Original Article

Aspects of improving the regulatory system of pharmaceutical products in the Republic of Kazakhstan

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ABSTRACT

The article discusses ways to improve the regulatory system for medicine production in the Republic of Kazakhstan based on the study of regulatory documents governing the pharmaceutical business. The article aims to study the regulatory framework governing the pharmaceutical business and consider the prospects for the development of legal support for this industry. To achieve this goal, the authors have identified and achieved the following objectives: performing an analysis of Kazakh and foreign literature on issues related to competition and assessment of the competitiveness of pharmaceutical organizations; exploring the legislative framework of the pharmaceutical business; predicting the prospects for the development of activities related to the provision of medicines for the population; studying the attitude of practitioners and the population to the regulatory framework and state regulation of the pharmaceutical business in the Republic of Kazakhstan. The subject of the study is the current state of the regulatory framework of the pharmaceutical business.

Keywords: pharmaceutical production, pharmacy, production of medicines, regulatory legal acts, regulatory legal support, the pharmaceutical business.

Introduction

The relevance of the problem of regulatory support of the pharmaceutical business is determined by the medical, social, and economic role of the field of medicine provision in the life of society [1, 2].

In his Message to the people of Kazakhstan dated October 5, 2018 and entitled "The improvement of the Kazakhstan citizens' welfare: improving income and quality of life", First President of the Republic of Kazakhstan and Leader of the Nation N.A. Nazarbayev noted the following: "The health of the nation is the state's top priority. This means that Kazakhs must consume high-quality goods. At present, there is no holistic policy to protect the population from poor-quality and goods and services dangerous for health and life". [3] Among other things, attention was paid to the quality and safety of medicines and medical services, which requires material and legal support of a modern laboratory base and the formation of a staff consisting of qualified professionals.

Currently, the role of special legal knowledge in providing the necessary support in the relevant areas of human life is rapidly gaining importance. This can be explained by the fact that an adequate regulatory framework allows regulating all areas of legal relations, thereby eliminating the possibility of illegal activities. A study of criminal practice showed that the imperfection of the legal framework created the prerequisites for illegal activities, including in the sphere of counterfeit medicine trafficking.

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Pharmaceutical institutions and organizations are actively involved in the realization of the highest goal of the country's economic strategy, namely preserving the health of the nation and raising its cultural level. The development of the pharmaceutical market, the implementation of socially-oriented state programs supported by financing, developing international cooperation, as well as new strategic plans in the field of healthcare, are the basis for the formation of a new vision of medicines policy.

A modern healthcare system must meet the new requirements of all interested parties, namely the population, the medical service providers, and the state [4]. In this regard, special attention should be paid to the quality of the pharmaceutical products, services, and knowledge provided, as well as cost-effective and evaluated treatment methods. [5-7]

The pharmaceutical sector of the Republic of Kazakhstan is an important and integral part of the country's healthcare system. Over 20 years, the country's medicine supply system has undergone dramatic changes: from a centralized supply chain to the development of an extensive network of private distributors and retail pharmacies. [8] Along with the natural processes of entrepreneurship development in the pharmaceutical sector, the state took measures to create an appropriate basis for the effective regulation of the pharmaceutical market, the conditions for a transition to the international standards in the industry. A regulatory framework has been established to regulate the circulation of medicines; the quality control system of medicines has been improved, while the basic quality requirements are determined by the developed and approved Pharmacopoeia of the Republic of Kazakhstan. Significant improvements can be noted in the medicine supply system.

Improving the legal regulation of the industry will entail changes in existing legislation, which must be harmonized with international practice, considering the integration into the Customs Union and the Eurasian Economic Union and the obligations undertaken by Kazakhstan during the negotiation process on Kazakhstan's accession to the World Trade Organization. [9, 10] When developing regulatory legal acts on medicines, one needs to follow modern and recommended international practices and the principles of simplifying legislation, eliminating the double interpretation of norms and eventual contradictions between different norms.

The intensity of the development of the pharmaceutical market in Kazakhstan depends on many factors. The main ones are the stimulating factor expressed in the inflow of investments, on the one hand, and the constraining factor expressed in the government regulation of the pharmaceutical business that works against the chaotic development of the pharmaceutical business, on the other.

To ensure the safety of medicines, the system needs to transition from quality control at one particular stage to ensuring quality at all stages of medicine circulation. The quality of medicines can only be ensured through the implementation of good laboratory practice (GLP), good clinical practice (GCP), good manufacturing practice (GMP), good distribution practice (GDP), and good pharmacy practice (GPP) standards (i.e., from development and clinical trials to production and sale of medicines), as well as completion of accreditation of medicine certification centers and organization of the vertical structure of the system of state quality control bodies.

At present, strict control over the procurement of medical products at the expense of budgetary funds, as well as the regulation of preferential provision of medicines to the population, is also necessary.

The pharmaceutical market is the fastest growing and most complex in terms of its social significance for the medicine supply of the population. Given this, one of the most important tasks of social and state development is the study of the problems of managing the pharmaceutical business. [11, 12]

The pharmaceutical business means activities carried out by wholesale organizations and pharmacy institutions in the field of the circulation of medicines, including wholesale and retail trade in medicines, as well as the manufacture and production of medicines.

The quality of medicines in the pharmaceutical market is regulated at the state level: a policy in the field of medicine circulation is formed in the Ministry of Health; quality control of medicines is carried out by supervisory bodies in the field of health and social development.

State control in the circulation of medicines includes control over preclinical research of medicines, clinical trials of medicines, medicine quality, production, manufacture, storage, transportation, import into the Republic of Kazakhstan, advertising, dispensing, sale, disposal, and use.

Methods

Since the research topic is interdisciplinary, in its development we relied on the fundamental provisions of law, philosophy, medicine, and pharmacy.

In the course of the study, we used systemic, historical, and interdisciplinary approaches, as well as empirical, theoretical, formal, informative, and other methods of scientific research.

In the process of work, we used general and special scientific methods, content analysis, sociological, statistical methods, as well as special sociological methods, document analysis, and observation. Besides, the study involved the comparative legal method, the historical legal method, the formal-logical method, the systemic structural method, and other methods.

The reliability and validity of the conclusions made in the study are ensured by using a significant number of legislative, monographic, periodic, legal, and sociological plans, and analysis of statistical data.

Results

The attractiveness of the medicine market contributed to the development of the pharmaceutical business, which is not always promoted by persons who are specialized in the field of pharmacy, although in addition to professionalism, it is important to adhere to moral principles in the field of medicines manufacture and sale. As the market was quite attractive, criminal offenses in this field were common. [13]

The existing legislative and regulatory framework is not perfect enough, controlling separate, fragmented issues, and, like any field, it needs constant development. For several years, there was no systematic and complete state regulation in the sphere of medicines sale and production. The role of government in these matters had been weakened. There was no clear infrastructure for managing the pharmaceutical industry. [14]

At present, the situation has changed, regulatory legal acts of various levels have been adopted, a lot of work is being done in this area. However, the formation of clear and precise state policy in the field of pharmacy, which must be provided by the legislation, remains a paramount issue today.

The analysis of the current legislation and regulations in this area revealed the imperfection of laws and the presence of conflicts of individual norms. [15] Today, a large number of new regulatory acts, decrees, orders, and instructions relating to this area are being developed. However, it can be difficult to fulfill the requirements of individual regulatory documents in connection with the imperfection of the terminological apparatus. Sometimes the concepts and terms that are used in documents contradict each other; most laws are indirect laws, and the requirements of many regulatory acts distort their meaning; many legal acts are of a referral nature, and the requirements of various documents do not correspond to each other.

In general, a large number of normative acts have been adopted, however, they mainly regulate the provision of medicines for the disadvantaged categories of citizens. At the same time, one of the central places in state policy in the field of pharmacy should be its normative regulation, i.e. improvement of existing or development of new industry standards, norms, rules, instructions, and orders, which should not contradict, but complement each other. [16, 17]

To eliminate or minimize conflicts of law, we propose from the experience of developed countries to introduce the practice of good documentation practice (GdocP), which will help to improve the monitoring and coordination of the developed legislative and regulatory documents in the field of pharmacy.

In modern conditions, the consistent expansion of the pharmaceutical industry is one of the highest priorities for the economic development of Kazakhstan. The organization of modern pharmaceutical production requires the integration of diverse approaches related to the integrated implementation of good pharmaceutical practice (G×P) standards system governing various aspects of its activities. Worldwide medicine regulatory systems depend on the knowledge available to organizations that develop, manufacture, test, and distribute pharmaceutical products. The provision of reliable data entered into registration dossiers and other documents on which everyday regulatory decisions are based is an important component of the responsibility of medicine market operators in terms of ensuring the safety, effectiveness, and quality of medicines. Only in these conditions can the state effectively monitor the market for medicines to protect public health. All this determines the relevance of implementing GdocP standards in pharmaceutical manufacturing.

According to the experience of international practice, it can be said that to regulate the processes of providing medicines, it is necessary to comply with the uniform norms and requirements of G×P. Good practices have been developed for each of the stages of medicine development, production, and promotion. Thus, when developing new medicines, various kinds of laboratory and clinical studies are being conducted. These studies should be guided by the GLP and GCP standards. After this stage, pharmaceutical companies apply for permission to sell the medicine, with which the next stage for the medicine begins, this is production and distribution. The GMP and GDP standards are established to regulate this area. The chain of these requirements continues in the retail sale of medicines with the GPP standards. Besides, there are such good practices as the good storage practice (GSP) (a standard that contains the requirements for the manufacturer and supplier premises in which raw materials and medicines are stored), good vigilance practice (GVP) (a standard necessary for the vigilance of registered medicines, documenting and presenting the results of medicine safety monitoring), good engineering practice (GEP) (proven engineering methods and standards that are used throughout the project to obtain adequate and cost-effective solutions), and GdocP as the standard, which is used for the correct creation of documents, their maintenance, storage and archiving.

A written, printed, magnetic or electronic medium containing information or data, in a fixed form, is a document or record. Documents necessary and required to accompany all these stages should be written or created clearly and legibly, they should be traceable, provide sufficient detail of actions, and an accurate chronology of events. Documents and records are evidence that the products are manufactured under the developed process and certain specifications.

GdocP is critical to the success of any operation or project in a regulated industry. Usually managed through the Document Management Plan under standard operating procedures (SOP), GdocP is implemented in the entire organization and allows including data, correcting records, and documents. [18]

GdocP is used in the pharmaceutical industry and is essential for the integrity of data collection and reporting to support the development, registration, commercialization, and life cycle management of pharmaceutical products. Following the GdocP system makes it possible to avoid errors in the production environment and during the analysis of the pharmaceutical product, which otherwise could affect the quality of the product, patient safety, condition of production facilities, and related activities. Compliance with the GdocP standard is required by

both American and European regulatory authorities, such as the FDA's CFR (the Food and Drug Administration Code of Federal Regulations) and EMA (European Medicines Agency). In addition to the United States Pharmacopeia (USP), which contains the main chapter <1029> [19], the World Health Organization (WHO) [20], HealthCanada [21], and EudraLex (a collection of rules and regulations governing medicines in the European Union) [22] published specific recommendations regarding GdocP. Besides that, GdocP is an important part of current good manufacturing practices (cGMPs) in the United States. [23]

In addition to regulatory requirements, it is also important to accurately record and document activities in the pharmaceutical industry, which allows critical assessment of internal procedures to increase their effectiveness. A study of foreign experience showed that when regulatory authorities check pharmaceutical developments and manufacturing facilities for compliance with GLP, GCP, and GMP, the inspectors check pharmaceutical companies for compliance with the document management norms. In particular, possible deficiencies could include incomplete records, unsystematic documents, non-compliance with standard operating procedures, non-conforming documents, unconfirmed electronic systems, uncertified copies, inappropriate methods of making changes, and additions to documents, etc. The document management practice that does not comply with GdocP standards can lead to problems expressed in receipt of FDA forms or warning letters. The consequences of both can cost the company time and money. Besides, this information is publicly available and may damage the organization's reputation. In recent years, numerous warning letters issued by the FDA have had observations regarding data integrity and record-keeping practices. These defects can be caused by organizational pressure on timelines, lack of experience, insufficient resources, attention and commitment to tasks, redundant and outdated processes and controls, and limited guidance and training. To solve these problems, it is recommended that foreign experts improve the qualifications of the staff, while the training of all staff for work according to GDocP is fundamental. It is necessary to train employees, as well as make sure that the training is fully documented and at the end of the training, the student is evaluated for understanding the course. If the staff uses the same set of documentation rules, whether it is employees producing medicines, checking raw materials storage logs, responsible for compliance with environmental standards, etc., the information for everyone will be equally clear, which will ultimately lead to the most effective achievement of goals. In this regard, certain procedures should be followed and the GdocP standard should be implemented in pharmaceutical enterprises and organizations.

According to the provisions of the WHO [24], the goal of GdocP is to:

1. define specifications and procedures for all materials and methods of production and control,
2. provide staff with knowledge about what and when to do,
3. provide authorized persons with all the information necessary for the release of the product,
4. ensure the availability of documented evidence, traceability, and sequence of records of all stages,
5. ensure the availability of data for verification and statistical analysis.

Documents should be developed, prepared, reviewed, and distributed for use under established procedures.

According to the requirements of GdocP, to ensure the listed requirements, the data must comply with the following integrity properties abbreviated as ALCOA: they should be Attributable, Legible, Contemporaneous, Original, Accurate. Attributable implies the ability to identify the person who completed the recorded task. This is necessary to ensure that a particular function has been performed by trained and qualified personnel. This also applies to changes made to the records: corrections, deletion, additions, etc. Legible means that all entries must be readable and the information must be written in a way that allows understanding it. This requirement is imposed on any information entered, including the original or modified.

Contemporaneous implies that all actions, events, or decisions should be recorded at the moment when they take place. Original is described as the first receipt of information, the source. Accurate means that it is important to ensure the correctness of the information, including the research data that are used in making important decisions about the quality of the product.

Under the provisions of the GdocP, the documentation should be as detailed as possible. For example, in the manufacture of pharmaceuticals, the following are mandatory for documentation: the purpose of the study (including the type of study, for example, a GLP, GCP, or GMP study, research, development/validation methods, process development, pharmaceutical analysis, bioassays, stability, etc.), protocol or study number, materials (source and batch number), standards, and results/conclusions, etc. Final records and documentation will demonstrate the accuracy and completeness of the data collected.

Besides, it is important and necessary to establish procedures for archiving and protecting documents so that they will be available, if necessary, during repeated studies, product registration, and inspections by regulatory authorities. To this end, a procedure is provided to prevent loss or damage to documentation during archiving, retrieval, and translation of documents.

Thus, for the smooth operation of the enterprise and to comply with regulatory requirements, it is important that the organization:

- provide enough resources to create documentation and document management,
- ensure compliance of documents with the ALCOA data integrity properties;
- conduct a thorough analysis of existing documentation, including providing a system for its preservation and impossibility to lose documents,

- conduct courses of initial and continuous training of personnel involved in the development and production of pharmaceutical products on the creation of documents, management, and security of documents,
- carry out quality control, which is necessary to ensure that the staff works with documents properly and correctly follows the standard operating procedures of the organization.

Discussion

Considering the pharmaceutical business as a network of equal relations based on the production, sale of products and services, property relations, and the balance of interests of market participants, it should be noted that the social mission of the pharmaceutical sector determines the need of its clear regulation and control at the state level.

One of the steps to increase the effectiveness of this sphere of human life is the introduction of GdocP. This will allow implementing the principle of production and personnel management through the state regulation system, as the pharmaceutical services market is most socially oriented and is distinguished by its specificity. The pharmaceutical market, as a market for services, is linked to other markets and contains classic components. The state of the pharmaceutical market, its technologies are directly dependent on legal norms, the development of the disease prevention and medical care system, the professionalism of specialists, etc. This market, unlike other markets, is most subject to government regulation. Moreover, state regulation in the pharmaceutical services market is necessary and carried out through a system of regulatory legal acts. The regulatory framework defines the actions of pharmaceutical market entities, ways, and means of achieving goals, combined with information transparency.

Conclusion

The above arguments allow us to draw the following conclusions:

- the effectiveness of state regulation of the pharmaceutical business depends on the quality of developed and regularly updated regulatory documents;
- the introduction of GdocP will ensure the legitimacy, transparency, and traceability of the pharmaceutical industries and other pharmaceutical institutions and organizations;
- heads of pharmaceutical organizations should have complete information about the functions, rights, duties, and responsibilities of regulatory authorities and organizations and keep relevant documentation;
- at the state level, it is necessary to coordinate the activities of regulatory organizations to reduce subjective administrative barriers.

Based on the foregoing, despite the presence of a large number of regulatory and legislative acts regulating the pharmaceutical business, some of its aspects remain unresolved, which gives rise to the possibility of committing criminal offenses. The introduction of GdocP will minimize such opportunities.

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