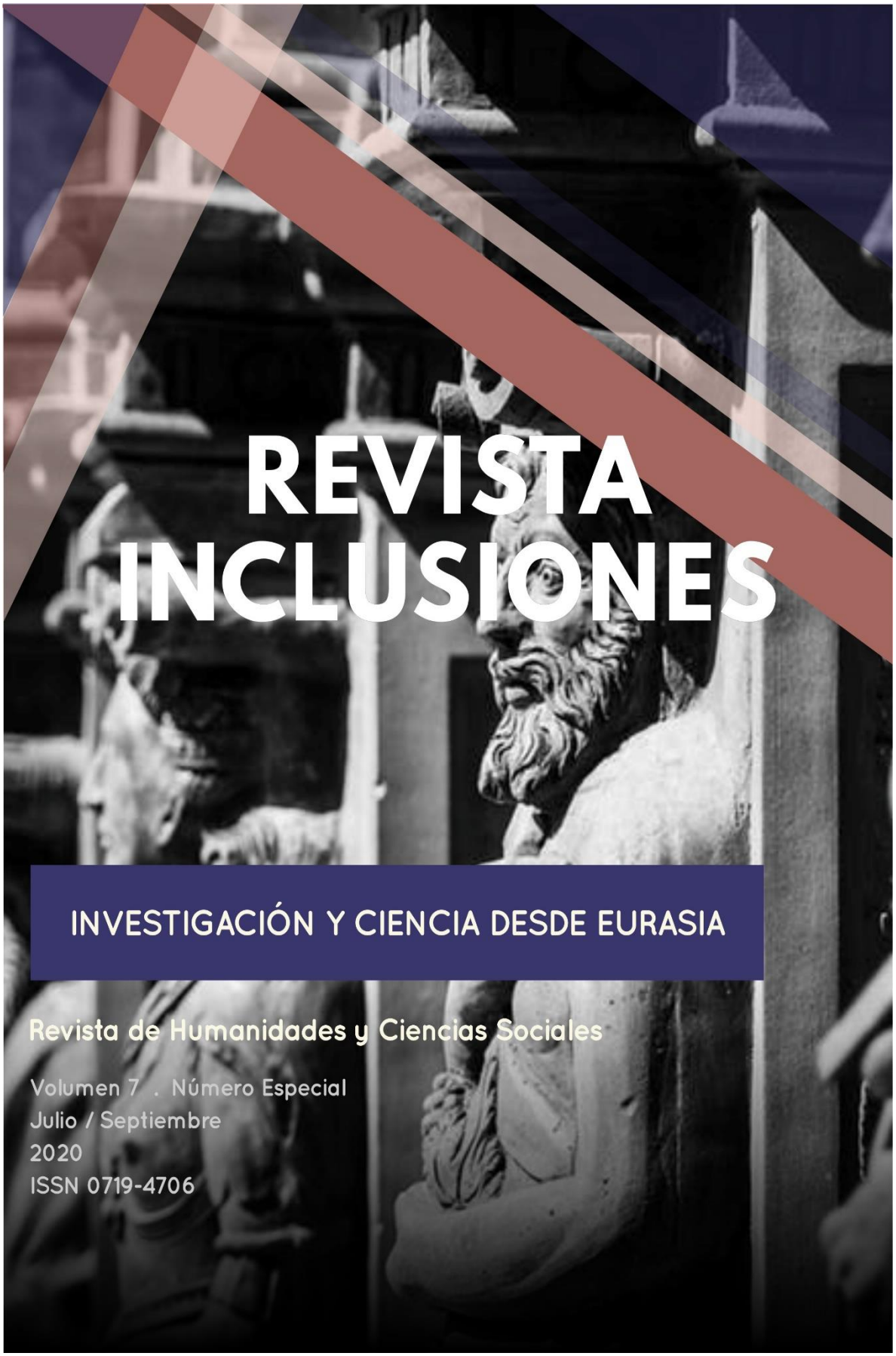

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ANALYSIS OF PROBLEMS SPECIFIC TO THE FIELD OF DRUG DEVELOPMENT BY INTERNATIONAL AND RUSSIAN MANUFACTURING COMPANIES

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Abstract

The article is devoted to the analysis of problems in the development of new medicines (drugs) typical for world and Russian manufacturers. It is established that Russian manufacturing organizations mostly focus both on the lack of approaches to the organization of the process and the lack of regulation documents at the national and local levels. On the contrary, regulators of the circulation system of medicines in many countries with developed economies have approved the documents regulating approaches to drug development which were designed taking into account the specifics of the organization of processes and international standards of good practices. In this regard, it is relevant to study the possibility and rationality of applying a systematic approach which allows a comprehensive study to the organization of new medicine developmental process at Russian pharmaceutical enterprises, as well as to the development of methodological support for the processes and procedures of drug development for Russian manufacturers.

Keywords

Drug development – Medicine – Documents regulating – Pharmaceutical enterprises

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Introduction

The key to successful business of an industrial enterprise for the production of medicines is an effective assortment portfolio of products. In this regard, the assortment policy of enterprises sets responsible specialists the task of developing and introducing new medicines, both original and reproduced, into production. The phases of drug development and launch of any drug into production by a pharma company are complex, comprehensive, and based on high-end technologies. Furthermore, accompanied by significant financial and time costs they pose risks for developers.

The problem of the manufacturer when including a new drug in the product portfolio has many components: the lack of data on the actual time spent on the project, the economic viability of the new product, data on the technology, production conditions and quality control parameters of the new product, its competitiveness, methods of promotion in the pharmaceutical market, etc.

When preparing for the drug development a manufacturing company has to collect information with the involvement of specialists of various qualifications from different fields. The process management system is of great importance for optimizing the work of these personnel and obtaining reliable data in a timely manner. This system includes the organization of processes, the sequence of their execution, and the control of their implementation. The final results of drug development largely depend on systematization, planning, initial preparation, and the ability to operate the phases of a drug development well.

Yet solving the problem of incorporating a new product into a drug portfolio, Russian pharmaceutical companies are currently independently building an algorithm of organizing a drug development process, while internationally, the regulatory documents dedicated to the developmental process have been adopted in order to formalize it.

The regulators of the drug circulation system in many developed countries (the European Union (EU), the United States of America (USA), Japan) have adopted documents regulating approaches to the drug developmental process within the International Council for Harmonization (The International Council Harmonization of Technical Requirements for Pharmaceuticals for Human Use) (ICH). The formulated regulations take into account the specifics of the organization of processes and international standards of good practice (good x practice - GxP): preclinical research – (good laboratory practice - GLP), clinical research – (good clinical practice - GCP), drug production – (good manufacturing practice - GMP), drug storage – (good storage practice - GSP), etc.[1]

[1] Good laboratory practice (GLP). 2015. Retrieved from: http://www.eurasiancommission.org/ru/act/texnreg/deptexreg/konsultComitet/Documents/GLP%20%D0%B2%D0%B5%D1%80%D1%81%D0%B8%D1%8F%203.pdf; Good clinical practice (GCP). 2005. Retrieved from: http://www.oncology.ru/law/2005/GOST_52379-2005.pdf; Good manufacturing practice (GMP). 2015. Retrieved from: http://www.eurasiancommission.org/ru/act/texnreg/deptexreg/konsultcomitet/documents/gmp%20%D0%B2%D0%B5%D1%80%D1%81%D0%B8%D1%8F%204.1%20%D0%BE%D1%82%2025%2003%202015.pdf y Good distribution practices (GDP). 2015. Retrieved from: http://www.eurasiancommission.org/ru/act/texnreg/deptexreg/konsultComitet/Documents/GDP%2020.04.2015.pdf

At the same time, approaches to ensuring proper quality in drug development have been developed and described in the ICH manuals: ICH Q8 «Drug Development»[2], ICH Q9 «Quality risk management»[3] and ICH Q10 «Pharmaceutical quality system»[4], ICH Q11 «Development and manufacture of drug substances»[5].

These standards have also become the regulatory framework for the development of documentation on the requirements for the drug development and the production of medicines for countries focused on bringing reproduced products to the world pharmaceutical market[6].

The EU has a hierarchical legislative system for regulating the circulation of medicines, including their development. In this system, the fundamental legal act is the Treaty on the Functioning of the EU (TFEU). In accordance with it, the EU directives, regulations, decisions and other documents are adopted, followed by national-level legislation of the EU member States[7]. Issues that are not covered by the EU law are governed by the national law of the EU member state[8].

In the United States, the main body regulating the sphere of drug circulation is the Food and Drug Administration (FDA). The agency's authority and functions are limited to protecting consumers' rights from dangerous and substandard products. The FDA encourages the development of new drugs, examines drugs before they are released into circulation[9].

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[2] ICH Q8 Pharmaceutical development. Retrieved from: http://www.ich.org.

[3] ICH Q9 Risk Quality Management. Retrieved from: http://www.ich.org.

[4] ICH Q10 Pharmaceutical Quality System. Retrieved from: http://www.ich.org.

[5] ICH Q11 Development and manufacture of drug substances (chemical entities and biotechnological/biological entities). Retrieved from: http://www.ich.org

[6] Z. A. Mamedyarov, Innovatsionnoye razvitiye mirovoy farmatsevticheskoy otrasli (Moscow: IMEMO RAS, 2019) y D. Carpenter y D. Tobbel, “Bioequivalence: the regulatory career of a pharmaceutical concept”, Bull Hist Med Vol: 85 num 1 (2011): 93-131.

[7] Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medical products for human use and investigative medical products for human use. Retrieved from: http://eurlex.europa.eu/homepage.html; Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Retrieved from: http://eurlex.europa.eu/homepage.html; Commission Regulation (EC) No 540/95 of 10 March 1995 laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, to medicinal products for human or veterinary use authorized in accordance with the provisions of Council Regulation (EEC) No 2309/93. Retrieved from: http://eur-lex.europa.eu/homepage.html y Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medical products for human. Retrieved from: http://www.apteka.ua/article/296331

[8] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medical products for human use, and repealing Directive 2001/20/EC. Retrieved from: http://eur-lex.europa.eu/homepage.html; Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medical products for human and veterinary use and establishing a European Medicines Agency. Retrieved from: http://eur-lex.europa.eu/homepage.html

[9] Ph. J. Hilts, Protecting America's Health: the FDA, Business, and One Hundred Years of Regulation and sources there (North Carolina: University of North Carolina Press, 2003) y U. S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Development and Use of Risk Minimization Action Plans (Washington, DC: U.S. Government Printing Office, 2005).

In 2011, the FDA was reorganized, resulting in the formation of the Global Regulatory Operations Division and the opening of international offices in 10 countries. These include developing countries such as China and India, which use FDA documents in their practice[10].

Currently, the International Council for Harmonization is discussing a set of standards for researchers involved in the development of medicines (i.e. good research practice (GRP) with recommendations for the development and launch of medicines). However, it is assumed that these regulations will be advisory in nature, and therefore, the requirements formulated in them may cause discrepancies for manufacturers and regulators in the Russian pharmaceutical market[11].

The adopted regulatory documents of the Eurasian economic Union (EEU), which includes the countries of Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russia, and Moldova, are also based on the international GxP principles. This documentation was aimed at such areas of drug treatment as registration, preclinical and clinical research, production, in terms of quality control and assurance, etc. However, it does not regulate the organization and management of the processes of drug development and medicine launch[12].

In this regard, representatives of the Russian pharmaceutical industry still have a number of strategic issues about the need to develop regulatory documents that formalize the order and sequence of the drug development process.

The new GMP standard was established in the Russian pharmaceutical industry in order to improve the quality of medicines produced locally and bring them to the international level[13]. However, it also did not consider approaches to drug development. The aim of this research was conduction of comparative analysis of problems arising in the organization of processes in a new drug development as well as formulation of the solutions to the problems by means of application of a systematic approach in the development of the methodological support.

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[10] Z. A. Mamedyarov, Innovatsionnoye razvitiye mirovoy farmatsevticheskoy otrasli (Moscow: IMEMO RAS, 2019).

[11] S. N. Bykovskiy; I. A. Vasilenko; N. B. Demina; I. E. Shokhin; O. V. Novozhilov; A. P. Meshkovsky y O. R. Spitsky. (eds.). Farmatsevticheskaya razrabotka: konzeptsiya i prakticheskiye rekommendatsii. Nauchno-prakticheskoye rukovodstvo dlya farmatsevticheskoy otrasli (Moscow: Pero Publishing house, 2015).

[12] Resolution of Eurasian Economic Commission Council of 3 November 2016, no. 79 "Concerning adoption of the Good clinical practice of EAEU". Retrieved from: http://www.fptl.ru/biblioteka/eaeunion_lekarstva/EAEU_GCP.pdf; Resolution of Eurasian Economic Commission Council of 3 November, 2016, no. 85 "On the Rules for conducting bioequivalence studies of drug products on the territory of EAEU". Retrieved from: http://www.fptl.ru/biblioteka/eaeunion_lekarstva/EAEU_issledovanija-bioekvivalentnosti.pdf;
Resolution of Eurasian Economic Commission Council, of 3 November 2016, no. 89 “On the Rules for conducting studies of biological medical drugs of EAEU”. Retrieved from: http://www.fptl.ru/biblioteka/eaeunion_lekarstva/EAEU_issledovaniya-biologicheskih-LS.pdf y Resolution of Eurasian Economic Commission Council of 3 November 2016 no. 81 "Concerning adoption of the Good laboratory practice of EAEU in the field of drug circulation". Retrieved from: w.fptl.ru/biblioteka/eaeunion_lekarstva/EAEU_GLP.pdf

[13] A. I. Poverinov y S. V. Kunev, “Problemy vnedreniya otraslevogo standarta GMP kak faktor snizheniya konkurentosposobnosti farmatsevticheskikh proizvoditeley”, Vesnik Mariiskogo gosudarstvennogo universiteta. Seria "Selskokhozyastvenniye nauki. Ekonomicheskiye nauki" Vol: 1 num 13 (2018): 100-104 y DSM Group. Farmatsevticheskiy rynok Rossii [Russian pharmaceutical market]. 2017. Retrieved from: http://www.dsm.ru/docs/analytics/june_2017_pharmacy_analysis.pdf

Materials and methods

Content analysis of data from national and international scientific publications, as well as official information databases, systematic and comparative analysis. Questionnaires and interviews of persons responsible for organizing the drug development process at individual Russian pharmaceutical companies.

Results and discussion

In the process of the research of primary and secondary materials, the systematic method, comparative and content analyses were applied, which allowed analyzing of scientific works reports made by foreign and Russian drug developers.

The materials obtained in the course of the study showed that the foreign authors have identified a number of problems specific to the field of drug development:

- productivity crisis – the number of annually approved medicines in the US and EU has been growing slightly in the last decade, while research costs have been growing rapidly[14];

- the success of the industry led to the emergence of effective drugs for many common diseases, this fact contributed to the development of a new direction, the therapy of complex and rare diseases, which has further led to the formation of new regulatory requirements for these groups of drugs[15];

- a large number of highly qualified specialists involved in the drug development process, which caused an increase in labor costs in this sector, this has led to a reduction in the scientific staff of a number of international organizations[16,17];

- strengthening of regulatory control over the quality requirements for medicines being launched[18];

- an imbalance in the management of pharmaceutical companies – the cost of development and launch of medicines does not always reflect the clinical benefits[19].

The works of Russian scientists have highlighted the following problematic aspects of the processes of drug development and product launch:

[14] Z. A. Mamedyarov, Innovatsionnoye razvitiye mirovoy farmatsevticheskoy otrasli (Moscow: IMEMO RAS, 2019) y J. W. Scannell; A. Blanckley; H. Boldon y B. Warrington, “Diagnosing the decline in pharmaceutical R&D efficiency”, Nature reviews Drug discovery Vol: 11 num 3 (2012): 191-200.
[15] Z. A. Mamedyarov, Innovatsionnoye razvitiye mirovoy…
[16] Z. A. Mamedyarov, Innovatsionnoye razvitiye mirovoy… y
[17] E. Rubin; S. Tummala; D. Both; C. Wang y E. Delaney, “Emerging technologies supporting chemical process R&D and their increasing impact on productivity in the pharmaceutical industry”, Chem. Rev Vol: 106 num 7 (2006): 2794–2810.
[18] J. W. Scannell; A. Blanckley; H. Boldon y B. Warrington, “Diagnosing the decline in pharmaceutical R&D efficiency”, Nature reviews Drug discovery Vol: 11 num 3 (2012): 191-200.
[19] Z. A. Mamedyarov, Innovatsionnoye razvitiye mirovoy…

- issues of the level of training and qualification of personnel are studied in the works of A.A. Lin, S.V. Sokolova[20], I.A. Narkevich, E.O. Trofimova[21];

- financial and investment issues in drug development are presented in the works of L.E. Yasinskaya[22], I.A.Narkevich[23];

- issues of productivity of scientific researches in the field of innovative medicine development are considered in the work of A.A. Semin[24].

One of the main issues of the Russian pharmaceutical industry described in the works of A. A. Lin was the almost complete absence of new high-tech developments. In his opinion, the main part of the product portfolios of Russian producers of drugs are low-profit generic drugs which does not allow manufacturing enterprises to count on a profit that allows them to allocate more than 1-2% of their total revenue for research and development of drugs[25].

Also, according to A.A. Lin, I.A. Narkevich, L.E. Yasinskaya, and others, large funds totalling from 250 million to 800 million US dollars are spent on the development of a new drug. The period from the idea of creating a new medicine to its release into the market is more than 10 years[26]. As a result, Russian manufacturers were not present among the developers of highly effective and expensive drugs, but were pushed into a highly competitive niche of cheap drugs[27].

The issue of the industry personnel potential is widely covered in the works of I.A. Narkevich, E.O. Trofimova, N.V. Pyatigorskaya. According to the results of their research, the transition of the Russian pharmaceutical industry to an innovative development scenario has required the modernization of existing pharmaceutical enterprises and the formation of new ways of development. This fact has determined the increased demand for qualified production personnel with secondary professional and higher education for all stages of production management[28].

Next in a series of issues related to the launch of new drugs into production, the works of V.V. Beregovykh, O.R. Spitsky, and others, suggest and describe an idea that the

[20] A. A. Lin; B. I. Sokolov y D. M. Slepnev, “Farmatsevtichesky rynok: proizvodstvo lekarstvennikh sredstv v Rossii”, Problemy sovremennoy ekonomiki Vol: 1 num 45 (2013): 191-195 y A. A. Lin; B. I. Sokolov y A. S. Orlov, “Farmatsevtichesky rynok: segment klinicheskikh issledovaniy lekarstvennykh preparatov”, Problemy sovremennoy ekonomiki Vol: 1 num 53 (2015): 288-293.

[21] I. A. Narkevich; E. O. Trofimova y T. U. Delvig-Kamenskaya, “Problema podgotovki kadrov dlya rossiiskoy pharmatsevticheskoy otrasli i puti yeyo preodoleniya”, Innovatsii Vol: 7 num 177 (2013): 3-8.

[22] L. E. Yasinskaya y E. O. Trofimova, “Gosudarstvennaya finansovaya podderzhka farmatsevticheskoy i meditsinskoy promishlennosti”, Remedium num 10 (2016): 6-16

[23] I. A. Narkevich; E. O. Trofimova y T. U. Delvig-Kamenskaya, Problema podgotovki kadrov…

[24] A. A. Semin, Institutsionalniye mekhanismy povysheniya produktivnosti nauchnykh issledovaniy v oblasti razrabotki innovatsionnykh lekarstvennykh sredstv. Ph.D. thesis. (Saint Petersburg: Saint Petersburg Chemical and Pharmaceutical Academy, 2017), 27-34.

[25] A. A. Lin; B. I. Sokolov y D. M. Slepnev, Farmatsevtichesky rynok: proizvodstvo…

[26] A. A. Lin; B. I. Sokolov y A. S. Orlov, Farmatsevtichesky rynok: segment klinicheskikh… y I. A. Narkevich; E. O. Trofimova y T. U. Delvig-Kamenskaya, Problema podgotovki kadrov…

[27] A. A. Lin, B. I. Sokolov, D. M. Slepnev. Farmatsevtichesky rynok: proizvodstvo…

[28] I. A. Narkevich; E. O. Trofimova y T. U. Delvig-Kamenskaya, Problema podgotovki kadrov…

processes of drug development and drug launch were not considered in detail and stated in regulatory documents. The technology transfer stage indicated in the life cycle of the medicine connects the development and production of drugs using data about the product and process obtained at the development stage. And, insufficient attention to the introduction of this stage of the life cycle in the production of drugs makes it difficult to achieve adequate quantitative and qualitative indicators established at the development stage[29].

According to S.N. Bykovsky, I. A. Vasilenko, N.B. Demina, and others, a key issue of introducing new drugs into production for the manufacturer is insufficient formalization and regulatory support of this process[30].

The obtained data allow us to conclude that the range of problems in terms of drug development and drug launch is different for international and Russian manufacturers.

While in the world market, the process of drug development and drug launch is formalized by the documented procedures, a large number of highly qualified specialists are involved in the development of new medicines, and one of the main problems is the "productivity crisis", in the Russian market, all trends are opposite. There is a shortage of human resources, insufficient financial and documentation support. In addition, the existing legal framework regulating the sphere of drug development in the Russian pharmaceutical market does not provide a detailed formalization of all procedures. This requires special approaches to the creation of local documentation of the manufacturer to support the processes of drug development and drug launch.

To correlate the issues presented in scientific reports with the issues faced in practice by Russian drug manufacturers implementing the development and introduction of a new product into production, we conducted a survey of senior specialists. The survey questions were aimed at defining approaches to the organization of drug development processes and the launch of a new drug, effective planning, economic analysis and evaluation of enterprise resources, management of the production process at enterprises, analysis of the methodology used for planning the drug development process.

The surveys and interviews were conducted at Russian enterprises specializing in the production of various drugs: pharmaceutical substances, medicinal products obtained by chemical, biological and biotechnological synthesis, and herbal medicines.

The surveys were attended by specialists of enterprises directly involved in the process of development and launch of medicines. The interviews were conducted with managers and persons responsible for expanding the range of products at pharmaceutical companies.

The main issues of Russian enterprises in the development and launch of new drugs are:

[29] V. V. Beregovykh y O. R. Spitsky, “Perenos tekhnologiy pri sozdanii prouzvodstva lekarstvennogo sredstva”, Vestnik RAMN num 12 (2013): 49-57.

[30] S. N. Bykovskiy; I. A. Vasilenko; N. B. Demina; I. E. Shokhin; O. V. Novozhilo;, A. P. Meshkovsky y O. R. Spitsky. (eds.). Farmatsevticheskaya razrabotka: konzeptsiya i prakticheskiye rekommendatsii. Nauchno-prakticheskoye rukovodstvo dlya farmatsevticheskoy otrasli (Moscow: Pero Publishing house, 2015).

- lack of internal documents regulating and registering the drug development process (75 %),

- shortage of qualified personnel (62.5 %),

- lack of funding (50 %),

- issues of the management of the process as a whole and its individual procedures (37.5 %)[31].

The addressing of a number of the above-mentioned problems of the drug development process is possible under the condition that a systematic approach is applied to the drug development organization at the enterprises leading to effective planning and optimization of resource allocation.

The system approach to management is based on the fact that every organization is a system consisting of integral parts. Each of these parts has its own goals, which, when combined, lead to the achievement of common goals of the organization. In this case, the company is considered as an integrated system.

Our use of this approach to the organization and management of the phases of the drug development was aimed at systemizing the work of the involved personnel and formalizing these processes.

In the course of the research, the drug development was considered as a system, the elements of the system were identified, the processes and their sequence were established in accordance with certain phases.

The elements of the drug development as a system were defined as the following:

- process (0) - a phase of the drug development process;

- input (1) – a process goal (0) according to the phase;

- resources (2) – a set of (labor, financial, temporary, material and technological, intellectual and informational) resources necessary to ensure the implementation of the process;

- management (3) – a system for managing a phase of the drug development process (0), which includes a set of tools, methods, and ways for solving management issues that arise in the course of a company's operation when organizing a phase of the drug development process (0);

- output (4) – the expected result of the realisation of the phase of the drug development process, depending on the goal.

[31] S. A. Rozhnova y A. V. Tsypkina, Analiz vozmozhnosti primeneniya printsipa QBD k protsesu razrabotki lekarstvennykh sredstv na otechestvennykh farmatsevticheskikh predpriyatiyakh. Razrabotka i registratsiya lekarstvennykh sredstv num 4 (2019): 14-20.

In the course of the study, each phase of the drug development process has been considered as an independent process of the system with corresponding elements. The obtained system allows project managers to manage these processes in the event of changes in the external and internal conditions characteristic of the manufacturing company, predict and take corrective and preventive measures to reduce the risks of deviations from planned indicators.

Conclusion

Thus, in the world and Russian pharmaceutical markets, there are different approaches to the organization of procedures for the development of new medicines, and in this regard, there is a different range of problems. One of the main issues for Russian manufacturers is the absence of a unified formalized approach to the organization of the process of drug development and documentation of the methodological support. A developed systematic approach for the process of new drug development enables to control processes and procedures at each phase of drug development, as well as to predict and take precautionary measures to manage risks, to affect the particular elements of the system provided there are changes in the external environment.

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