



ANALYSIS OF INDUSTRIAL PRACTICE OF DRUG QUALITY RISK MANAGEMENT IN RUSSIAN PHARMACEUTICAL ENTERPRISES

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The aim of the research was to study the current industrial practice of drug quality risk management in Russian pharmaceutical enterprises, including the assessment of the main problems during the implementation of the risk management system and its compliance with the accepted international approaches.

Materials and methods. In the period from 6 April to 10 May 2020, an online survey of the leading employees in the field of quality assurance of Russian manufacturers was conducted. In the survey, the questionnaire was based on the results of the authors' analysis of the national regulatory legal acts of the Russian Federation, the European Union countries, international guidelines of the EAEU, ICH and WHO in this area. 111 people took part in the survey, the return of questionnaires was 11.5%.

Results. The data obtained indicate the prevalence of a superficial approach to quality risk management in the Russian pharmaceutical industry, the presence of objective and subjective reasons that hinder the effective implementation of these methods, the fragmentation of the systems used and, in most cases, their ineffective use. The respondents believe that the most significant reasons for the difficulties in implementing this methodology, are the lack of recommendations from the Ministry of Industry and Trade of Russia on creating an effective quality risk management system and a shortage of the specialists who are ready to work in the area of this industry. The survey revealed rather large gaps in the deployment of a risk management system at the enterprise and separation from the established international practice.

Conclusions. The data obtained indicate the extreme urgency of developing recommendations for a quality risk management system, which should be based upon and supported by Russian regulatory legal acts and international experience in this area. The authors propose highlights for these recommendations.

Keywords: quality risks; drugs; Russian pharmaceutical industry

Abbreviations: EU – European Union; EAEU – Eurasian Economic Union; ICH – The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; SOP – Standard Operating Procedures; GMP – Good Manufacturing Practice; FMEA – Failure Mode and Effects Analysis; HACCP – Hazard Analysis and Critical Control Points; FMECA – Failure Mode, Effects and Criticality Analysis; PHA – Preliminary Hazard Analysis; FTA – Fault tree analysis; MHRA – Medicines and Healthcare products Regulatory Agency; PDA – Parenteral Drug Association; ISPE – International Society of Pharmaceutical Engineering; ASTM – American Society for Testing and Methodology

АНАЛИЗ ОТРАСЛЕВОЙ ПРАКТИКИ ПО УПРАВЛЕНИЮ РИСКАМИ ДЛЯ КАЧЕСТВА ЛЕКАРСТВЕННЫХ СРЕДСТВ НА РОССИЙСКИХ ФАРМАЦЕВТИЧЕСКИХ ПРЕДПРИЯТИЯХ

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Цель работы: изучение текущей отраслевой практики по управлению рисками для качества лекарственных средств на фармацевтических предприятиях России, включая основные проблемы при внедрении системы управления рисками и соответствие общепринятым международным подходам.

Материалы и методы. В период с 6 апреля по 10 мая 2020 года был проведен онлайн-опрос ведущих сотрудников в области обеспечения качества российских производителей. Анкета, использованная при опросе, разработана по результатам анализа национальных нормативных правовых актов Российской Федерации, стран Европейского Союза, международных руководств ЕАЭС, ICH и ВОЗ в данной области. В опросе приняли участие 111 человек, возврат анкет составил 11,5%.

Результаты. Полученные данные свидетельствуют о превалировании в российской фармацевтической отрасли поверхностного подхода к управлению рисками для качества, наличия объективных и субъективных причин, мешающих эффективному внедрению этих методов, фрагментарности используемых систем и, в большинстве случаев, их неэффективному использованию. Наиболее значимыми причинами сложностей при внедрении этой методологии респонденты считают отсутствие рекомендаций Минпромторга России по созданию эффективной системы управления рисками для качества и дефицит в отрасли специалистов, готовых к проведению работ в этой области. Опрос выявил достаточно большие пробелы российских предприятий в развертывании системы управления рисками на предприятии и разрыв с устоявшейся международной практикой.

Заключение. Полученные данные свидетельствуют о крайней актуальности разработки рекомендаций по системе управления рисками для качества, опирающихся на положения российских нормативных правовых актов и международного опыт в этой области. Авторами предложены тезисы для этих рекомендаций.

Ключевые слова: риски для качества; лекарственные средства; российская фармацевтическая отрасль

Список сокращений: ЕС – Европейский союз; ЕАЭС – Евразийский экономический союз; ICH (The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) – Международный совет по гармонизации технических требований к регистрации лекарственных препаратов для медицинского применения; СОП – стандартные операционные процедуры; GMP (Good Manufacturing Practice) – надлежащая производственная практика; FMEA (Failure Mode and Effects Analysis) – анализ видов и последствий отказов; HACCP (Hazard Analysis and Critical Control Points) – анализ рисков и критических контрольных точек; FMECA (Failure Mode, Effects and Criticality Analysis) – анализ видов, последствий и критичности отказов; ПНА (Preliminary Hazard Analysis) – метод предварительного анализа опасностей; FTA (Fault tree analysis) – Анализ дерева отказов; MHRA (Medicines and Healthcare products Regulatory Agency) – Агентство Великобритании по контролю оборота лекарств и медицинских товаров; PDA (Parenteral Drug Association) – Ассоциация парентеральных препаратов; ISPE (International Society of Pharmaceutical Engineering) – Международное общество фармацевтического инжиниринга; ASTM (American Society for Testing and Methodology) – Американское общество по испытанию материалов

INTRODUCTION

The quality risk management system is a part of enterprises' quality management system in different industry sectors. Such industries include, for example, food industry, production of medical devices, car manufacturing, aircraft engineering and others¹. Risks can be present at all stages of the product life cycle. The risk-based approach contributes to ensuring the quality of products, achieving control of technological processes, and a proper allocation of resources [1, 2]. Herewith, it is only in the pharmaceutical industry that a quality risk management, is a mandatory element of the pharma-

ceutical quality system at any enterprise, specified by good manufacturing practices (GMP), and included in licensing requirements². Requirements for the proper use of drug quality risk management, are specified by regulatory authorities in many countries, as well as international organizations [3–5]. The fundamental principles of a quality risk management at Russian pharmaceutical enterprises, are reported in the Rules of Good Manufacturing Practice, approved by Order of the Ministry of Industry and Trade of the Russian Federation dated June 14, 2013, No.916. A systematic approach to the quality risk management, aimed at improving the efficiency of the application of the Good Manufacturing Practice Rules, is reported in Order of the Ministry of Industry and Trade of the Russian Federation dated 12

December, 2013 No.1997 “On the approval of Recommendations for the organization of production and quality control of medicines”. GMP rules of the Eurasian Economic Union, approved by the Resolution of the Council of the Eurasian Economic Commission dated 3 November, 2016 No.77, in relation to the quality risk management, do not differ from the Russian ones: Part 3 (chapter “Quality risk management”) provides

¹ 1. GOST R 51705.1-2001. Quality systems. HACCP principles for food products quality management. General requirements. 2. GOST R 54617.1-2011. Risk management in nanoindustry. General principles. 3. GOST R 54617.2-2011. Risk management in nanoindustry. Identification of hazards. 4. GOST R 54762-2011. Prerequisite programmes on food safety. Part 1. Food manufacturing. 5. GOST R 58045-2017. Aircraft equipment. Risk management for quality assurance through life cycle stages. Risk assessment methods and acceptability criteria. 6. GOST R 58050-2017. Aircraft equipment. Risk management for quality assurance through life cycle stages. Areas of uncertainty classification. 7. GOST R 58139-2018. Quality management systems. Requirements for automotive organizations. 8. GOST R ISO 17666-2006. Risk management. Space systems. 9. GOST R ISO 17776-2012. Petroleum and natural gas industries. Offshore production installations. Techniques and methods for hazard identification and risk assessment. Basic principles.

² clause 5 of the Rules of Good Manufacturing Practice (approved by Order of the Ministry of Industry and Trade No. 916 of June 14, 2013).

similar recommendations on the organization of risk management activities; part 3 is non-regulatory³. Most countries, including the EU, EAEU countries and the Russian Federation, apply the risk management procedure given in the ICH Q9 guideline and presented in the international standard ISO 31000 (GOST R ISO 31000).

However, the application of the risk management system causes difficulties for manufacturers [6-10]. For example, in the FDA (Food and Drug Administration) warning letters database, the issues regarding the risk management system, are posted quite often⁴ [11]. In the official statistics of Good Manufacturing Practice (GMP) inspection deficiencies published by United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA UK), in 2018 solely⁵, there are 74 non-conformities in the quality risk management, 54 (almost 73%) of which were assessed as critical or significant. The similar data on the results of GMP inspections in the Russian Federation are not publicly available. Implementing a quality risk management system into an enterprise's quality management system can be challenging. Enterprises have a wide range of products, different medicines are produced in different conditions: from non-sterile to aseptic, production processes have different stages and methods of control. Each enterprise needs to make its own individual choice of risk assessment methods, methods of risk communication, working out its documentation, etc., taking into account the peculiarities of its production and quality system [12–16]. The carried out search and analysis of the literature showed that the national and international regulatory documents contain only guidelines to quality risk management, while there are no explanatory methodological materials containing specific examples of possible approaches to the quality risk management, including specific industries.

The importance of applying the quality risk management in pharmaceutical production, is due to several reasons: first, the risk management makes it possible to ensure the acceptable product quality, and therefore, to reduce risks to patients' healths. Second, it allows the company's management to focus on the issues associated with the highest risks for patients, therefore, it affords a more efficient allocation of resources. Third, it helps with making the most well-argued decisions regarding the development, quality control, production of medicines, etc. Fourth, the application of the risk management is the fulfillment of the requirements of regulatory authorities [1, 8, 9, 17, 18].

³ Rules of Good Manufacturing Practice of the Eurasian Economic Union approved by the Resolution of the Council of the Eurasian Economic Commission No. 77 dated 3 November 2016

⁴ <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters>

⁵ <https://www.gov.uk/government/statistics/good-manufacturing-practice-inspection-deficiencies>

There are no publications on the state of this issue at domestic pharmaceutical enterprises. All of the above indicates the relevance of studying the current industry practice of drug quality risk management at Russian pharmaceutical enterprises, including main problems during the implementation of a risk management system and compliance with currently accepted international approaches.

THE AIM of the research was to study the current industrial practice of drug quality risk management at Russian pharmaceutical enterprises, including the assessment of the main problems during the implementation of the risk management system and its compliance with the accepted international approaches.

MATERIALS AND METHODS

To obtain information about the existing approaches to drug quality risk management, a questionnaire method was chosen. The questionnaire was developed on the basis of the analysis of the requirements and recommendations for the quality risk management specified in national and international regulatory documents and guidelines⁶.

RESULTS AND DISCUSSION

The following essential requirements for the quality risk management system, accepted in the international pharmaceutical industry, have been selected by the authors and used in their questionnaire [10, 19–22].

⁶ 1. Good Manufacturing Practice Rules (approved by Order of the Ministry of Industry and Trade No. 916 of June 14, 2013). 2. Rules of Good Manufacturing Practice of the Eurasian Economic Union approved by the Resolution of the Council of the Eurasian Economic Commission No. 77 dated 3 November 2016. 3. Order of the Ministry of Industry and Trade of the Russian Federation of December 12, 2013 N 1997 On the approval of the Recommendations on the organization of production and quality control of medicines. Recommendations for the preparation of Site Master File, quality risk management, pharmaceutical quality system, batch certification (part III). 4. Decision of the Board of the Eurasian Economic Commission No.1 "On Approval of the Guidelines for establishing acceptable limits for health effects in order to identify risks in the production of medicines on common production (technological) lines" dated January 14, 2020. 5. Department of Health and Human Services, U.S. Food and Drug Administration, Guidance for Industry, Q9 Quality Risk Management, 2006. 6. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Q8 (R1), Pharmaceutical Development, 2008. 7. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Q9, Quality Risk Management, 2005. 8. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Q10, Pharmaceutical Quality System, 2008. 9. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Q11, Development and manufacture of drug substances (chemical entities and biotechnological/biological entities), 2012. 10. MHRA Good Manufacturing Practice (GMP) – Quality Risk Management: Frequently asked questions, Available at <http://www.mhra.gov.uk>. 11. World Health Organization WHO Guideline on Quality Risk Management, Working document QAS/10.376/Rev.1 Draft for discussion, August 2011, pp. 9–10, Available at <http://www.who.int>.

Essential requirements for the quality risk management system accepted in the international pharmaceutical industry

1. An enterprise should have a high-level document (SOP, an enterprise standard, policy) that regulates its quality risk management system and approaches used to manage risks.

2. The areas of application of the risk management system within the pharmaceutical quality system, should be determined.

3. The following papers should be documented:

- commitment of the management to the principles of the system;
- responsibilities and functions of the key personnel in this system;
- scope of application, planning and scheduling;
- monitoring of work and evaluation of its efficiency and progress;
- the approval procedure of work/jobs and the information distribution;
- personnel training programs that include information about a risk management system;
- training requirements for teaching the personnel actually performing the work related to the quality risk management;
- the risk assessment tools and methods used at the enterprise;
- the inclusion of the risk management in the pharmaceutical quality system;
- application of the change management procedure during risk management activities;
- cross-references to the risk management system in the main control procedures of the enterprise.

4. Risk analysis and assessment:

- should be carried out by experienced specialists, including the involvement of third-party consultants, with due regard to modern scientific knowledge;
- should be documented;
- should be subjected to the agreement/approval;
- should be based on the systematic risk identification;
- should be carried out using both qualitative and quantitative methods and tools,
- the results of the assessment should be regularly revised;
- the decisions based on the results of the risk assessment should not contradict GMP rules and regulatory requirements;
- the level of formality and documentation should be appropriate to the degree of the risk to the patient.

5. There should be a risk register containing a refreshable list of the main identified risks, a list of risk assessments carried out or a link to this list, a brief description of the measures to mitigate the main identified risks, and a justification for reassessing risks.

6. The effectiveness of the risk management system should be regularly evaluated. The procedure for assessing

the effectiveness of the risk management system and the effectiveness of the risk management plans, should include:

- frequency of assessment;
- responsibility of performers;
- a formal list of the documentation to be inspected during the assessment;
- the ways of information distribution on the results of the assessment;
- the procedure for developing recommendations for improvement;
- the procedure for implementing the subsequent actions and their verification.

The questionnaire contains 25 questions, some of which correlate to each other. The clarity of the questions was tested by 42 people from the pharmaceutical industry.

The survey was conducted online by Sechenov University in cooperation with the National Chamber of Pharmacy from 6 April to 10 May, 2020. The letter with a link to the electronic questionnaire, was sent to e-mails of the qualified persons who had been trained and certified at Sechenov University (981 people, 48 constituent entities of the Russian Federation, more than 300 enterprises).

111 specialists of the pharmaceutical industry took part in the survey, the return of the questionnaires was 11.3%. About a third of the respondents (35%) were under 40 years old, 15 percent were over 55. More than half of the respondents work at medium and large pharmaceutical enterprises (45% and 13%, respectively), the rest – at small enterprises and in micro organizations. This distribution generally reflects the structure of the Russian pharmaceutical industry (Fig. 1).

Most of the respondents (63%) work at the enterprises producing drugs of the chemical origin and have more than 10 years of professional experience at a pharmaceutical enterprise (67%) (Fig. 2).

The majority of respondents (87.4%) work at the enterprises with a cyclical turnaround; the collected information also includes the respondents from market authorization holders that use contract manufacturing sites (4.5%).

As Fig. 3 shows, all major dosage forms produced in Russia, were covered with this questionnaire, including those requiring and not requiring isolation. Based on the above data, the authors arrived at the conclusion that the sample obtained was sufficiently representative.

In the first part of the survey, general approaches and problems of domestic pharmaceutical enterprises in implementing the systems of drug quality risk management were studied.

In the Russian pharmaceutical industry, the quality risk management is applied at various stages of the product life cycle: most of the enterprises apply risk management at the stage of the industrial production (95%), and only 28% of enterprises apply a risk-based approach when scaling the process (Fig. 4).

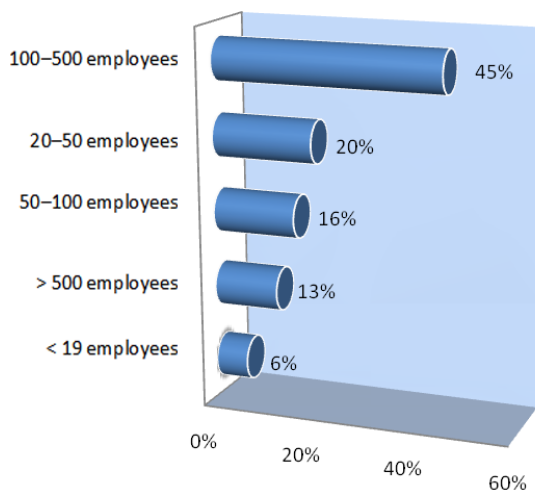


Figure 1 – Distribution of respondents by the size of their enterprise

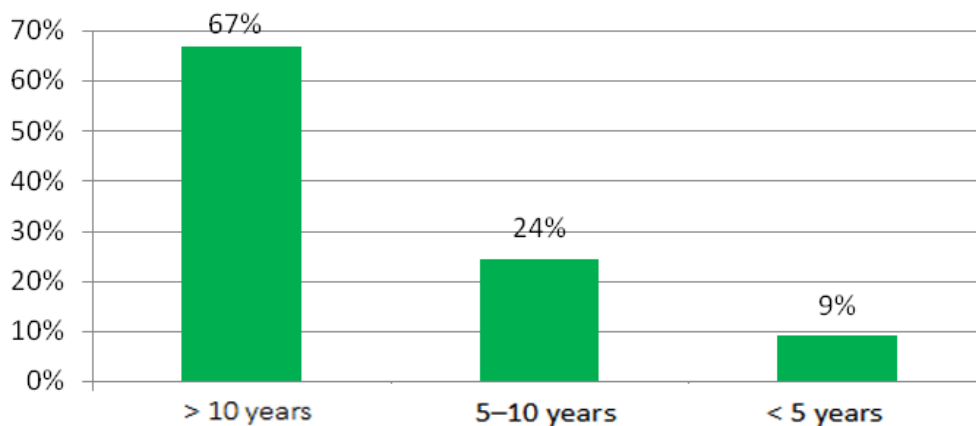


Figure 2 – Distribution of respondents by work experience in the pharmaceutical industry

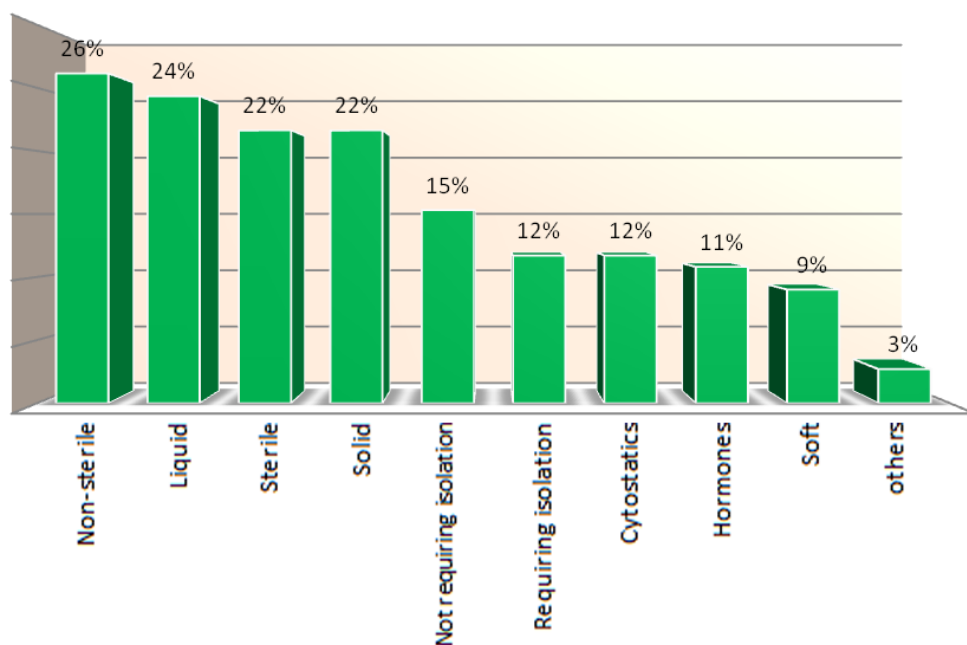


Figure 3 – Manufactured dosage forms

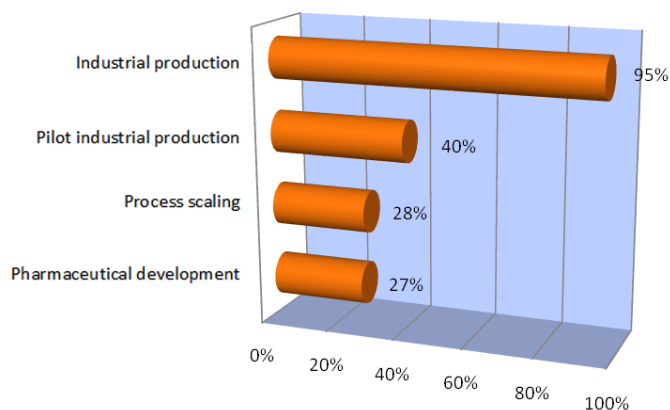


Figure 4 – Stages of product life cycle at which quality risk management is applied, in Russian pharmaceutical industry

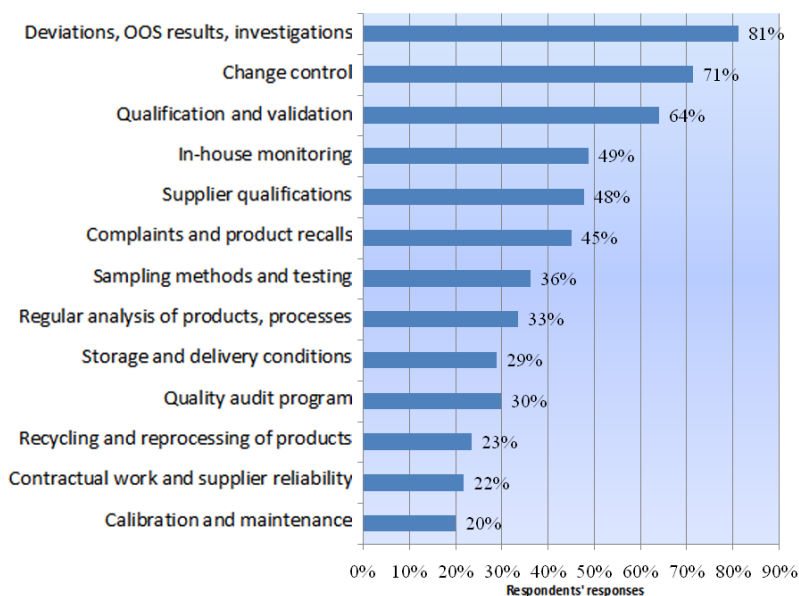


Figure 5 – Areas where quality risk management is most commonly used

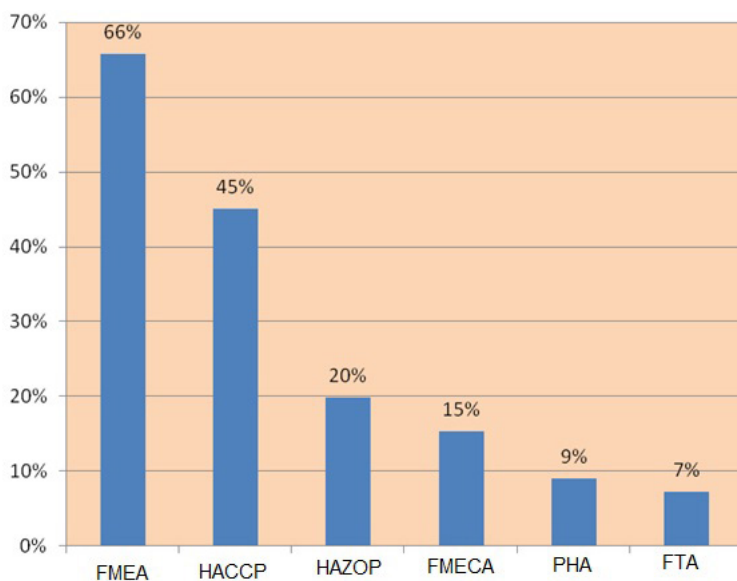


Figure 6 – The most commonly used risk assessment tools and methods

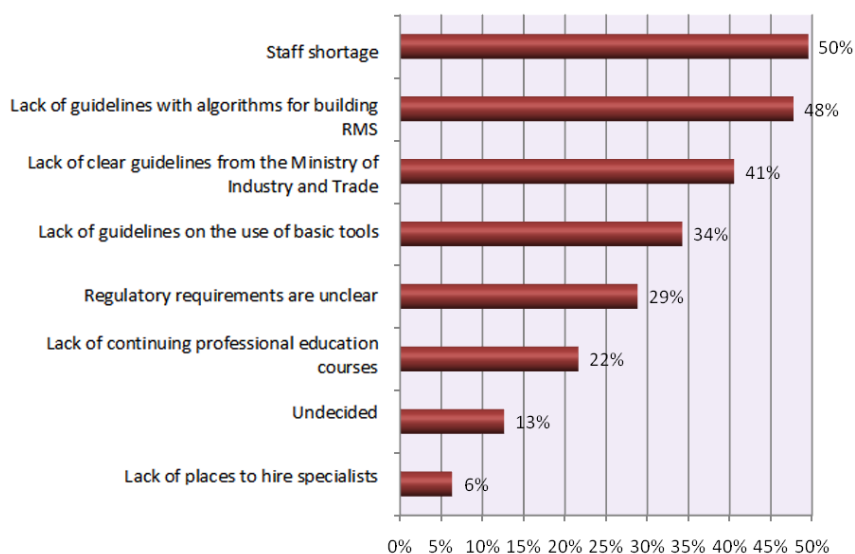


Figure 7 – The main difficulties faced by enterprises during the implementation of a quality risk management system

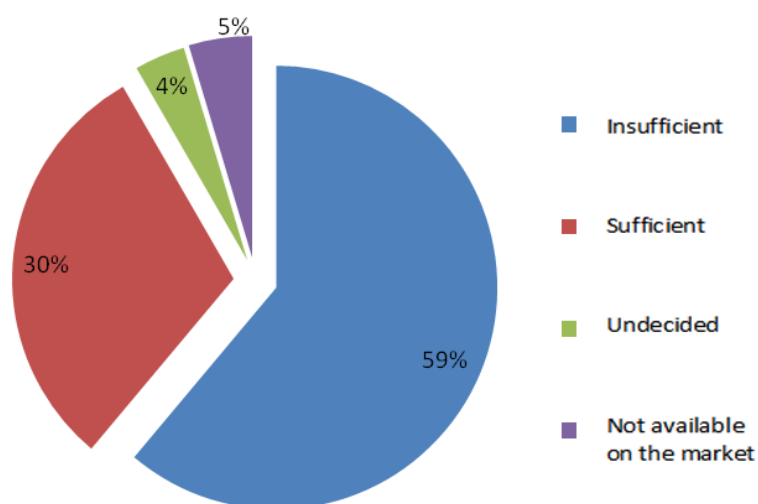


Figure 8 – Sufficiency of the number of employees with the necessary knowledge and experience in risk assessments

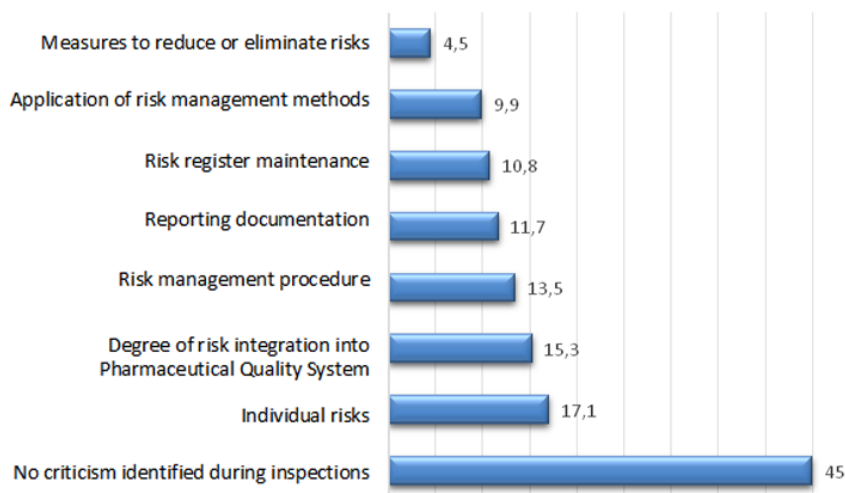


Figure 9 – Criticism of quality risk management system identified during external inspections

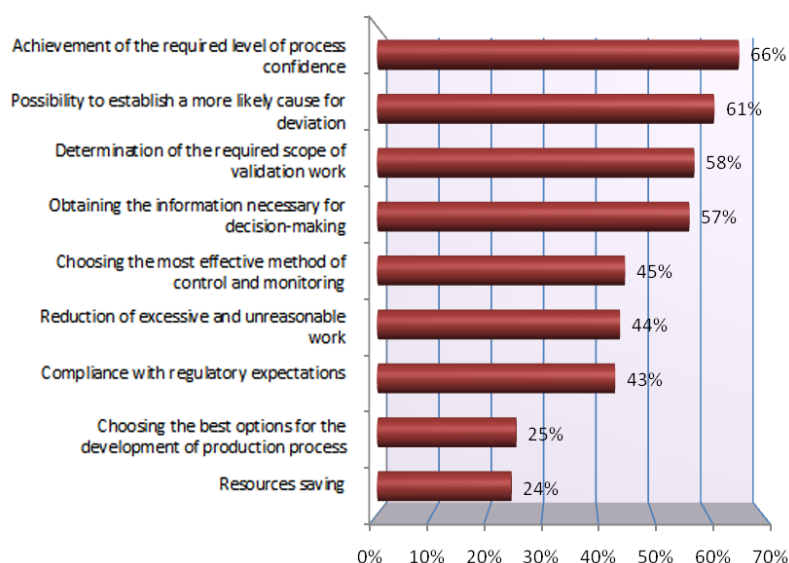


Figure 10 – Positive effects of the quality risk management implementation at the enterprise

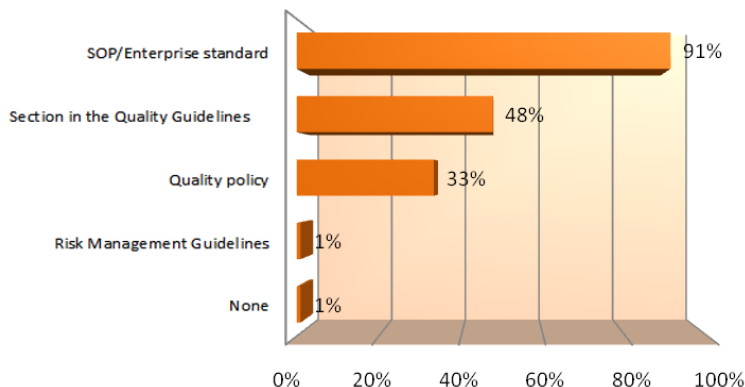


Figure 11 – Available high-level documents regulating the quality risk management system



Figure 12 – Approaches to formalization of the quality risk management system

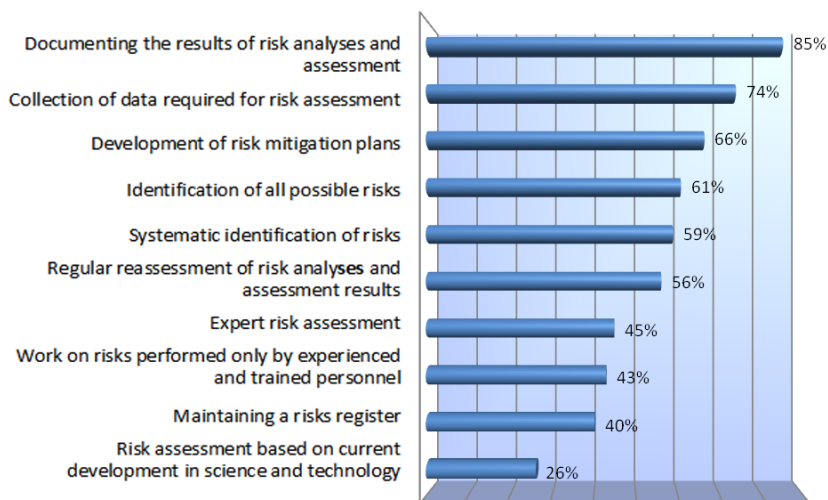


Figure 13 – Actions in relation to the quality risks

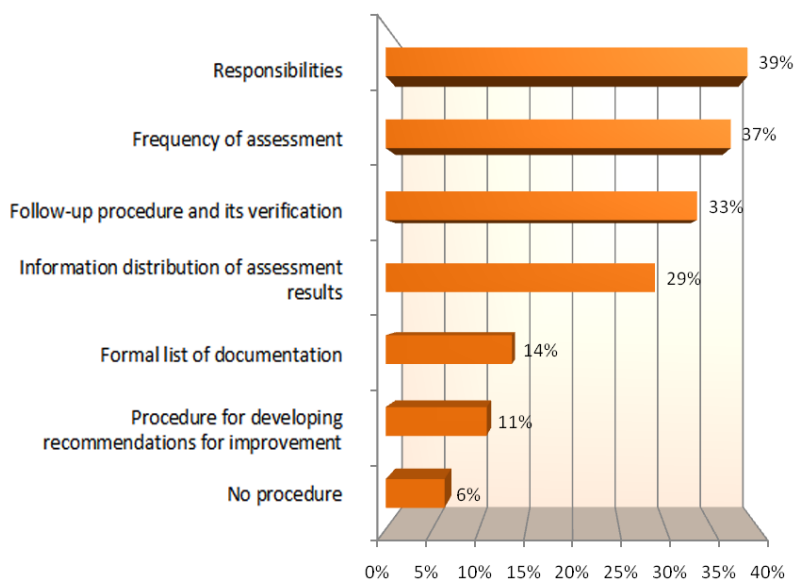


Figure 14 – Contents of the quality risk register

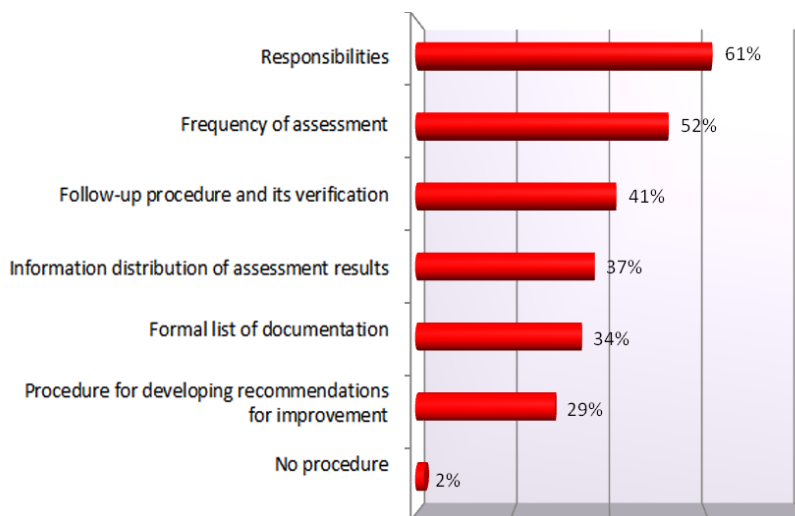


Figure 15 -Information in the Procedure for assessing effectiveness of risk management system and risk management plans

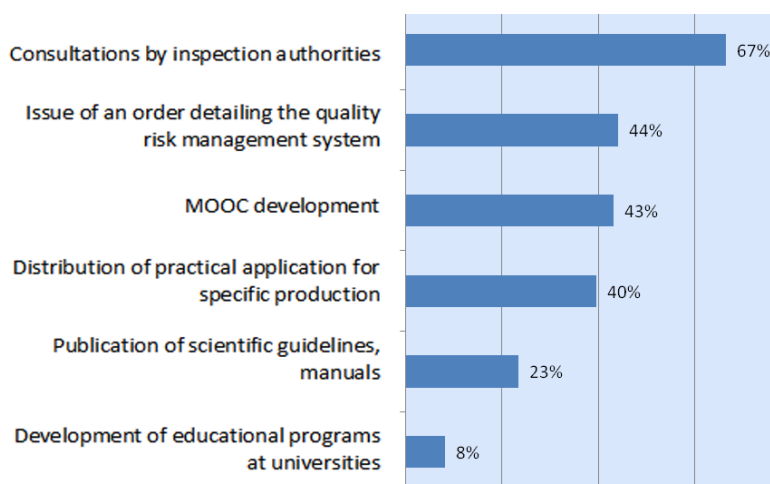


Figure 16 – Measures that can help improve the effectiveness of quality risk management in Russian pharmaceutical industry

Fig. 5 shows the areas where the quality risk management is most commonly used. In general, the figure shows that they coincide with the pharmaceutical enterprises' areas of activities, proposed in Order of the Ministry of Industry and Trade of the Russian Federation No.1997 "On approval of recommendations for the organization of production and quality control of drugs", where the quality risk management is applicable. Noteworthy is the small percentage of the enterprises using this methodology for organizing calibration and maintenance work (20%), during product processing and reprocessing (23%), and during storage and delivery (29%).

In most of the cases, domestic enterprises use quantitative methods to assess and analyze risks (FMEA, HACCP, FMECA, PHA, FTA, etc.). The most frequently used methods of the 7 ones, specified in the ICH Q9 guideline and in Order of the Ministry of Industry and Trade of the Russian Federation No.1997 "On approval of recommendations for the organization of production and quality control of drugs", are the following: FMEA (66%), HACCP (45%), HAZOP (20%), FMECA (15%) (Fig. 6).

The implementation of the quality risk management methodology is difficult in practice for various reasons (Fig. 7).

According to the respondents, the main difficulties are: staff shortage (50%), lack of guidelines and manuals with algorithms for decision-making and building a risk management system (48%), lack of clear guidelines from the Ministry of Industry and Trade (41%), lack of guidelines on the use of the basic risk analysis tools (34%). When summed up, the lack of additional guidelines from the Ministry of Industry and Trade of Russia, is the prevailing reason for the complexity of the implementation of the quality risk management system. An extended analysis of the responses regarding staff shortages, revealed approximately the equal percentage of responses

among the employees of small and micro enterprises: the problem of staff shortages was notified by 59% of respondents working at the enterprises with 20 to 50 employees, 53% – from 50 to 100 employees, 50% – from 100 to 500 employees, 43% – above 500 employees.

The problem of a shortage of personnel with the necessary knowledge and skills in the field of quality risk management, was also revealed when analyzing the answers about the sufficiency of such employees at the enterprise: 59% of the respondents indicated this shortage (Fig. 8).

Herewith, 88% of respondents stated that external consultants are not involved in dealing with risks at their enterprise.

Some interesting data were obtained when analyzing the issues of the drug quality risk management system discovered by external auditors (Fig. 9). Just over half of the enterprises received comments on their risk management systems. At the same time, auditors' reports on various aspects of the risk management contained approximately the same number of issues, except risk mitigation and preventive measures of identified quality risks.

In general, the respondents positively assessed the impact of the risk management system on the company's activities (Fig.10). More than half of the respondents notified that the risk management provides the necessary level of confidence in the processes (66%), the ability to determine the most likely cause of deviations (61%), determining the required amount of validation work (58%), obtaining the information necessary for decision-making (57%). Attention should be paid to a rather low percentage of the enterprises, which conducted an economic assessment of the application of the risk management system – 24%, and used a risk methodology for a pharmaceutical development – 25%

(see also Fig. 4, where 27% of respondents apply this methodology in pharmaceutical development). A fairly large number of respondents (57%) who do not consider these works mandatory for compliance with the established regulatory requirements is noteworthy, although this requirement came into force almost 7 years ago. In the authors' opinions, the number of enterprises (57%) which use a risk-based approach for decision making, is also too few.

A coincidence of the data obtained from different questions, indicates the validity of the data.

The results obtained, made it possible for the authors to conclude that a superficial approach to the quality risk management prevails in the Russian pharmaceutical industry, and this is due to a number of objective and subjective reasons. Among the most significant ones are the lack of recommendations from the Ministry of Industry and Trade of the Russian Federation on creating an effective quality risk management system and the shortage of specialists who are ready to work in this area.

In the second part of the survey, the authors examined the way the Russian enterprises implement various elements of the risk management system and their compliance with essential requirements for the quality risk management system in the international pharmaceutical industry (see above).

91% of the respondents confirmed the existence of the document regulating the quality risk management system at the enterprise, and 33% notified the existence of a policy in the field of the risk management system (Fig. 11). Almost half of the respondents (48%) reported that the risk management system is included in the quality guidelines.

The approaches used in the Russian pharmaceutical industry to formalize the risk management system, are shown in Fig. 12. As can be seen from the above data, all international criteria are met with, but the degree of their implementation varies from 78% to 34% of cases. It should be notified that external auditors do not attract manufacturers' attention to the absence of such important aspects as the adherence of the management to the principles of the system, the responsibility and functions of the key personnel in this system, the procedure for coordinating work and distribution of information about them, applying the change management procedure to the risks management, cross-linking to the risks system in the main control procedures of the enterprise (see Fig. 9). A significant number of enterprises do not pay due attention to personnel training in the field of the risk management system (54%), to the establishment of requirements for personnel training (61%), and to the importance of ensuring information flows in the risk man-

agement system (55%). With close reference to the data shown in Fig. 10, the lack of formalized confirmation, in other words, commitment, adherence to the principles of the risk management system, indicates a low awareness and interest of the top management in more than half of pharmaceutical enterprises in Russia in the risk management system and its business opportunities.

Approximately the same data were obtained for the work/jobs that constitute the quality risk management (Fig. 13): compliance with international criteria ranges from 85% to 26%. 15% of the respondents notified that they do not document the results of the risk analysis and assessment. The further research showed that such an informal approach is more often observed at small enterprises (with 20 to 50 employees). The data obtained, also indicate a lack of the systematic quality risks management in more than half of the surveyed pharmaceutical companies. A low percentage of the enterprises that use a scientific approach to work with risks (only 26%), should be also notified.

A very big gap was identified in the maintenance of the quality risk register (Fig.14). First, only about 40% of the respondents answered that their company has a quality risk register (Fig. 13 and Fig. 14). Second, the content of the risk register of a Russian manufacturer also differs from the international practice. Thus, only 39% of the enterprises include a list of the conducted risk assessments or links to this list in the register; only 33% of the enterprises have a refreshable list of the identified key risks. It should be notified that there is a very low percentage of the enterprises that include justifications in the register for risks reassessment and for establishing the frequency of reassessment (14% and 6%, respectively), as well as the data on the residual risks (11%).

The procedure for assessing the effectiveness of the risk management system and the effectiveness of the risk management plans in the Russian pharmaceutical industry, also differs from the international approaches (Fig. 15). Despite the fact that the absence of this procedure was confirmed by only 2% of respondents, 61% of the respondents confirmed that it contains a description of responsibilities, 52% confirmed the established frequency of the assessments, 41% – the procedure for implementing subsequent actions and their verification, 37% – the ways of sharing information about the results of the evaluation, 34% – a formal list of documentation, 29% – the procedure for developing recommendations for its improvement.

The size of the enterprise (by the number of employees) or its products did not influence the distribution of the respondents' answers.

It should be notified that many disadvantages of the implementation of the quality risk management system

at Russian enterprises are typical and are also encountered by foreign manufacturers, including ineffective application of the risk management methods, the absence of periodic reassessment of identified risks, and the lack of credibility of the decisions taken [1, 9, 10, 17, 18, 23]. Therefore, foreign experience could be useful for developing measures to improve the current situation.

The opinions of the surveyed pharmaceutical industry employees on the measures that can help their companies implement the effective quality risk management, are shown in Fig. 16. The most popular response was to consult with the inspection authorities (67%), but this type of measure is not used in any country with a developed pharmaceutical industry. In terms of the number of pharmaceutical companies in the country, Russia is comparable to the United Kingdom, France and Germany [24, 25].

Based on the authors' experience and observations, foreign inspection bodies (as well as Russian ones) do not give direct individual consultations. It is a common practice to organize seminars: independent seminars on behalf of the regulatory body, and as parts of congresses and conferences [8, 18, 26]. Such events also take place in our country. The practice of creating massive open online courses (MOOC) by regulators or with their participation, is not yet:

No regulatory legal acts by foreign regulators with a detailed description of the quality risk management system, have been found by the authors. The quality risk management guidelines have only been issued by the MHRA (UK) and are not legally binding. There are recommendations from professional communities: PDA (Parenteral Drug Association) and ISPE (International Society of Pharmaceutical Engineering). A risk-based approach to an equipment validation is described in ASTM (American Society for Testing and Methodology) standard manual E2500-13⁷.

A possible contribution to improving the situation by universities and research institutes, was rated by the respondents as extremely low. Abroad, on the contrary, universities, often with the assistance of regulators and with grants from regulators, summarize various data, develop and distribute various scientifically based recommendations for the pharmaceutical industry.

CONCLUSION

In the course of the study, the authors analyzed the requirements for the risk management in the pharmaceutical industry, and identified the essential elements of an effective drug quality risk management system.

⁷ ASTM E2500-13. Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment.

The survey provided valid information about the industry practice of implementing the risk management system at Russian enterprises, the difficulties faced by pharmaceutical companies during this process, and the opinions of specialists on the measures to support the application of risk system. The results of the analysis of the current industry practice of the quality risk management at Russian pharmaceutical enterprises, revealed the prevalence of a superficial approach to the quality risk management, the presence of objective and subjective reasons that hinder the effective implementation of the quality risk management systems, the fragmentation of the quality risk management systems used and, in most cases, their ineffective use. The main problems of implementing a quality risk management system are: an oversimplified description of the regulator's requirements for a quality risk management system and the lack of explanatory methodological materials containing specific examples of possible methodological approaches to the quality risk management, including the ones for specific productions. It should be emphasized that the situation is systemic in nature, and is the same in all the studied segments.

Considering the above, the development of recommendations for a quality risk management system is of a great current interest.

Based on the general requirements for the quality risk management system in the pharmaceutical industry, the authors formulated 17 steps to implement the quality risk management system in pharmaceutical companies. Their development takes into account the results of the industry practice analysis on drug quality risk management in the Russian Federation. Particular attention was paid to the description of the elements of the risk management system that are practically absent at many Russian enterprises. Closer attention was paid to the issues of the risk management system (the requirements for them had not been determined by the regulatory legal acts of the Russian Federation).

Recommendations for quality risk management at pharmaceutical enterprises

1. Develop a high-level document (a standard operating procedure, an enterprise standard, policy) that regulates the quality risk management system at the enterprise, and the approaches used to manage risks. In the document, specify the following:

- the areas of application of the risk management system;
- the persons responsible for decision-making;
- the responsibilities and functions of the key personnel in the risk management system;
- the responsibilities of both managers and employ-

ees involved in the risk analysis and assessment;

- the applied methods and tools for the risk analysis;
- recommendations on the risk classification and documentation of the processes;
- the information on the training of employees, participating in the risk analysis and assessment.

2. Include the risk management system in the the quality guidelines.

3. Create a risk register, including the following:

- a list of conducted risk assessments or a link to this list;
- a list of key identified risks;
- a brief description of the measures to mitigate the identified risks;
- justifications for reassessment of risks and for a specified frequency of reassessment;
- the data on residual risks.

4. Regularly review the results of the quality risk management process, taking into account new knowledge and experience, since earlier decisions may have been based on unreliable data; an earlier identified risk may have been underestimated or exaggerated, and earlier developed mitigation measures may have been underresourced. The frequency of revision should be determined taking into account the priority of risk.

5. Update the risk register in a timely manner, considering the results of risk assessments and revision of the results of the quality risk management process.

6. Include references to the risk system in the main control procedures of the enterprise.

7. Develop risk communication mechanisms. Establish a documented procedure for the information distribution on the works performed for the quality risk management.

8. Consider the possibility of applying the quality risk management system in the areas of work where such methods and tools are not currently used, for example, in the change control, supplier qualifications, qualification and validation, processing and reprocessing of products, in-house monitoring, calibration and maintenance, developing a quality audit program, evaluating storage and shipping conditions.

For a self-assessment on the coverage of the areas of work, use Order of the Ministry of Industry and Trade of the Russian Federation dated 12 December, 2013 No. 1997 "On the approval of the Recommendations for the organization of production and quality control of medicines."

9. Consider the possibility of applying the risk management system at the stages of pharmaceutical development, pilot production and process scaling.

10. Create an enterprise working group to conduct a risk analysis and assessment. This group should be as multidisciplinary as possible and have narrowly focused specialists, so that the risk assessment could be carried out from different points of view, and a constructive exchange of information about the identified risks would be ensured. Assign the responsibility for the organization of risk analyses and the assessment to individual experts who are well versed in the risk assessment methodology, methods and tools for risk analyses.

11. Include information about the risk management system in the company's personnel training programs. Document training requirements for the personnel directly involved in the quality risk management. Develop procedures for training personnel in methods and tools for the risk analysis and assessment.

12. Document the possibility of attracting external consultants for analysis and risk assessment when there is an insufficient number of employees with the necessary knowledge and experience to carry out these works.

13. Develop standard operating procedures containing a description of procedures for control, agreement and approval of the results of the risk assessment and reassessment, as well as the forms of protocols for the risk analyses and assessment.

14. Document all the analyses and risk assessments performed.

15. Based on the results of the conducted risk assessments, develop work plans to reduce significant risks.

16. Develop a procedure for evaluating the effectiveness of the risk management system and the risk management plans, specifying the following:

- frequency of evaluation;
- responsibility of performers;
- a formal list of documentation to be verified during assessment;
- the ways of information distribution of the assessment results;
- procedure for developing recommendations for the improvement;
- procedure for subsequent actions and their verification.

17. Document the application of the change management procedure to the risk management.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTION

- A.B. Kashirina – literature analysis, article writing, research planning; conducting all stages of the research, formalization of the list of references;
- Zh.I. Aladysheva – idea, research design development, consultations on all stages of the research, article writing;
- N.V. Pyatigorskaya – research planning; consultation on all stages of the research, article writing;
- V.V. Belyaev – literature analysis, article writing, consultations on research planning and data processing, data processing, formalization of the list of references;
- V.V. Beregovykh – consultations on the individual stages of the study.

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