INNOVATIVE METHODS FOR COUNTERACTING PHARMACEUTICAL CORRUPTION IN THE PRECLINICAL RESEARCH AND CLINICAL TRIALS PHASE: THE SEARCH FOR COMMON INTERNATIONAL STANDARDS

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ABSTRACT

The issue of preventing and combating corruption at the stages of preclinical research and clinical trials of medicines is very relevant, because the quality, impartial, objective and reliable research depends on the safety and quality of the investigational medicinal products, and ultimately the lives and health of the large number of patients who will receive these medicinal products.

Materials and Methods.

The materials of this article are current ethical and international legal norms for conducting preclinical research and clinical trials of medical products, The following methods such as doctrinal, comparative-legal, structural-functional, method of informational search and system-analytical method are applied.

Results.

Analyzing the reports of international organizations, such as WHO, Transparency International and others, current law, including the jurisprudence of different countries of the world, the current scientific doctrine of combating corruption in the pharmaceutical sector, as well as by questioning relevant experts, we can conclude that corruption offenses at the stage of preclinical research and clinical trials, medicines are and remain a significant problem, which seriously violates human rights to health.

Conclusions

Substantial reduction of pharmaceutical corruption problems in the preclinical research and clinical trials phase can be achieved by building a system of drug research using the following methods of counteracting corruption: banning direct funding for drug research by those research clients research and the creation of a special public institute engaged in the organization of such research; monitoring and comparing research results; transparency and accountability of research; digitization of research and management processes; revitalization of civil society institutions; internal organizational compliance of anti-corruption requirements of pharmaceutical companies, research institutions and regulatory bodies; WHO monitoring activities. In doing so, this system should be at the heart of an international treaty in order to harmonize research standards at international and national levels.

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INTRODUCTION

According to the data Transparency International (2016), for example, studies in Canada, France and the Netherlands have shown a general decrease in recent years in the number of new medicines offering therapeutic advantages to previously approved drugs. Research has shown that clinical trials funded by industry are more likely to produce positive results than RCTs funded by other sponsors. One study found that 94 per cent of industry funded RCT results dealing with antidepressants were framed in a way that suggested positive results, while an analysis of those same trials by the US Food and Drug Administration (FDA) found that only 51 per cent of those RCTs had positive results [1].

MATERIALS AND METHODS

The material of this article is current ethical and international legal norms for conducting preclinical research and clinical trials of medicinal products, as well as the international scientific doctrine of combating corruption in the pharmaceutical sector. The following methods are applied: doctrinal, comparative-legal, structural-functional, information search, system-analytical.

RESULTS

According to K. Dmytryk, corruption is a global problem, including in the pharmaceutical sector, which takes place at all levels of pharmaceutical activity, from the stage of research to distribution. Yes, corruption exists at the following stages of pharmaceutical activity: research and development (for example, it may involve manipulation of clinical trial data); production (deviation from the norms of good manufacturing practice); registration of medicinal products (bribery of officials for registration of medicinal products without proper documents); promotion (corruption links with health care facilities and individual doctors, etc.); public procurement (procurement procedures by prior arrangement with the customer); distribution (assignment of drugs, etc.) [2].

In addition, the most widespread corruption practices of major international pharmaceutical campaigns include sponsoring programs where pharmaceutical monopolies provide ready-made reports to experts conducting drug and side-effects investigations, as well as the recruitment of former government officials responsible for authorizing medicinal products decisions on obtaining such authorizations and the corresponding blocking of such authorizations for other, possibly even better and more affordable drugs [3].

For many years, health and politics have been considered by the Poles to be the most corrupt spheres of public life. Corruption in health care arises, first of all, in doctor-patient contacts, when purchasing equipment and medicines, as well as in contacts between doctors and pharmaceutical companies [4, p. 38].
According to M. Fedotov, in the US it is quite common practice to apply fines of a sufficiently high amount to pharmaceutical companies for corruption offenses. So. In 2011, Johnson & Johnson, the largest medical device manufacturer, was accused of bribing doctors and officials to promote its products and paid a $ 70 million fine. In 2012, Pfizer, the largest international pharmaceutical company, was fined $ 60 million. US for bribery subsidiaries of pharmaceutical giant foreign officials and doctors. In 2012, the British pharmaceutical company Glaxo Smith Kline agreed to pay $ 3 billion. US to address fraud scam by confessing to illegal marketing of Paxil and Wellbutrin drugs for adults under 18 years of age. This company concealed adverse drug safety data from Avandia diabetics from the Food and Drug Administration [5, p. 41].

Recent jurisprudence in Ukraine testifies to the activation of civil society in this Central European country in the fight against corruption, in particular the possible corruption manifestations during the necessary clinical trials. This information is contained in the Supreme Court ruling of May 30, 2018, in case No. 758/10744/14-c [6]. In the context of this proceeding, the civil action of a limited liability company that is the subject of pharmaceutical activity to the charity "Patients of Ukraine" charity was considered. The claims of the pharmaceutical company consisted in refuting information which, in the opinion of the company, was negative and unreliable, damaging the business reputation of the company, as well as in damaging non-pecuniary damage. The aforementioned information was published on the charity's official

website"Patients of Ukraine Charitable Foundation, in particular, of the following content," Based on the verification of the documents of manufacturers of the Ukrainian drug "INFORMATION_3", it was found that the drug did not pass any clinical trials on patients who could buy it. "" CF «Patients of Ukraine» ... «As we can see, our suspicions have come true, because no wonder the company hid from the patients, the people whose life depends on the quality of their drug, the results of its tests. After all, they were banal. The Supreme Court, having examined all the material in the case, put a stop to the case, because, according to the position of the aforementioned court, the preparation of the aforementioned pharmaceutical company did not properly undergo clinical investigations, and therefore the claim of the company was denied [6].

According to the researchers Joel Lexchin, Jillian Clare Kohler, Marc-André Gagnon, James Crombie, Paul Thacker, Adrienne Shnier (2018), corruption occurs in the pharmaceutical industry when the entities allegedly responsible for promoting the health and well-being of the population allow them to divert from this duty to other considerations. The end result of corruption means that instead of medicines being, in the first place, a means of improving health care, they are primarily a means of increasing business profits. Exploring ways to combat corruption is fueling new discussions about the potential for systemic change. This type of change is necessary to realize the goals of social governance and the transformation of corporate social responsibility ideas so that consumers and the beneficial outcomes of their treatment remain the ultimate goal of pharmaceutical companies in the international market. These authors give an interesting opinion that it is necessary to separate the process of clinical trials of medicines from financing by pharmaceutical companies [7]. According to the Public Health Sector Transparency Assessment of the World Health Organization, clinical trial regulation should be implemented. A national regulatory authority must have qualified inspectors with experience in conducting on-site inspections. They must receive training in accordance with GCP principles. According to national rules, inspectors may inspect regularly, occasionally and / or for specific reasons. They should be able to compare the procedures and methods used by the researcher with those described in the protocol and report presented by the researcher or sponsor in the MRA. Inspectors should determine whether the researcher maintains the necessary documentation or, otherwise, ascertain who has assumed this responsibility. Inspectors should have free access to all patient files and outputs used and obtained in clinical trials, ensuring confidentiality of information [8, p. 74].

The work "Increasing transparency and accountability in national pharmaceutical systems" by renowned anti-corruption researchers in pharmacy Anne Paschke, Deirdre Dimancesco, Taryn Vian, Jillian C Kohlerd & Gilles Forte (2018) emphasizes the need to disclose information on pharmaceutical system standards, government decisions on the pharmaceutical system. In addition, the achieved results and the circumstances of the deviation from the standards of the pharmaceutical system and the response should be taken for the effective implementation of a policy of openness and accountability, the political will of the authorities is important, as well as the strengthening of the capacity of civil society [9, 787].

Rakhal Gaitonde, Andrew D Oxman, Peter O Okebukola and Gabriel Rada noted in their scientific work "Interventions to reduce corruption in the health sector that" All interventions to reduce corruption are in need of evaluation. . Randomized trials can be used to evaluate the effects of interventions to reduce corruption (Björkman 2007; Björkman 2009; Blais 2007; Ferraz 2005), and should be used whenever possible to reduce the risk of bias in non-randomized evaluations (Johnsøn 2013; Peisakhin 2011). When randomized trials are not possible, ITS studies should be used when possible; and even when randomized trials are possible, controlled ITS analyzes should be used when possible (Fretheim 2015) [10].

Andrew Shaoyu Chen, Mahnu V. Davar, Kathleen Harris, Tirzah S. Lollar, John Tan, Jacqueline Mulryne, Eliseo R. Puig's expressed their points of views in their scholarly work «Clinical Trials and Anti-Corruption Laws: Managing Risk in a Rapidly Changing Environment» (2019). It stated the following "Given the importance of laboratory research and clinical trials to support marketing applications, senior leaders, general counsels, and chief compliance officers should invest into their companies' global R&D compliance programs accordingly. To mitigate potential liabilities before the government comes calling, companies should consider a careful assessment and remediation of areas of exposure, with particular attention to the rigor of monitoring and auditing plans for foreign clinical trials, the risks inherent in engaging third parties such as CROs to undertake trials, and the related interactions with HCPs and government officials "[11].

According to Doctor of Pharmaceutical Sciences, Professor, Professor of the Department of Natural Sciences for Foreign Students and Toxicological Chemistry of Zaporizhzhia State Medical University Volodymyr Parchenko, in order to counteract corruption in the pharmaceutical sector of healthcare effectively, it is necessary to strengthen the legal responsibility for the mentioned corruption strictly. However, according to the scientist, the achievement of significant results in combating corruption in pharmacy is not possible without an effective fight against corruption in medicine, since these two activities are linked in one area inextricably. This sphere is health care.
According to Doctor of Pharmaceutical Sciences, Professor, Head of the Department of Economics and Management of Pharmacy, Medical and Pharmaceutical Law of Zaporizhzhia State Medical University Yevhenii Knysh, it is necessary to prevent corruption in pharmaceutical activity at the stage of preclinical and clinical trials of a medicinal product, appling a control method, namely, performing these tests in two institutions, comparing their results.

Thus, enhancing the effectiveness of counteracting corruption in pharmaceutical activity has the following main areas:
- strengthening legal liability for corruption offenses in the pharmaceutical healthcare sector;
-separating pharmaceutical manufacturers (or pharmaceutical companies interested in organizing the market circulation of certain pharmaceuticals) from direct financing of clinical trials of medicinal products;

-implementation of transparency and accountability programs in the pharmaceutical industry;
-strengthening the capacity of civil society organizations whose focus is on combating health care corruption.

Strengthening legal liability for corruption offenses in the pharmaceutical sector should mean increasing the severity of criminal and administrative penalties for such corruption offenses. In this context, we believe that huge (as in the US) criminal and administrative penalties should be introduced for pharmaceutical companies whose officials are bribing scientists, medical companies, and healthcare professionals to increase the profits of these commercial corporations. Moreover, in this case, both pharmaceutical companies (legal entities) and officials of these companies should be brought to legal responsibility. In addition, corruption in the field of health care should belong to serious or particularly serious crimes under the national law of the states. They must impose the most severe sanctions against the above-mentioned employees of pharmaceutical companies. In some cases, they can cause to life imprisonment with confiscation of property with additional punishment in the form of imprisonment. This law must provide their engagement in certain activities or their occupations of certain positions. At the same time, it is also necessary to revoke the license for pharmaceutical activities of pharmaceutical companies at the decision of the competent state body.

In order to separate interested pharmaceutical companies from the direct financing of preclinical research and clinical trials of medicinal products, it is necessary to set up a special public institution to deal with such research. This institution (which, for example, can be called a health institute) should operate with the broad involvement of the medical, pharmaceutical and scientific community in the governing bodies of the institution. In order to carry out drug research, the interested pharmaceutical company applies to the health institute with the appropriate application and supporting documentation, providing the required amount of the investigational medicinal product. A computerized automatic distribution system must code and distribute the materials, obtained from the pharmaceutical campaign, .among research organizations. There must be not less than two such organizations. Research organizations should make the research protocols available to the public on their own websites. The results reported in the abovementioned protocols are subject to comparison by specially authorized committees of the Institute of Health and the national regulatory authority in the field of medicines. The national regulatory authority and the institute of health are entitled to inspect the quality of the research carried out by the research organization. In case of significant differences between the research organizations' research results, an appropriate investigation shall be conducted to identify the circumstances and causes of such discrepancies. Moreover, a special commission consisting of the relevant specialists of the national regulatory authority and specialists of the public health institute should carry out this investigation. In case of detecting signs of offenses, the results of the investigation are sent to the relevant law enforcement agencies for pre-trial investigation. If the investigation results in a deliberate falsification of the research results, such

research institution should be fined a large amount of fine and be deprived of the right to conduct drug research for at least ten years. As for the employees of the research institution who have falsified the clinical trial protocols and their guilt has been brought to justice, such persons should be held criminally responsible as for a serious crime with confiscation of property and deprived of the right to occupy certain positions and engage in certain activities indefinitely.

A significant advantage of the modern era of social civilization is the high advances in digital computer technology, which should be widely implemented to ensure transparency, openness, and accountability of preclinical research and clinical trials of medicines. Obviously, it is necessary to create a separate platform to reflect the results of preclinical research and clinical trials of medical institutions. The administrator of this separate platform should be the national regulatory authority. In addition, the most important moments of preclinical research and clinical trials should be recorded in video and photo files. These multimedia files should be stored for some time in research institutions. They must be forwarded to a health institute and a national regulatory authority. In addition, they must be available for review by a citizen or a non-government organization. Moreover, it also requires the disclosure on the above mentioned platform about the non-compliance of clinical trials of a medicinal product in two different research institutions, as well as the results of a verification of the non-compliance.

It is important for the effectiveness of preventing and counteracting corruption during clinical trials the civil society members' active position, their personal interest in the honesty and transparency of the research conducted. The Bioethics Committee of the Institute of Health should work with them in order to conduct appropriate seminars. These seminars will explain every volunteer their rights and responsibilities at professional level and at high level of social responsibility, which they bear before society, because of the objectivity and the reliability of clinical trial results will further be influenced by the quality of treatment, and sometimes even the life and health of many patients. The Bioethics Committee should explain to patients, in particular, that it is their right and legitimate interest to familiarize themselves with the clinical trial protocol, to clarify in detail the technical details of such familiarization, to study and collate the reference data, the algorithm of action in case of detection of falsified or inaccurate medical information about a clinician means. In particular, adherence to the ethical principles of preclinical research and clinical trials of medicines is an important means of preventing corruption. Corruption can occur when socially maladapted populations or individuals, who are physically or mentally unable to give informed consent to the test are acting as objects of research. Clinical trials of medicinal products, where prisoners are sentenced to should not be allowed. They are depended on the will of the administration of places of incarceration, which causes an increased level of corruption risks. According to the Declaration of Helsinki, each potential entity should receive adequate information about the purpose, methods, sources of funding, any possible conflicts of interest, institutional affiliation of researchers, expected benefits and the potential risks of the study. and the inconvenience it may cause, and any other relevant aspects of the

study. The potential subject of the study should be informed of the right to refuse to participate in the study or to withdraw its consent to participate at any time without claiming it. For a potential incompetent object of study, the physician is required to obtain informed consent from his or her legal representative [12].

CONCLUSIONS

Thus, analyzing the views of many scientists, as well as the best practices of individual countries, the recommendations of international organizations (such as WHO and Transparency International), the main modern methods of counteracting pharmaceutical corruption in the preclinical research and clinical trials of medicinal products are the following ways to reduce it: prevention of direct financing of pharmaceutical research by interested pharmaceutical companies; creation of independent public institutions for the research of medicines (with the participation of the state, scientists, representatives of civil society); conducting randomized trials of medicinal products at least in two research institutions with analysis of results; the obligation to triple-check the results of drug tests by a public institution. the national regulatory authority and the relevant WHO structure; the obligation to publish the research results on a dedicated platform in the public domain within a short time after their completion; the obligation to photograph and videotape the results of the research and send the relevant materials to the controlling bodies, to familiarize with these materials the representatives of civil society at the appropriate request; compulsory public awareness-raising activities regarding the observance and protection of the rights, freedoms and legitimate interests of volunteers participating in clinical trials of medicinal products; the implementation of internal measures to prevent and counteract corruption by pharmaceutical companies, which are the clients of medicinal research; to apply to the violators of anti-corruption norms at the stage of research of medicines the most severe measures of punishment of both personal and property character (and, to all categories of such violators: pharmaceutical companies and research organizations as legal persons, their employees, officials of public institution and national regulatory authority).

In addition, the complex structure of the methods of preventing and combating corruption at the stages of preclinical research and clinical trials should not lead to the burden of the above processes, since these methods should be carried out by means of total digitization of public life. In order to put the above standards into practice in the research of medicinal products of nation-states, it is necessary to develop and adopt by national states an appropriate international treaty implementing the relevant national legislation, and to comply strictly with the above uniform standards. Only a systematic integrated implementation of modern methods of counteracting pharmaceutical corruption at the stage of preclinical research and clinical trials of medicines will be able to provide truly significant results in this area.

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