem cannot be eradicated. The problem of falsified and illegal medicines is widespread in countries with low economic potential, especially in the regions of Africa and the Middle East [32].

A large number of studies concerning the quality of medicinal products testify to the relevance and importance of the problem in the world. However, some methods aren’t available for the financial capacity of different countries. Moreover the lack of comparison and structuring of methods makes it difficult to choose in favor of one or another method, in accordance with the requests of controlling institutions. For Ukraine in times of war, economic crisis and reduction in financial capabilities of citizens, quality control of medicines is of great importance and requires detailed study.

The purpose of the study was to determine effective methods of quality assessment and methods of combating falsification of medicines that would meet the demands of the country in conditions of war and economic crisis.

2. MATERIALS AND METHODS

To achieve the goal, the following tasks were set: to research and systematize data on modern effective methods of determining the quality of medicines, to determine ways to combat the appearance of falsified and illegal medicines on the pharmaceutical market, to assess the awareness of citizens and doctors about methods of combating low-quality medicines that are used in practice. To systematize the results, an analysis of the literature over the past 5 years was carried out, the authors created Table **1** with the definition of the advantages and disadvantages of the main modern methods of drug quality assessment by using methods of analysis and synthesis. The activity of controlling institutions in the fight against falsified medicines, improper distribution and storage of medicines was analyzed by studying the project of Law

of Ukraine "On Amendments to the Law of Ukraine "On Medicinal Products" (Regarding the Labeling of Medicinal Products)" [33]. An analysis of sales of drugs with 2D marking and their analogues in the network of pharmacies that participated in the project was conducted based on the reports of 5 pharmacies for the period January-March 2020. The results of the reports were published after receiving consent for publication from the administration of the pharmacy network. Groups were compared using Student's t-test for independent variables. A survey was conducted of 175 employees of pharmacies, pharmaceutical factories and distributors of drugs who participated in the pilot project to assess the attitude of participants to 2D marking of drugs. We conducted a survey of 254 respondents who did not participate in the project, regarding awareness of methods of determining the quality of drugs in practice. The main characteristics of the respondents are shown in Tables **2** and **3**. The survey was confidential and complied with the ethical norms of conducting surveys. The obtained results were summarized in conclusions.

3. RESULTS

Having analyzed the literature data, Ukrainian manufacturers and pharmaceutical regulatory institutions need to choose high-quality and at the same time economically available methods of qualitative drug analysis. Chemometric methods such as chromatography, chromatography combined with mass spectrometry, benchtop NMR spectroscopy with low-frequency spectrometers (NMR) (40–100 MHz), quadrupole mass spectroscopy, and high-resolution mass spectrometry are described in the literature as among the available and cost-effective methods, as well as capillary electrophoresis, which can provide effective analysis of the quality of drugs under difficult economic conditions. If the production control stage is successful because manufacturers adhere to high standards, it is much more difficult to control the distribution process to track the appearance of a falsified medicinal product.

In Ukraine, in order to strengthen control process on false medicines, a pilot project on the marking of

Table 2: Main Characteristics of the Respondents who Participated in the Pilot Project of 2D Marking Drugs

Characteristic		Amount	%
Sex	Male	67	38.3
	Female	108	61.7
Age	20-30 years	32	18.3
	30-40 years	54	30.9
	40-50 years	37	21.1
	50-60 years	35	20.0
	> 60 years	17	9.7
Occupation	Parmacist	68	38.9
	Distributor	59	33.7
	Worker of pharmaceutical production	48	27.4

Table 3: Main Characteristics of Respondents who did not Participate in the Pilot Project of 2D Marking Drugs

Characteristic		Amount	%
Sex	Male	143	56.3
	Female	111	43.7
Age	20-30 years	45	17.7
	30-40 years	54	21.3
	40-50 years	57	22.4
	50-60 years	57	22.4
	> 60 years	41	16.2
Occupation	Doctor	98	38.6
	Other	156	61.4

medicinal products was created in 2019. For this, the manufacturer (importer) applied marking (identification mark – two-dimensional bar code) on the outer packaging of medicines. The two-dimensional barcode contained a data matrix with the ability to machine read, detect and correct errors of encrypted data equivalent to Data Matrix ECC200. The code contained information about the registration certificate number, unique package number, batch number, and expiration date. The list of medicines, manufacturers and distributors is given in Table **4**.

As can be seen from the table, drugs of various groups, including antibiotics, which are widely used in medical practice, participated in the project. Among the companies on the list were large pharmaceutical manufacturers of Ukraine and wholesale distributors, which indicates the interest of manufacturers and distributors in the introduction of marking medicines in the way of combating falsification of medicines. We conducted an analysis of the sales of medicines with 2D-marking and their analogues in the network of pharmacies that participated in the project, based on the reports of 5 pharmacies for the period January-March 2020 (Figure **1**). The results were compared using Student's t-test. The results indicated no significant difference between the amount of 2D marked drugs and their analogues t=0.04, (p=0.48), based on results of t-Student test.

We conducted a confidential survey of 175 employees of pharmaceutical manufacturers, pharmacies and distribution companies that participated in the pilot project and determined that the results of the project were positively evaluated by all participants (Figure **2**). The results of the project were positively evaluated by most participants. Among the positive factors, the respondents identified the safety from counterfeit drugs and the convenience of marking for drug accounting. Among the negative factors, the respondents identified an increase in fees for drug marking. Despite the lack of an increase in the supply of 2D-marked drugs, the government imposed a requirement for voluntary 2D drug marking in accordance with the standards of the European Union after 2026 and mandatory 2D drug marking after 2028.

To determine the level of awareness of citizens and medical professionals regarding the possibility of influencing the quality of pharmaceuticals and methods of checking pharmaceuticals, a survey was conducted, which included the following questions: "Have you encountered medicines of poor quality?", "Have you turned to someone with this question?", "Do you know about drug marking?", "How do you feel about drug

Table 4: List of Medicinal Products and Organizations that Participated in Medicinal Product Marking Projects

The Trade Name of the Drug	International Non-Proprietary Name	Manufacturers/Distributors
AMIXIN® IS	Tyloron	Pharmaceutical company "INTERCHEM"
NOOBUT® IS	Phenibut	"Borshchagiv Chemical Pharmaceutical Plant"
TRANQUILAR® IS	Mebikar	"Pharmaceutical company "Darnytsia"
INGEST	Progesterone	Pharmaceutical company "Farmak"
INGESTA® OXY	Hydroxyprogesterone	"LeoKon Group" distributor
ANDROPHARM®	Cyproterone	"ONLY ORIGINAL" distributor
TESTOSTERONE PROPIONATE	Testosterone	"Retsepty zyttia" pharmacy
CEFAZOLIN-BHFZ	Cefazolin	"Apteka ANC" pharmacy
VINPOCETIN DARNYTSIA	Vinpocetine	"APTEKA 235" pharmacy
VERAPAMIL DARNYTSIA	Verapamil	"Linda-farm" pharmacy
GENTAMICIN SULFATE-DARNYTSIA	Gentamicin	"BaDM" distributor
METOCLOPRAMID-DARNYTSIA	Metoclopramide	"Venta.LTD" distributor
SULFOCAMPHOCAINE-DARNYTSIA	Sulfocamphocaine	
T-TRIOMAX	Thiazotic acid	
GLUCOSE-DARNYTSIA	Glucose	
PENTOTREN	Pentoxifylline	

Source: created by the author on the basis of the Resolution of the Cabinet of Ministers of Ukraine [34].

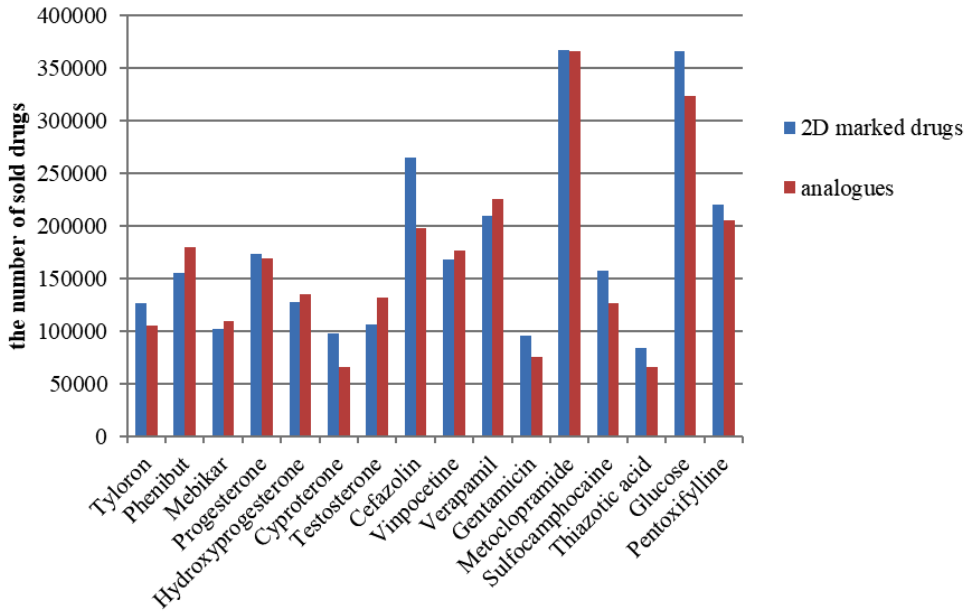

Figure 1: Comparison of sales of 2D marked drugs and their analogues t=0.04, (p=0.48). Created by authors.

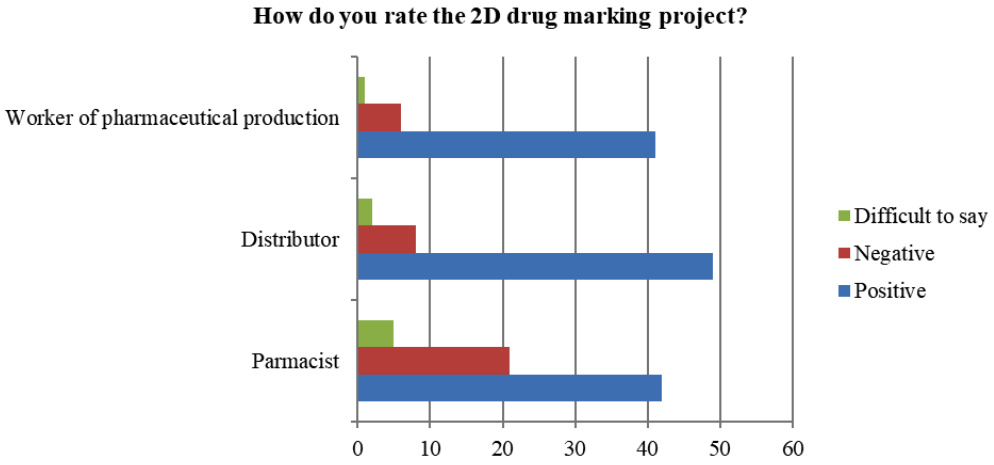

Figure 2: Participants evaluation of pilot project of 2D marking drugs.

marking?", "What information do you think would be useful for improving the quality of drugs?" (Table **5**).

Among the respondents, 89 (35.0%) responders noted that they found some medicines of inadequate quality, between those responders only 45 (17.7%) turned to the pharmacy for returning of medicines, and among those, who turned to pharmacy, only 12 (4.7%) received a positive solution to the issue, which included the replacement of medicines. As for 45 (17.7%) respondents, who encountered low-quality drugs, most 40 (15.8%) responders turned to a doctor to replace the drug with an analogues. Only 3 (3.06%) responders, who by the way were doctors, filled out the electronic form of the State Medical Service of Ukraine for Medicinal Products and Drug Control.

Only 155 (61.0%) respondents know about marking of the medicines, most of them were doctors 95 (61.3%). Among the interviewed doctors, 95 (96.9%) know about drug marking, 85 (89.6%) of them felt positive about marking. Among the answers of those doctors who had a negative attitude to marking was the impossibility of selling medicines in blister packs and possibility of increasing price of drugs. Among custumers without medical education, most

Table 5: Survey Results of Awareness of Methods of Determining the Quality of Drugs in Practice

Questions	Yes		No
Have you encountered medicines of poor quality?	89 (35.0%)		165 (65.0%)
Have you turned to someone with this question? Who do you turn to with poor quality drugs?	45 (17.7%) Pharmacists 42 (16.5%) Doctors 40 (15.8%)		44 (17.3%)
Has the pharmacy replaced the low-quality medicine?	12 (4.7%)		30 (11.8%)
Have you filled out the electronic form of the State Medical Service of Ukraine for Medicinal Products and Drug Control	3 (1.2%) (all doctors by occupation)		42 (16.5%)
Do you know about drug marking? Doctors Other occupation	155 (61.0%) 95 (61.3%) 60 (48.7%)		99 (39,0%)
How do you feel about drug marking? Doctors n=95 Other occupations n=60	Positive 85 (89.6%) 11 (18.3%)	Negative 5 (5.2%) 3 (5.0%)	Neutral 5 (5.2%) 46 (76.7%)
What information do you think would be useful for improving the quality of drugs?	possibility of checking medicines using a smartphone 102 (40.2%) hotline for checking the quality of medicines 84 (33.1%) presence of a temperature indicator 56 (22.0%) other answers 12 (4.7%)		

Source: Created by authors based on the survey.

respondents felt neutral about the presence of drug marking 46 (76.7%) responders, only 11 (18.3%) responders were positive, and 3 (5.0%) were negative. Among the suggestions from the public regarding useful quality control measures 102 (40.2%) of respondents mentioned the possibility of checking medicines using a smartphone, 84 (33.1%) - hotline for checking the quality of medicines and 56 (22.0%) of respondents mentioned the presence of a temperature indicator, which is important during energy supply problems in Ukraine to control the storage conditions of medicines. Thermal indicators are especially necessary on vaccines and biological drugs.

Thus, the survey revealed a low awareness of the population about the control of medicinal products and the possibility of combating counterfeits by filling out the electronic form of the State Medical Service, and a low evaluation of the marking of medicinal products among respondents without medical education, which explained the lack of a positive effect of sales of markrd medicines. There was a high awareness and appreciation of drug marking among doctors, which confirms the importance of drug marking from a professional point of view. Thus, in order to popularize high-quality and tested marked drugs, it is advisable to conduct educational work among the population, since there is a request from the population for the availability of hotlines and the possibility of independent testing of drugs.

4. DISCUSSION

Our analysis of analytical methods applied to medicinal products, identifying their number and the possibility of combining them with each other to increase efficiency and reduce cost. Despite the fact that in Ukraine it is necessary to search for the most financially optimal methods, it is important to take into account innovative opportunities. Beccaria and Cabooter [27] see the prospect of developing miniaturized liquid chromatography systems, such as microfluidic chips and nano-liquid chromatography systems, which are characterized by higher validity and have high potential in the future. Microchip electrophoresis, which combines microfluidic-based technologies in 2D and 3D systems with laser-induced fluorescence and electrochemical studies, is also innovative and is able to reproduce as closely as possible the effect on the cell and organs. The effects on cell is based on the effect on nitric oxide, and the effect on organ is based on modeling of organoids using 3D-printing. This possibility helps to minimize the risks of clinical research [35]. Buledi *et al*. [36] recommend improving the available electrophoresis method by upgrading the sensors with nanomaterials that would increase the anodic/cathode current response and increase the sensitivity of the method. In this way, a large number of quality assessment methods allows us to turn to an alternative way of checking medicinal products in conditions of economic crisis.

Despite the lack of increased sales of 2D labeled drugs, labeling is important and prevents counterfeiting, which is supported by the literature. Bakker *et al*. [18] describe the latest developments in anti-counterfeiting using microscopic, spectroscopic and X-ray fluorescence techniques. Good results were shown by such inexpensive methods as Minilab, colorimetry and the indicator of falsified drugs. Digitization also makes it possible to scan 2D codes with a phone to obtain the necessary information [37].

Our survey indicated low awareness of the population about methods of combating low-quality medicines, which has a negative meaning, because there are mechanisms to combat counterfeits in the country. For example after receiving information with the details of the drug, the State Medical Service is obliged to check the medicinal product, and in case of non-compliance issue an order banning the circulation of such a medicinal product. The response of the State Medical Service will also be the basis for reimbursement by the pharmacy. The problem of lack of feedback from consumers of low-quality drugs is also described in the literature, which emphasizes the importance of educational work [2, 6].

5. CONCLUSION

Our research revealed the most optimal methods of determining the quality of medicines from those proposed in the modern literature, which show effectiveness at a moderate cost. The importance of detecting counterfeits at the stage of distribution of medicines and the interest of large pharmaceutical manufacturers and distributors in the fight against low-quality medicines through the use of drug 2D marking have been determined. The conducted survey revealed low awareness among the population and insufficient awareness among doctors in ways to control the quality of medicines and the possibility of reporting low-quality medicines to the control institutions, which requires additional training of medical personnel and educational work among the public.

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CONFLICT OF INTEREST

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