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# Study of Prospects and Analysis of Peculiarities Related to Introducing GMP Standards in the Russian Federation

**N. Bekhorashvili, M. G. Rayisyan**
*Sechenov First Moscow State Medical University, 119991, Russian Federation, Moscow, Trubetskaya Street, 8*

**Abstract**

The article analyzes the current state and problems related to introducing international GMP standards in the pharmaceutical sector of the Russian economy. The characteristics of the system of international GMP standards are given. The stages of introducing GMP standards into the Russian pharmaceutical practice are considered. Based on the expert survey, the activity of the Federal Budgetary Institution State Institute of Drugs and Good Practices (hereinafter – the FBI SID & GP), the authority inspecting medicines' manufacturers, has been analyzed in terms of its compliance with GMP standards. It is concluded that the introduction of GMP standards will have positive impact on the quality of medicines on the Russian pharmaceutical market.

**Keywords**: medicines, pharmaceutical sector of economy, GMP standards.

## INTRODUCTION

The international experience of regulating the pharmaceutical sector encourages focusing on the existing and potential foreign partners. Thus, on the state level, it is planned to improve the national regulatory provision of production and medicines' quality control, which in its turn will enable Russian producers not only to ensure the quality of pharmaceutical products for the domestic consumer, but also to enter the international market with their pharmaceutical products.

The studies of the problems on the domestic production of medicines in our state are still unclear, because the underdevelopment of the stock market considerably reduces the investment attractiveness of not only the pharmaceutical industry but also other industries and the mechanism that would enable citizens to buy shares of enterprises with good prospects and thus invest in their development. The national pharmaceutical industry is gradually approaching the time when GMP standards should be fully implemented in the production of medicines. However, today there are no imperative economic prerequisites for the accelerated movement in this direction. It means that benefits go to the manufacturers that do not modernize their production capacities but produce cheap low quality pharmaceutical products with high sales.

The modern pharmaceutical sector is one of the most globalized ones. This is proved by the fact that all countries are consumers of pharmaceutical products. A considerable part of the latter is sold through export and import. Defining peculiarities of the modern world pharmaceutical sector and its structure has considerable impact on the functioning and development of this sector of economy.

In the modern system of world commodity markets, the pharmaceutical sector of economy has a significant role in solving both economic and important social problems related to health protection (national security interests). In general, the pharmaceutical market is characterized by:

Low dependence on cyclic fluctuations. This peculiarity is due to the fact that pharmaceutical products are always (under any economic, social, and political conditions) demanded by all social categories and age groups of the population,

High profitability, and

Ongoing need in constantly increasing expenditures for research and advertising.

Thus, based on the fact that the pharmaceutical sector is one of the most profitable and high-tech, the overwhelming part of the production and sale of its products is focused in the developed countries of the world.

Today, the Russian population is provided with a wide range of medicines and medical products of national and foreign production. However, the main problem of the pharmaceutical sector is still their quality. In order to ensure high quality of medical products (and they should be such-like), it is not enough only to control their quality. It is also necessary to create a system to ensure production quality and at the same time to use its existing potential that requires immediate actions that focus on the national production complying with the GMP (Good Manufacturing Practice) world standards. These are requirements and recommendations to organizing and implementing production, the purpose of which is to minimize the probability of selling low quality and dangerous pharmaceutical products to customers [1].

It is necessary to note that GMP standards were developed in the 1960s as one of the elements of the systems aimed to improve the medicines' safety. Due to the cases that caused serious adverse reactions to certain medicines at that time, there was the need to protect the population from the possible unforeseen harmful impact of pharmaceutical products provoked by production disturbances.

Today, the importance of GMP standards increases. This system is being constantly improved. This will benefit both consumers who get access to high-quality medicines and pharmaceutical companies due to the reduction in the number of legal claims caused by selling low quality pharmaceutical products.

The main elements of GMP include the following [2]:

Compliance of the technological and control documentation at the enterprise with the registration dossier for the relevant medicine,

Strict control over the compliance with the rules of medicines' production in accordance with the requirements of GMP, and

Providing the population with efficient and safe high-quality medicines with a high level of guarantee.

Medicines' production according to GMP standards is, first of all, the psychological focus of the whole team on the production of high-quality pharmaceutical products. Every member of the team must be confident that he/she produces high-quality products. Such confidence is possible only when everyone conscientiously treats his/her functional duties, and the work is well organized and provided with appropriate material resources, as well as the quality control system functions properly.

The compliance with the GMP requirements is obligatory for pharmaceutical companies – producers from most world countries, and GMP certification must be an essential prerequisite for licensing medicines, their registration and distribution.

In Russia and in the countries of the Eurasian Economic Union (EEU), the adoption of international and European standards related to medicines stipulates economic and political goals, and is an essential prerequisite for:

Ensuring the quality of medicines in the consumers' interests,

Creating barriers that guarantee only high-quality medicines and medical products on national markets; technical barters in the international medicines' trade, and

Entry of national producers to the world pharmaceutical markets and increase in the export potential.

Thus, in order to ensure their own development, production reconstruction, and make them comply with international norms, large national pharmaceutical companies need to have additional sales markets. This opens up prospects that may be related to the entry to Asian markets (http://rbcdaily.ru/industry/562949996452698) [3].

At the same time, according to experts, the entry to European markets is almost an irresolvable task. Thus, the majority of Russian producers that export their products are skeptical about the possibility to enter markets in Western Europe and other developed countries where it is necessary to prove that the medicine is not only properly produced (compliance with GMP standards), but has also been studied in a laboratory (GLP) and a clinic (GCP), because there is a complex system to be included in the Reimbursement List (the list of medicines), the cost of which is compensated by insurance companies [4].

As for the European Union, there are principles and rules for the production of medicines for humans, introduced by the Directive of the EU Commission 91/356/EU "On establishing basic principles and rules of Good Manufacturing Practice (GMP) of medicines for humans" that are obligatory for all EU countries, as well as for third countries that exporting medicines to the EU.

Today, there is no single GMP standard adopted throughout the world. Taking into account the fact that it is impossible for the majority of countries to achieve the full compliance with GMP standards, the World Health Organization (WHO) has developed a list of the most important GMP requirements that define the necessary minimum of standards.

Russia had taken the EU GMP standard as a basis, and in 2004 it developed the first version of the Russian GMP standard that was prepared by the Association of Microcontamination Control Engineers (AMCCE). Based on this standard, in 2004 Decree of the State Standard of Russia No. 160-st, GOST R 52249-2004 "Rules for the Medicines' Production and Quality Control" dated March 10, 2004 was approved that was harmonized with the EU GMP rules (Good Manufacturing Practice for medicinal products) (http://docs.cntd.ru/document/1200036160).

It is necessary to note that at the first stage of introducing GMP, the national pharmaceutical industry suffered some losses as a result of the considerable financial expenses, but then funds for the production of medicines were saved. It was achieved due to strict mechanisms of control and surveillance at all stages of production (certification or validation of production processes at the enterprise), which allowed the medicine quality system to function adequately and to increase production volumes.

The next stage of implementing GMP was the approval of order of the Ministry of Industry and Trade of Russia No. 916 "Rules of Good Manufacturing Practice" dated June 14, 2013 (http://docs.cntd.ru/document/499029882). Then the GMP standards' implementation was developed by the approval of the "Rules for the organization and conduct of inspection of medicines' producers for compliance with the rules of good manufacturing practice, as well as issuing conclusions on the medicine producer's compliance with the set requirements" (http://minpromtorg.gov.ru/activities/services/licensing/1_11/1_11_3/). On May 6, 2017, the national medicines' markets of five EEU states (Russia, Belarus, Kazakhstan, Kyrgyzstan, and Armenia) united and began their work in a single space format in accordance with the "Rules of Good Manufacturing Practices of the Eurasian Economic Union" (http://docs.cntd.ru/document/456026099).

Since GMP is an obligatory rather than a voluntary set of rules, it is subject to state verification. Since December 2015, the FBU SID & GP has been authorized in Russia to inspect producers of medicines for compliance with the GMP standard. It consists of highly qualified specialists who undertook an internship in leading European GMP/GDP organizations on the inspection of enterprises for compliance with the requirements. The inspection should be carried out at the stages of licensing the production of medicines, periodically or for other reasons. First of all, national and foreign enterprises are subject to the registration inspection (except for the cases when according to international agreements or participation in appropriate certification systems the results of inspection of a national inspection of another state are recognized).

Taking into account that as on December 2017, the ratio of sales of the imported and national medicines on the Russian commercial pharmacy market was 41.2% (import) against 58.8% (Russian medicines) by volume, and 70.2% (import) against 29.8% (Russian medicines) in the value terms, respectively (URL: http://dsm.ru/docs/analytics/december_2017_pharmacy_analysis.pdf) [5], it is necessary to note that the inspection of not only Russian, but also foreign enterprises that produce pharmaceutical products for Russian consumers for compliance with GMP standards is important.

Due to this, the purpose of the study is to analyze peculiarities of inspecting medicines' producers that operate outside the Russian Federation in terms of their compliance with the requirements of GMP standards.

Study hypothesis: the efficiency of introducing GMP standards in the Russian Federation will considerably increase if the control over good manufacturing practice is carried for all medicines' producers both within and beyond the Russian pharmaceutical market.

## MATERIALS AND METHODS

The main tasks to achieve the set study goal are the following:

to analyze the factors that are taken into account when inspecting medicines' producers for the compliance with the GMP standard carried out by the FBI SID & GP, and

to set possible goals and results to be achieved by these inspections.

To achieve the set goal and to prove the hypothesis, an expert survey was conducted. The experts – inspectors from the FBI SID & GP (25 people) – took part in it. They had a number of questions on the nature of the factors that are taken into account during the inspections for the compliance with the requirements of GMP standards.

## RESULTS

According to the experts, during the work of the FBI SID & GP, a lot of inspections were carried out, training and development programs for inspectors were developed, and the national inspectorate took serious positions on the international level.

The first question was related to the reasons why inspections outside the Russian Federation were generally carried out. According to the experts, during these events, inspectors should evaluate the state of pharmaceutical productions that supply medicines to Russia; define whether this information coincides with the data presented in the registration dossier; and check the compliance of the activity of the inspected site with the Russian standards.

At the same time, the first inspections of foreign production sites took place only in April 2016: it took some time for submission of applications from producers, approval of the inspections schedule, making up a plan for inspecting production sites, and taking all necessary preparatory measures.

In total, in 2016, the Ministry of Industry and Trade of the Russian Federation received 620 applications for site inspections.

According to the experts, 465 of them were given to the FBI SID & GP. 188 inspections were carried out. In 2017, 620 applications were sent to the inspectorate, and there were 513 inspections. In 2017, 403 opinions (against 88 in 2016) were given, and 110 opinions were refused (38 in 2016).

If we talk about the geography of foreign inspection trips, in general for 2016-2017 more than 700 sites of foreign producers from more than 40 countries have been inspected. The most frequent trips were organized to India, Germany, Hungary and Slovenia. Poland and France took the last positions in Top 5.

In total, according to the results of inspecting foreign production sites (in 2016), 1,801 discrepancies were identified, including 126 (7%) that were classified as critical, 770 (43%) - as major, and 905 (50%) - as minor (other). On average, 0.67 critical, 4.1 major and 4.8 minor discrepancies were detected according to the results of one carried out inspection.

In this list, it is necessary to especially note the considerable discrepancies – their percentage is large enough, and indeed they can have impact on the quality of medicines (and, consequently, on the patient's life and health).

The experts single out five main categories of these discrepancies:

- Procedures for manufacturing products by an authorized person,
- Measures to prevent cross contamination,
- Quality control procedures for the finished products,
- Risks of microbiological contamination and issues of sterility, and
- Noncompliance with the registration dossier.

Let's consider these categories in details (http://gosgmp.ru/download/gmp_2017/materials/day_1/Chadova-NN-presentation.pdf) [6].

In the first category, the most often comments are related to the lack of proper interaction and traceability when exchanging information among the authorized persons of various production sites (if these sites jointly participate in the medicines' production) and the improper assignment of powers among the authorized persons in the relevant quality agreements.

In the second category, inspectors most often faced the noncompliance of the requirements for toxicological evaluation during the validation of equipment cleaning, as well as the nonuse of all knowledge about the properties of the produced substances (e.g., solubility, adhesiveness); the fact that during the validation of cleaning not all units of equipment involved in the technological process were evaluated; and after introducing new products into the existing production scheme by using the combined equipment, their impact on the validated status of the cleaning procedures was not evaluated.

Comments on the third category were related to the production of medicines according to the results of control over bulk/unpackaged ("bulk") products in those cases when processes of the primary and/or secondary packaging could have negative impact on the indicators of the finished product quality; selection of archival/control samples in the amount insufficient for full double control in accordance with the requirements of the registration dossier; and the further study of the stability of the finished medicines by using unpackaged ("bulk") products.

The fourth category includes the comments on the absence or considerable discrepancies in the system for continuous monitoring of particles in A/B purity class zones; failure to comply with the rules for the validation of aseptic filling (known as "media fill test"); and noncompliance with the rules for zoning production into purity classes when performing operations on aseptic filling.

The last fifth category includes the implementation of certain stages of medicines' production at production sites that are not listed in the registration dossier; the use of quality control methods that do not meet the requirements of the registration dossier; and the submission of medicines for sale in the Russian Federation without the full range of tests specified in regulatory documents for the medicine.

## DISCUSSION

Speaking about the priorities for the development of GMP inspection, the experts say that at the very beginning of the Russian inspectorate work there was insufficient preparation of sites for the inspection. As a result, many producers were refused to get opinions on the compliance with GMP standards.

Since the second half of 2017, the experts say, there has been more serious preparation of production sites, which in its turn has its impact on the number of issued GMP opinions. According to the experts, it proves the importance of inspections – if the producer has received a certificate of its products' quality confirmed by inspectors, it can be trusted, and its products can be confidently bought.

The experts emphasized that in addition to the direct activity on inspecting and reporting on the results of inspecting foreign sites, inspectors of the Russian GMP inspectorate were involved by the Ministry of Industry and Trade of the Russian Federation as an expert organization to inspect Russian producers for licensing. According to the experts, it provides the national producer with the opportunity to enter the international pharmaceutical markets with its products, and, consequently, it allows seriously asserting itself on the national market.

Consequently, the spread and implementation of GMP in the practice of Russian pharmaceutical companies is strategically justified. However, if Russia hopes to become an exporter of medicines, these are target markets that will determine which level of compliance with GMP standards for its country is necessary. It is necessary to note that in the EU countries, the rights, duties and qualification requirements for the authorized person, as well as the requirements for treating the animals used when producing medicines are established on the legislative level in accordance with the provisions of Directive 2001/83/EU and Directive 86/609/EU.

Besides, inspectors of the Russian GMP inspectorate take an active part in discussions and disputes on improving the system of state regulation of the medicines' circulation, as well as in the organization of joint training programs for inspectors and representatives of the pharmaceutical industry both in Russia and the EEU countries.

At the same time, it is important for the Russian GMP inspectorate to integrate Russia into the world pharmaceutical community, participate in forming the regulatory framework for a single pharmaceutical market among the EEU member countries, and establish an international independent expert inspectorates' council. The latter project, according to the experts, is the most interesting one in terms of its prospects: it means the creation of an inspectorate confidence index, and will also increase the level of inspections, make transparency in the mutual recognition of GMP, reduce the burden on medicines' producers, and improve the quality of production.

The experts note that while until recently the main criteria that determined the drug sales volume have been low costs

and low prices for medicines, today the main criteria are efficiency, safety and quality of medicines. At the same time, the volumes of the Russian pharmaceutical market, like before, directly depend on the purchasing power of the citizens. That is why, according to the experts' opinion, the Russian pharmaceutical industry needs support from the state: the encouragement of investments (granting tax credits) and export, the establishment of real time borders to achieve a certain standard of products, as well as the creation of a reliable funding system to provide the population with medicines.

According to the experts, some directions on introducing GMP standards can be implemented without considerable investment. Thus, to train personnel, small funds are needed, but due to them, it is possible to considerably improve the degree of the enterprise's compliance with the GMP requirements.

According to the experts, the FBI SID & GP should join the System of Cooperation with Pharmaceutical Inspection Council (PIC/S), which will ensure the recognition of the results of its inspections on the international level. For this purpose, in 2017 the Russian Ministry of Industry and the FBI SID & GP submitted an application for the Russian inspectorate to join the PIC/S (the System of Cooperation with Pharmaceutical Inspection Council) according to the pre-application procedure. The membership in this Council will allow to equally cooperate with inspectors from around the world, share the accrued experience, and openly discuss issues on conducting inspections with foreign colleagues.

## CONCLUSIONS

The GMP rules have been effective in the world since 1963. Their observance guarantees that the medicines will be produced and delivered to consumers in the strict compliance with all necessary technologies, and therefore these drugs' quality will be guaranteed. However, even under a well-considered and carefully controlled system of quality rules, today it is impossible to entirely control all pharmaceutical productions that exist in the world. It means that there will always be the need in the Russian GMP inspectorate that, firstly, helps to provide people with safe medicines, and secondly, proves the seriousness of the Russia's position on the medicines' efficiency.

Consequently, the introduction of the GMP requirements to medicines' production at Russian pharmaceutical enterprises is one of the decisions taken by the state government that implements the constitutional right of every citizen to get efficient, safe and high-quality medicines that will ensure the safety of the entire population, as a whole.

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