https://doi.org/10.33380/2305-2066-2021-10-3-148-165
UDC 615.1(075)

Review article / Обзорная статья

The Integrated Model of Quality Management System of Laboratory Studies of Medicines (Review)

Arina I. Selezneva[1]*, Vladimir A. Smirnov[1], Vyacheslav V. Goryachkin[1], Nataliya N. Chadova[1], Sergey V. Polyakov[1], Vladislav N. Shestakov[1], Rimma A. Abramovich[2]

[1] State Institute of Drugs and Good Practices, 6, Lavrov lane, Moscow, 109044, Russia
[2] Peoples Friendship University of Russia (RUDN University), 6, Mikluho-Maklaya str., Moscow, 117198, Russia

***Corresponding author:** Arina. I. Selezneva. **E-mail:** selezneva@gilsinp.ru

ORCID: Arina. I. Selezneva – https://orcid.org/0000-0002-5281-1169; Vladimir. A. Smirnov – https://orcid.org/0000-0002-7206-3313; Vyacheslav. V. Goryachkin – https://orcid.org/0000-0002-1069-8647; Nataliya. N. Chadova – https://orcid.org/0000-0002-9132-1015; Sergey. V. Polyakov – https://orcid.org/0000-0003-4234-1156; Vladislav. N. Shestakov – https://orcid.org/0000-0002-7929-4982; Rimma A. Abramovich – https://orcid.org/0000-0003-1784-881X.

Received: 18.05.2021 **Revised:** 18.08.2021 **Published:** 25.08.2021

Abstract

Introduction. The publication is devoted to the role of laboratory research in ensuring the quality of domestic medicines and is a review and analysis of regulatory documents and current publications on this topic.

Text. A number of different types of laboratories are involved in Drug life cycle and ensuring their effectiveness and safety. Today there are a large number of regulations governing laboratory research. Common to all types of laboratories and regulatory documents is the need to organize an effective quality management system (QMS) for the drug life cycle laboratories. The aim of this review is to analyze approaches to regulating the quality of laboratory research of domestic drugs and to consider the most effective QMS model, which is fundamental for all types of laboratories in the life cycle of drugs.

Conclusion. The laboratory research quality system serves as a basic tool for achieving the ultimate goal - the clinical value of drugs and is designed to ensure that risks for patients are minimized. At the same time, each stage of the drug life cycle provides a solution to a specific problem on the way to this goal, which must be taken into account when building a QMS in each type of laboratory. The range of regulatory documents and external assessment systems (accreditation, certification, inspection control, etc.) in the field of domestic laboratory research is quite diverse. In this regard, it is advisable for the laboratory to build a harmonious QMS based on priorities in accordance with the goals and objectives. The most effective method for building such a system is an integrated management system model.

Keywords: laboratory research, quality system, good pharmaceutical practices, drug quality

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interest related to the publication of this article.

Contribution of the authors. Arina I. Selezneva, Vladimir A. Smirnov, Vyacheslav V. Goryachkin conducted a comprehensive analysis of regulatory documents and scientific literature of foreign and domestic authors. Vladislav N. Shestakov, Sergey V. Polyakov, Nataliya N. Chadova, Rimma A. Abramovich the approaches to organizing the QMS of the drug life cycle laboratories have been studied and systematized, and an optimal fundamental model of the QMS has been proposed.

Acknowledgment. This work was carried out with the support of FSI «State Institute of Drugs and Good Practices».

For citation: Selezneva A. I., Smirnov V. A., Goryachkin V. V., Chadova N. N., Polyakov S. V., Shestakov V. N., Abramovich R. A. The integrated model of quality management system of laboratory studies of medicines. *Razrabotka i registratsiya lekarstvennykh sredstv = Drug development & registration*. 2021;10(3):148–165. (In Russ.) https://doi.org/10.33380/2305-2066-2021-10-3-148-165

Интегрированная модель системы менеджмента качества лабораторных исследований лекарственных средств (обзор)

А. И. Селезнева[1]*, В. А. Смирнов[1], В. В. Горячкин[1], Н. Н. Чадова[1], С. В. Поляков[1], В. Н. Шестаков[1], Р. А. Абрамович[2]

[1] ФБУ «Государственный институт лекарственных средств и надлежащих практик» (ФБУ «ГИЛС и НП») Минпромторга России, 109044, Россия, г. Москва, Лавров пер., д. 6
[2] ФГАОУ ВО «Российский университет дружбы народов» (РУДН), 117198, Россия, г. Москва, ул. Миклухо-Маклая, д. 6

***Контактное лицо:** Селезнева Арина Игоревна. **E-mail:** selezneva@gilsinp.ru

ORCID: А. И. Селезнева – https://orcid.org/0000-0002-5281-1169; В. А. Смирнов – https://orcid.org/0000-0002-7206-3313; В. В. Горячкин – https://orcid.org/0000-0002-1069-8647; Н. Н. Чадова – https://orcid.org/0000-0002-9132-1015; С. В. Поляков – https://orcid.org/0000-0003-4234-1156; В. Н. Шестаков – https://orcid.org/0000-0002-7929-4982; Р. А. Абрамович – https://orcid.org/0000-0003-1784-881X.

Статья поступила: 18.05.2021 **Статья принята в печать:** 18.08.2021 **Статья опубликована:** 25.08.2021

Резюме

Введение. Публикация посвящена роли лабораторных исследований в обеспечении качества отечественных лекарственных средств (ЛС) и представляет собой обзор и анализ нормативной документации и актуальных публикаций на данную тему.

Текст. В создании ЛС и обеспечении их эффективности и безопасности участвует целый ряд видов лабораторий. На сегодняшний день существует большое количество нормативных документов, регламентирующих лабораторные исследования. Общим для всех видов лабораторий и нормативных документов является необходимость организации эффективной системы менеджмента качества (СМК) лабораторий жизненного цикла ЛС. Целью данного обзора является анализ подходов к регулированию качества лабораторных исследований отечественных ЛС и рассмотрение наиболее эффективной модели СМК, фундаментальной для всех видов лабораторий жизненного цикла ЛС.

Заключение. Система качества лабораторных исследований служит базовым инструментом для достижения конечной цели – клинической ценности ЛС – и призвана гарантировать минимизацию рисков для пациентов. При этом каждый этап жизненного цикла ЛС обеспечивает решение конкретной задачи на пути к этой цели, что необходимо учитывать при построении СМК в каждом из видов лабораторий. Спектр нормативных документов и систем внешней оценки (аккредитация, сертификация, инспекционный контроль и др.) в сфере отечественных лабораторных исследований достаточно многообразен. В связи с этим лаборатории целесообразно выстроить гармоничную СМК, основанную на приоритетах в соответствии с целями и задачами. Наиболее эффективным методом для построения такой системы является модель интегральной (интегрированной) системы менеджмента.

Ключевые слова: лабораторные исследования, система качества, надлежащие фармацевтические практики, качество лекарственных средств

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. А. И. Селезнева, В. А. Смирнов, В. В. Горячкин провели комплексный анализ нормативно-правовой документации и научной литературы зарубежных и отечественных авторов. В. Н. Шестаковым, С. В. Поляковым, Н. Н. Чадова и Р. А. Абрамович были изучены и систематизированы подходы к организации СМК лабораторий жизненного цикла ЛС и предложена оптимальная фундаментальная модель СМК.

Благодарность. Работа выполнена при поддержке ФБУ «ГИЛС и НП».

Для цитирования: Селезнева А. И., Смирнов В. А., Горячкин В. В., Чадова Н. Н., Поляков С. В., Шестаков В. Н., Абрамович Р. А. Интегрированная модель системы менеджмента качества лабораторных исследований лекарственных средств. *Разработка и регистрация лекарственных средств*. 2021;10(3):148–165. https://doi.org/10.33380/2305-2066-2021-10-3-148-165

INTRODUCTION

Great attention is paid to organization of the pharmaceutical quality management system (PQS) at a drug enterprise, mainly due to a rigid external regulation and control. The arrangement of quality system of laboratories also takes a special position in the formation of drug quality basis. Throughout drug life cycle, a great number of laboratory studies are performed. Thus, the development of a new molecule and/or new dosage form is always accompanied with laboratory studies of its action, efficacy and safety, analytical tests, development of a new technology. On the stage of clinical trials, patients' health depends on reliability and quality of laboratory tests. During production and after its release to civil circulation, drug quality is continuously controlled with laboratory test methods. Therefore laboratory tests are essential during an entire drug cycle and provide its efficacy, safety and quality. The approach to the organization of laboratory quality management system (QMS) plays a key role in achievement of the goal. External control and regulation of quality of laboratory tests represents a rather more complex system that drug manufacture. The aim of the review is to analyze approaches to regulation of quality of laboratory tests of national drugs and review of the most effective QMS model which is fundamental for all types of laboratories in a drug life cycle.

Types of laboratories in drug life cycle

A drug life cycle is a way of any drug from an idea to the drug withdrawal from the circulation. On this way, several key stages and corresponding types of laboratories may be conditionally specified (figure 1, table 1).

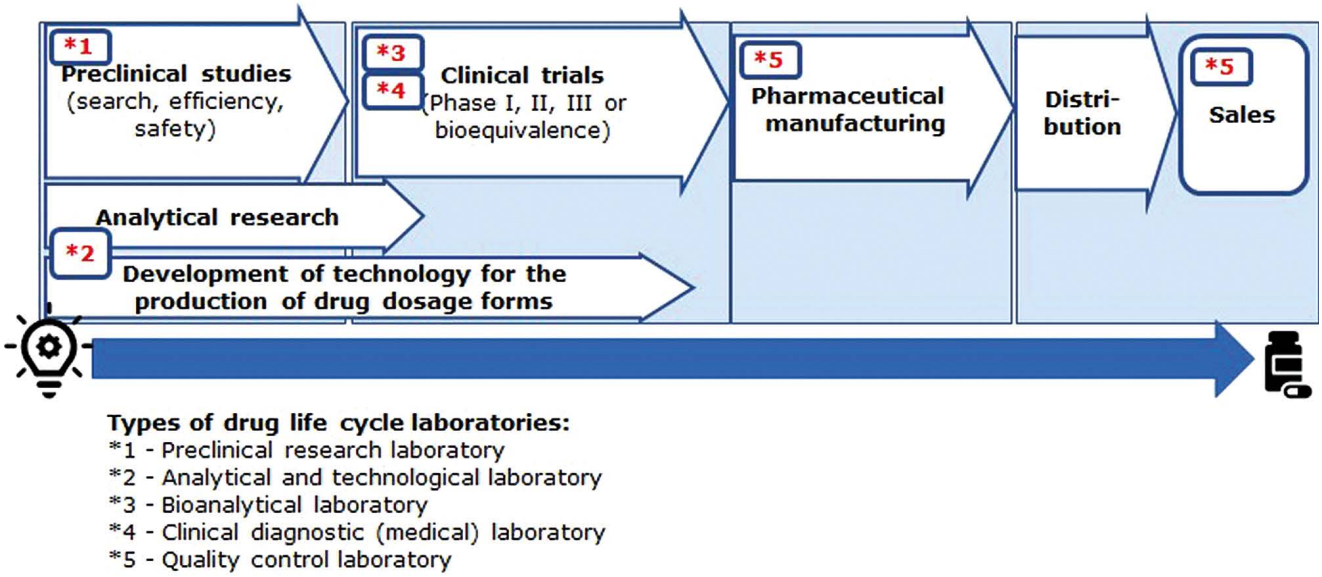

Figure 1. **Types of laboratories at the stages of the drug life cycle**

Table 1. **Types and tasks of laboratories at the stages of the drug life cycle**

№	Type of laboratory*	Stage of drug life cycle	Tasks to be performed
1	2	3	4
1	Preclinical Research Laboratory	• Basic research (search for a molecule); • Safety research in animals to initiate clinical trials	• Selection of promising candidates for drugs, prediction of effective and safe doses in a search experiment. • Characteristics of the toxicological profile of drugs (toxic and adverse effects with prolonged use, mutagenicity, genotoxicity, effects on the fetus and the reproductive system, etc.). • Determination of the range of safe and effective doses in experimental animals for the purpose of extrapolation to clinical trials
2	Analytical and technological laboratory	Drug development	• Development of the composition of drugs, design and justification of specifications. • Development and validation of analytical control methods . • Development of technology for obtaining drugs, NTD on drugs and transfer of technology to the production site. • Development of methods for quality control of substances and drugs: – study of the stability of pharmaceutical substances and medicinal products; – incoming quality control of raw materials, excipients and reagents; – quality control of intermediate products and intermediates formed during the production of medicines; – establishment of conditions and terms of storage of substances and medicinal products
3	Bioanalytical laboratory	Clinical trials	• Development and validation of bioanalytical methods for determining the pharmacokinetics of drugs. • Determination of the pharmacokinetic properties of drugs, incl. toxicokinetics, bioavailability/bioequivalence, etc.

Окончание таблицы 1

№	Type of laboratory*	Stage of drug life cycle	Tasks to be performed
1	2	3	4
4	Clinical diagnostic (medical) laboratory	Clinical trials	Assessment of the safety and tolerability, as well as the effectiveness of drugs based on dynamic clinical observation of objective data on the condition of volunteers (clinical analysis of blood, urine, biochemical studies, etc.)
5	Drug quality control laboratory	• Drug manufacturing. • Post-registration stage (selective quality control of medicines by authorized authorities)	• Sampling, assessment of compliance with regulatory documents (specifications), procedures for organizing, documenting and releasing, ensuring that the necessary tests are carried out, and also ensuring that starting and packaging materials are not authorized for use, and products are not for sale and delivery until then, until their quality is found to be in compliance with the established requirements. • Confirmation of drug compliance (through sampling) with the requirements of the Pharmacopoeia Monograph or, in its absence, regulatory documentation

Note. * The concept of "Testing laboratory" requires a separate discussion. In this article, we refused to use this term, since in most cases it is interpreted ambiguously in professional literature. However, for the sake of clarity, we provide a brief summary of the origin and meaning of this term.

On each of the stages of a life cycle, a separate type of laboratories performs tasks for the achievement of the common goal – provision of a clinical value, safety and quality of drugs (table 1).

Term **"Testing laboratory"** in national regulatory documents has originated from the field of technical regulation where it was first used in the series "SDA" documents [1–3]. The series of regulatory "SDA" documents describes terms and rules in the uniform system for conformity assessment in industrial, ecological safety, energy and construction safety.

SDA062009 presents a basic determination of term **"Testing laboratory (TL)** – conformity assessment body accredited for test performance".

The term as follows (more expanded) is mentioned in SDA152009 [3]:

"Testing laboratory (TL):

- conformity assessment body accredited for test performance;
- conformity assessment body performing one or several of the following types of activity:

  – tests;

  – calibration;

  – sampling related to further tests or calibration".

It should be noted that SDA152009, together with IL, also presents term **"Analytical laboratory (AL)** – conformity assessment body accredited for a qualitative and quantitative tests of various components in natural and industrial objects".

In All-Union State Standard GOST/IEC 170252019 "General requirements to competence of testing and calibration laboratories" [4], the determination of term **"Testing laboratory"** is absent, but it provides term "**Laboratory** – the body performing one or several types of activity:

- tests;
- calibration;
- sampling related to further tests or calibration".

As TL is determined in the fundamental documents as the conformity assessment body, the meaning of the term specified by GOST ISO/IEC 170002012 [5] (cl. 2.1) and mentioned in SDA documents as follows should be clarified:

Conformity assessment – evidence that specified requirements to a product, process, system or body are met. In accordance with cl. 0.5 GOST ISO/IEC 170002012, term "conformity assessment" is associated with phase "meeting specified requirements" rather than wider concept "conformity". "**Specified requirement** (cl. 3.1 GOST ISO/IEC 170002012) – the declared need or expectation. Specified requirements may be established by regulatory documents such as regulations, standards and specifications". In accordance with GOST ISO/IEC 17000-2012: "Conformity assessment is related to such areas as management systems, metrology, standardization and statistic".

In Federal law № 61FZ "On circulation of medicines" [6] term TL is used twice (articles 36 and 52). In both cases, the term is used in the context of assessment of drug conformity to the established requirements which is performed in laboratories for drug quality control.

In cl. 3 of article 11 of Federal Law 61, types of organizations which may carry out preclinical studies (PCS): "For organization and conduct of a preclinical study on a medicinal product, drug developers may engage research organizations, higher education institutions with the necessary material – technical base and qualified specialists in the corresponding field of research".

Due to that, laboratories performing research works and preclinical safety studies cannot be fully called testing laboratories as the studies do not represent conformity assessment activity. The type of laboratories carries out studies of substances which properties are often not definitely known. The purpose of PCS is to determine the properties. During preclinical studies, toxic effects and doses, effective therapeutic dose and other substance parameters are determined. Therefore a preclinical laboratory is a research one, unlike, for example, quality control laboratory which evaluates conformity to the already established requirements.

The fact is also confirmed by cl. 7 part II of Decision of the EEC № 81 (GLP rules), where instead of term "Testing laboratory", term "**Test facility is given in the glossary – a laboratory (organization)** with the necessary material-technical base and qualified personnel for conduct of preclinical (non-clinical) studies of drugs in the corresponding field" [7].

The applicability of term "Testing laboratory" to bioanalytical laboratory tests, as well as to analytical and technological laboratories on the stage of pharmaceutical development should be specified. In the event when properties of the substance and requirements hereto are certainly not known, a laboratory has research activity, unlike activity of testing laboratories which main purpose, according to the regulatory documents is to evaluate conformity to the specified requirements.

Therefore term "Testing laboratory" is the most applicable only to one type of laboratories for a drug life cycle. The use of this term in relation to other types of laboratories should be clarified, as well as degree of applicability to the requirements of corresponding regulatory documents hereto (in particular, GOST R ISO/MEK 17025).

Quality assurance on drug development stage

The development of a new drug begins from exploratory studies of drug "candidates" for which an optimal dosage form and composition of excipients should be yet developed. Therefore in parallel to exploratory preclinical studies, activities in analytical and technological laboratories also begin. The complex of activities is the drug development stage. In accordance with law № 61FZ, ch. 5, art. 10, cl. 1: "Drug development includes the search of new pharmacologically active substances, further investigation of their drug properties, preclinical studies, development of technologies for manufacture of pharmaceutical substances, development of compositions and technologies for drug manufacture" [6].

It should be noted that drug development stage is the most science-based among all further stage of a drug life cycle. Exactly on the stage, developers get the first basic knowledge on efficacy and safety, physical–chemical properties of a drug substance, technological aspects of a finished dosage form, analytical methods are developed. On this stage, quality basis of a future drug is formed.

Research investigations on drug development stage suggest a wide rage of expected results, and sometimes, the absence of such. It differs laboratory studies on drug development stage from laboratory studies for quality control, bioequivalence and clinical laboratory diagnostics where results are compared with definitely known values (pharmacopeial monograph, specification, standard values). It is apparently why the global pharmaceutical society has longstanding debate on regulation aspects of drug development stage. Some experts state that quality assurance regulation and requirements on drug development stage should be more flexible than on further stage to provide space for research discoveries. Many authors [8–10] pay attention on quality assurance of drug development process and consider the more systemic approach to the stage as necessary. Such approach may include the analysis of previous knowledge, study results with planning, quality risk management and knowledge management used throughout a product life cycle. The systemic approach was formulated as concept "Quality by Design" (QbD) [11, 12] and was presented in 2005 at the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) in Pharmaceutical development guideline ICH Q8(R2) [13]. ICH Q8 (R2) guideline was followed by ICH Q9 "Quality risk management" [14] and ICH Q10 "Pharmaceutical quality system" [15]. The three guidelines were positioned as the integral part of the whole – the approach to development of a new drug in quality context.

According to modern regulations adopted in the countries with the developed pharmaceutical industry, drug development stage is committed to implement planned **quality principles**. Quality by Design (QbD) concept fully reflects the principles. Planned quality provides "systemic approach to development based on reliable scientific data and risk management for product quality which begins from objective determination and pays special attention to understanding of a product and technological process, as well as control of the latter" [11, 12]. Only in the context of the planned quality, drug development is a peculiar guarantee of manufacture of good quality, effective and safe drug products [16].

Several approaches were offered for the implementation of QbD principles. In particular, in the beginning of drug development stage, in exploratory studies, for QbD implementation both in research and industrial conditions, the mathematic modeling methods were implemented. Among them, the method of Design of Experiments (DoE) is most widely used [17].

Despite the presence of international guidelines and standards, the drug development stage is less systematized among all stages of drug life cycle. In practice, the systematization of drug development stage is complicated as it begins from the search of a molecule, continues up to clinical trials and may last 6 to 12 years. Totally 3 types of laboratory participate in the drug development stage: preclinical, analytical and technological.

Preclinical studies (PCS) on the drug development stage are exploratory and do not fall directly under Good laboratory practice (GLP) requirements imposed to post-authorization studies. As a rule, PCS on the drug development stage are carried out within research and development (R&D) activities. R&D requirements and performance control are performed by the work contractor. External quality regulation of the exploratory stage is absent, except for the requirements imposed to execution of R&D results [18]. However, results of the exploratory stage form the basis for selection of the most effective and safest drug candidate. An error on the stage may cause at least financial and time losses, at

maximum – patients' health and safety on clinical trial stages. There are some recommendations and guidances on exploratory studies, most of them form the concept of "Good research practice" [19, 20]. However, the system is of advisory nature, regulation system is not formed therefore the quality of exploratory studies depends fully on the executor and contractor's responsibility and competence levels.

Analytical and technological laboratory develop production technologies for pharmaceutical substances, compositions and technologies for drug manufacture. The principles of analytical laboratory work are similar to such principles of quality control laboratory. Therefore, requirements identical to quality control laboratories may be imposed to the laboratories (see section "Organization of QMS of quality control laboratories"). However, the functionality of an analytical laboratory on the drug development stage is wider than such of a laboratory for quality control, the main goal of which is to assess compliance to a pharmacopieial monograph or specification. When a new drug is developed, analytical studies carry out studies allowing to prepare draft regulatory documents (specification, manufacturer's monograph, etc.), and to evaluate compliance of developed test samples of a new drug to the documents. External control and quality regulation of analytical and technological laboratory works on the drug development stage are absent in Russia.

Drug development is an interdisciplinary process in which the achievements of related fields of science are used: genomics, proteomics, biochemistry, molecular biology, medicine, pharmacology, computer modeling. Due to that, the necessity of clear regulation of professional competencies of specialists participating in all stages of drug life cycle becomes especially challenging [21].

Therefore, the presence of quality management system based on up-to-date international standards and a high level of the system implementation are parameters of work competence of preclinical, analytical and technological laboratories. The factors may be considered as the selection criteria for service providers for sponsors, as well as ranking markers for corresponding types of laboratories.

To develop the integral quality management system in preclinical, analytical and technological laboratories, it is appropriate to use the principles shown in ICH Q8 (QbD), ICH Q9, ICH Q10, Good research practice and GLP, as well as basic quality management principles ISO 9001 [22]. The efficiency of the practical use of the integral quality management system developed on the base of standards provides the highest quality level of drug laboratory studies in general.

Quality assurance on the stage of preclinical studies

Preclinical studies (PCS) are carried out for selection of optimal drug candidates, search of effective and safe doses to be administered in humans. As it has been already described in the previous section, PCS are also carried out on the drug development stage (exploratory studies), however, the main part of PSC is on the stage of safety evaluation in humans for initiation of clinical development. On this stage, PCS should be carried out in strict accordance with the Rules of Good Laboratory Practice (GLP). The requirements to the work of laboratories carrying out PCS are established in the regulatory acts of the Eurasian Economic Union [7], in Law № 61FZ (chapter 5, art. 11) [6], as well in documents of OECD series on Principles of Good Laboratory Practice and Conformity monitoring [23]. PCS are performed with test systems: cells and tissues, laboratory animals, etc.

Compared to drug manufacturing processes where management system are actively used including pharmaceutical quality system (PQS) [24], which are characterized with a high degree of normative regulation, PCS activity is less regulated. According to some authors, it significantly increases risks of non-performance of the main goal – getting evidence of drug

safety, quality and efficacy – and updates the problem of implementation of risk management to the field of activity [25].

The active implementation of QMS by Russian preclinical laboratories has begun since 2016, since the occurrence of Decision of the Council of the Eurasian Economic Commission № 81 "On approval of Rules of Good Laboratory Practice of the Eurasian Economic Union in drug circulation". The reason of facilitation of QMS implementation in preclinical laboratories may be that EEC Decision № 81 shall be performed and regulates the quality assurance system in detail for preclinical laboratories. But despite the implementation, preclinical laboratories do not have a uniform understanding of QMS arrangements.

The leading national preclinical laboratories have made attempts to analyze national and international regulatory documents in quality management and develop its efficient QMS system on its basis. Most of them took the principles of ISO 9001 standard as the basis for QMS development [25–27]. The great contribution to clarification of QMS in preclinical laboratories was made by All-Union State Standard, GOST 33044-2014 [28] and 31883-2012 [29] being translation of authentic foreign guidances on GLP and quality assurance of preclinical studies in accordance with the rules.

To develop efficient QMS, some authors also reviewed the approaches to quality management from the positions of risk management [30]. Other authors reviewed the appropriateness of establishment of management system integrating QMS approaches, as well work safety management system (WSMS) in a preclinical laboratory [25].

Such analytical articles have started appearing in national editions predominantly in the recent 5 years, however, there are only few of them. Despite the interest and theoretical elaboration of approaches to QMS implementation [31], from practical point of view, preclinical laboratories should make much work in this field.

Quality assurance in the bioanalytical laboratory

A bioanalytical laboratory "enters the game" on the stage of clinical trials of drugs. Due to that, the requirements of the Rules of Good Clinical Practice (EEC Decision № 79) [32] are applicable to the type of laboratories, where the necessity of quality assurance and control is described in general features, however, we speak about mainly on clinical diagnostic laboratories. Nowadays, studies of generics are carried out in Russia. Due to that, the most part of activities of the bioanalytical laboratory is represented by works within bioequivalence studies to which the Drug Bioequivalence Rules are applicable (EEC Decision № 85 dated November 3, 2016) [33]. In particular, the rules of work of bioanalytical laboratories are given in more detail in Annex N 6 "Requirements to validation of bioanalytical test methods and analysis of biological test samples" of EEC Decision № 85.

However, the documents describe the private issues not disclosing the methodology of QMS organization. To a definite extent, GOST ISO/IEC 170252019 "General requirements to competence of testing and calibration laboratories" can be applied to such type of laboratories [4].

It should be noted that bioequivalence studies represent only a part of bioanalytical laboratory activities. Its goals are to determine pharmacokinetic properties of drugs (ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity) with further development and validation of bioanalytical methods for determination of drug pharmacokinetics. Along with bioequivalence studies (where pharmacokinetic parameters of reference products are initially known), a bioanalytical laboratory performs research work as a result of which it determines previously unknown parameters. Accordingly, as preclinical, and unlike quality control laboratory, a bioanalytical is not a conformity assessing organization.

The leading experts note gaps in quality regulation of bioanalytical studies in Russia [34]: "Meanwhile, preclinical studies are regulated in general in accordance with GLP rules, then the requirements to bioanalytical

studies in Russia are not regulated. Sponsors may require GMP, GCP, GLP certificates, certificate ISO 9001 or GOST 17025 accreditation from laboratories. The largest leading laboratories are certified voluntarily. However, state regulation for bioanalytical laboratories is absent. Meanwhile, bioanalytical laboratories in Europe and USA are inspected regularly [35]. When significant non-conformities are found, a regulator may withdraw a marketing authorization". Report by Vasily Kazey "About the provision of transparency and control of clinical trials and bioequivalence studies of generics" [36] reviewed cases of data falsification in some bioanalytical laboratories, when blood plasma was poured into 2 vials and given as samples of two study stages, as well as cases when a reference product was given to volunteers on two study stages replacing the study products. The cases mentioned by the authors challenge the approach to understanding of quality of bioanalytical studies in Russia and general.

Despite certain convergences, global society believes that bioanalytical stage of clinical trials should be regulated by GLP rules with some clarifications [35, 37]. As it is described in the EMA Reflection paper for laboratories that perform the analysis or assessment of clinical trial samples [38]: "In the absence of any comprehensive guidance issued by regulatory or surveillance authorities for laboratories performing analysis and evaluation clinical trial samples, some laboratories use GLP principle. Several GLP aspects are applicable to clinical sample analysis. However, it should be noted that GLP field of application is developed for preclinical studies and, consequently, does not consider all aspects which may influence safety and rights of clinical trial subjects".

According to the open data, over 30 bioequivalence studies are carried out yearly in Russia. The most important condition for obtaining reliable results of such studies is the quality control both on the planning stage and on stages of the study performance [39, 40].

Therefore, for QMS generation for bioanalytical and preclinical laboratories, in the absence of clear regulation, the complex approach to regulatory documents is required. Integral QMS may efficiently solve the problem.

Quality assurance in a clinical diagnostic laboratory

Clinical diagnostic laboratories in a drug life cycle perform monitoring function of objective data of volunteers' health condition on the stage of clinical trials (complete blood count, urine analysis, biochemistry tests, etc.). Such laboratory should be considered as the integral member of drug life cycle as this type of laboratories gives grounds for conclusions on drug efficacy and safety on stages of clinical trials. The requirements of Good Clinical Practice (GCP) is applicable to such type of laboratories, as well as, GLPM may be partially used. However, due to the "gap" in normative regulation between GLP and GCP, in 2003, the Research Quality Association offered (RQA) the guidance on the gap elimination [41]. Based on the offer, the World Health Organization (WHO) introduced the concept of Good Clinical Laboratory Practice (GCLP) intended to become a valuable instrument for improvement and quality assurance of laboratory practice in clinical trials, reliability, quality and integrity of work, and clinical trial [42, 43].

In accordance with the Rules of Good Clinical Practice (GCP, EEC Decision № 79) [32], since the beginning of clinical trials, a sponsor is responsible for data quality, reliability and integrity, and functionally – a monitor. And such laboratories work predominantly as contract organizations and perform a large number of functions, along with drug clinical trials which complicates evaluation of their QMS functioning by the sponsor.

One of the main regulatory documents used by clinical diagnostic laboratories is GOST R ISO 15189-2015 "Medical laboratories. Particular requirements to quality and competence". The All-Union state standard is based on ISO/MEK 17025 [4] and ISO 9001 [22], and serves as laboratory instrument for development of in-house QMS and evaluation of own competence [44].

The description of the requirements to QMS of a clinical diagnostic laboratory is also found in GOST R 53022-2008 "Clinical laboratory technologies. Quality

requirements to clinical laboratory studies" [45], GOST R 53079-2008 "Clinical laboratory technologies. Quality assurance of clinical laboratory studies" [46] and GOST R 53133-2008 "Clinical laboratory technologies. Quality control of clinical laboratory studies" [47].

GOST R 530792-2008 establishes the rules for organization of quality management system including administrative and documentation management system regulating activity of clinical diagnostic laboratories of medial organizations of all property forms.

GOST R 53133-2008 describes intralaboratory quality control in quality management system of clinical laboratory studies in detail and complex quality control of clinical laboratory studies.

GOST R ISO 15189-2009, GOST R ISO 53079-2008 and GOST R ISO 53022-2008 clarifying the implementation of GOST R ISO 9001 in laboratory medicine, provide the instrument for effective management of key processes [22, 44–46]. "Quality Guidance" is the fundamental document of a clinical diagnostic laboratory [22, 46].

The abundance of normative documents regulating QMS of clinical diagnostic laboratories, according to the industry representatives, complicates correct organization of their QMS [48].

In some EAEU countries [49], low awareness of specialists of basic requirements to QMS is observed. Therefore, in accordance with the sociological survey of specialists of clinical diagnostic laboratories in Kazakhstan (110 responders), 39.1 % of all surveyed do not know the main normative documents regulating activity of clinical diagnostic laboratories.

The main difficulty which clinical diagnostic laboratories face is the understanding how to implement quality management system in real practice in a certain organization [50]. For that, the WHO approved the guidance as website "Instrument of stagewise quality implementation in a laboratory" (SQIL) [51, 52]. The instrument is intended to help laboratories to implement efficiently quality management system.

O. V. Lyang et al approved that there is no national system for quality standard conformity assessment (neither mandatory nor voluntary) for medical organizations and laboratories which rather complicates the implementation of quality management system. As a decision of the current situation, some experts consider the implementation of medical activity accreditation system or change of license requirements (for example, with implementation with preliminary and test requirements) and organization of expert preparation and evaluation system by GOST R ISO 15189 [50].

The accreditation system provides, as a rule, conformity evaluation of each separately taken normative document. QMS is a complex system based on the entire complex of regulatory standards. Accreditation for conformity to each of them requires large time and financial expenses from laboratories. Due to that, in this case, as with other types of laboratories, it is appropriate to consider integral QMS model.

It should be emphasized that drug efficacy, safety and pharmacokinetics data are the main result of laboratory studies within a drug life cycle. The main criteria for laboratory activity are data transparency, reliability and integrity which is the main aim for laboratory QMS.

QMS Organization of quality control laboratories

Quality control laboratories (QC) take a special position in a drug life cycle. This type of laboratories should be present at a drug enterprise (as part of the QC department) and already on the stage of drug sales (external QC laboratories). These laboratories are "guarantees and caretakers" of production and circulation of high-quality and safe drugs.

By the nature of tasks performed (see table 1), QC laboratories can be fully referred to conformity assessment organizations, and this type of laboratory can be characterized by the term “testing laboratory”. The requirements for these types of laboratories are given in GOST ISO/IEC 17025-2019 [4]. This All-Union State Standard is closely related to other regulatory documents

ISO/IEC. It describes that a laboratory management system should at least provide: management system documentation, document management of management system, record management, actions related to risks and opportunities, improvements, corrective actions, internal audits and management analysis. At the same time, GOST 17025-2019 claims that the laboratory that has established and maintains the management system in accordance with the requirements of ISO 9001 and can confirm, and demonstrate constant compliance with the requirements of sections 4–7 of GOST ISO/IEC 17025-2019, shows the readiness to fulfill the requirements outlined above. Thus, GOST P ISO 9001-2015 underlies QMS requirements for QC laboratories [22].

However, in addition to the series of GOST ISO/IEC, the Rules of Good Pharmaceutical practices (GxP) are fully applicable to quality control laboratories. Thus, EEC Decision № 77 (Rules of Good Manufacturing Practices, GMP) [53] gives a special attention to drug quality control. The conditions of the pharmaceutical quality system described in Chapter 1 of Part 1 of the EAEU GMP Rules apply to quality control laboratories. Moreover, the concept of **"Good Laboratory Practice of Quality Control"** appears in the GMP Rules, and chapter 6 of the present rules describes the principles of this practice.

It should be noted that the general principles of QMS establishment are actually applicable for external QC laboratories and QC laboratories at a manufacturing enterprise.

Drug quality control establishes the priority of the state regulation of safety, quality and efficacy of drugs being circulated in accordance with Federal Laws of the Russian Federation "On circulation of medicines" [6] and "On protection of consumers' rights" [54]. For evaluation of a technical level of manufacture and drug quality, the WHO established the "System of quality compliance of pharmaceutical products in international trade" [55].

In 2011, to harmonize and standardize the requirements to QC laboratories on the international level, the WHO developed a specific GPCL concept: "Good Practices for Pharmaceutical Quality Control Laboratories" [56, 57]. The practice describes separately QMS for the type of laboratories. GPCL is intended to establish the network of international quality control laboratories by the uniform standard. The recommendations are intended to become the basis for national programs of many countries of the world to confirm reliability and accuracy of test results.

As the description of regulation of drug laboratory studies shows, regulatory requirements to various types of laboratories significantly differ but have a common basis. In this case, the establishment of integral QMS (including several subsystems) which fundamental model was offered to review in the following section.

Model of effective QMS of laboratories of a drug life cycle

As the description of variety of normative requirements shows, for establishment of effective quality system, the most harmonious combination of approaches should be developed and implemented which is a difficult task for an organization.

The need in implementation of several multidirectional management system has occurred due to the increase of the level of consumer requirements on the saturated global market. As a result, to the beginning of the present century, many organizations both abroad and in EAEU countries show more and more interest to integral management systems (IMS).

IMS – the management system meeting the requirements of two or more standards of management systems and functioning as the single entity. Among the most relevant standards used for ISM formation, there are ISO 14000 standards for ecological management system, OHSAS 18000 standards (Occupational Health and Safety Assessment Series) for management system of occupational health and safety, standard SA (Social Accountability) 8000 for the system of social and ethical management. IMS is most often formed on the basis of the requirements of standard ISO 9001, as well as with the standards developed on the basis of ISO 9000

standards to be used in certain industries. In formation of IMS, the standards are used which are based on HACCP principles (Hazard Analysis and Critical Control Points) – the risk analysis and critical control points [58, 59] and, definitely, the principles of Good Pharmaceutical Practices (GLP, GCLP, GCP, GMP, GPCL) [60].

The implementation of IMS formed with the use of the requirements of multidirectional standards is nowadays the most effective method for improvement of organization management.

It should be noted that IMS are more and more demanded among national organizations [61]. However, there is no uniform standard today containing the requirements either to IMS themselves, or their audit, and certification. Some recommendatory data on IMS are contained in documents "Integrated Management System. Definition and Guidance on Structuring" (prepared by the Chartered Quality Institute Integrated Management Special Interest Group) [62], as well as in PAS 99:2006 "Specification of common management system requirements as a framework for integration" [63]. Based on the abovementioned, it is appropriate to assume that the new international standard will be soon developed based on the documents. Therefore it can be stated that the phase of integral quality management is nowadays only developing, and its academic and research methodology for various industries is only being formed.

In addition to the basic principles and standards mentioned above, the principles of quality risk management system are one of the essentials for development of quality system [14]. Based on the definition given in ICH Q9 (part 3): *"Risk is the combination of probability and severity of consequences. In other words, risk criticality is always determined with the value of hazard probability multiplied to severity value of its consequences"*.

Risk = Probability × Severity of hazard consequences.

The methodology of risk management in various organizations may differ. However, all methods for risk evaluation are based on the successive determination of potential hazards related to an evaluation object ("What may happen?"), detection of probability of their occurrence ("How probable is it that it may occur?") and evaluation of possible consequences ("What consequences may be?"). I. e. regardless from the used method, we get a response to each of the three key issues declared in ICH Q9. Responses to the questions lead to risk value which may be declared qualitatively (unacceptable, serious and insignificant risk) или quantitatively (risk value in scores, table 2, figure 2) [64].

Table 2. An example of a quantitative risk assessment (in points)

Probability (P)	Consequences of harm (S)	Risk (P × S)	Risk profile		
			Unacceptable	Serious risk	Minor risk
1–10	1–10	1–100	More than 30	9–29	Less than 9

		Consequences of harm		
		Low	Central	High
Probability	Low	Minor risk	Minor risk	Serious risk
	Central	Minor risk	Serious risk	Unacceptable
	High	Serious risk	Unacceptable	Unacceptable

Figure 2. Risk Matrix

While developing the model of effective QMS, any laboratory may use the most convenient methods including extrapolation of the method described for one type of a laboratory to other types.

Thus, for example, for clinical diagnostic (medical) laboratories, the WHO approved the Guidance of stagewise quality implementation in a laboratory (SQIL) [51, 52]. The guidance describes in detail QMS stages and levels which are evidently shown as the quality management pyramid (figure 3), as well as, presents the main elements of quality system (figure 4).

The method for QMS development can be successfully used in work of all types of laboratories of a drug life cycle.

Therefore, the most effective model for all types of laboratories of drug life cycle is the integral quality management system based on the harmonious system of regulating documents (figure 5). As the scheme shows, as the basis of QMS development, quality standard ISO 9001 which is the most universal for all industries can be used. For consolidation of the essentials, it is appropriate to use key elements of quality management from documents ICH Q8, Q9 and Q10 as the standard most specific for pharmaceutical industry. As the next "stage", it is appropriate to develop the principles of Good Pharmaceutical Practices with the more detailed requirements to a certain industry and laboratory type and being mandatory for regulatory control.

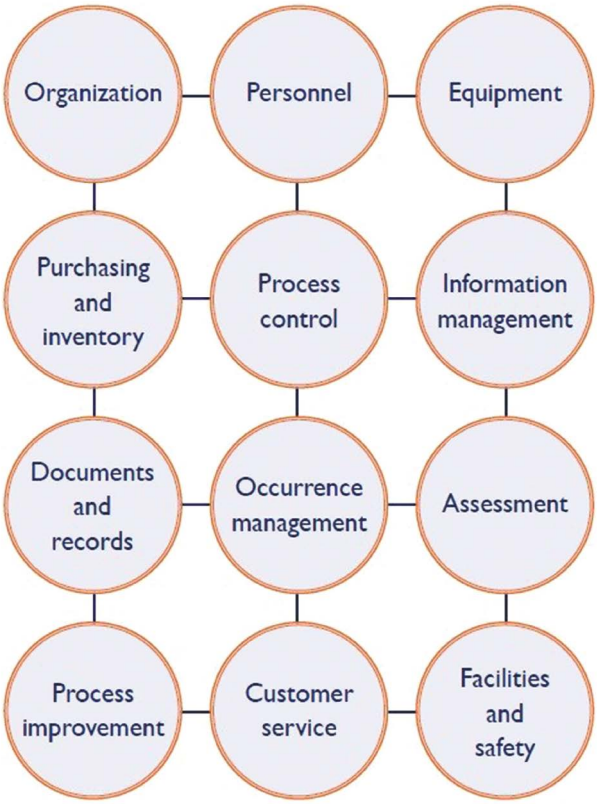

Figure 4. **The quality system essentials (QSEs) [51]**

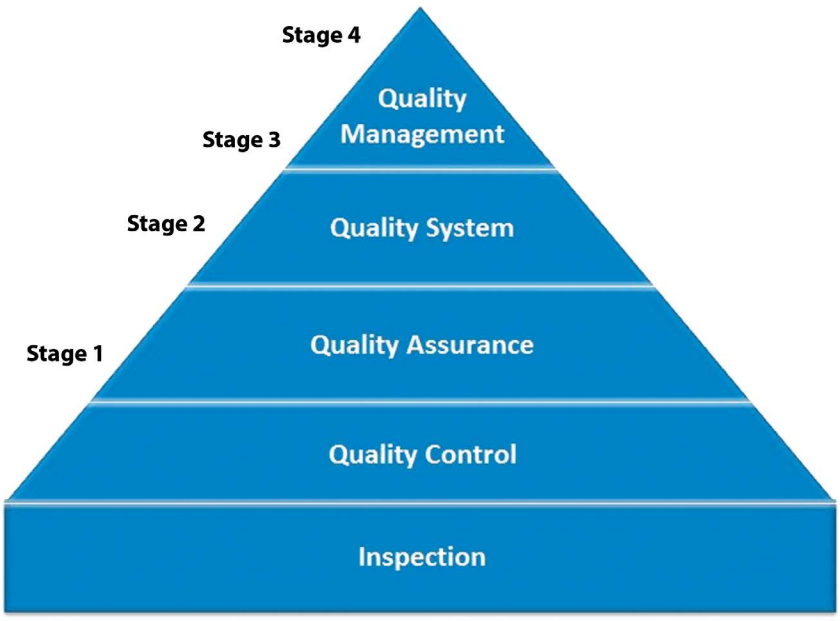

Figure 3. **Quality Management System pyramid [51, 52]**

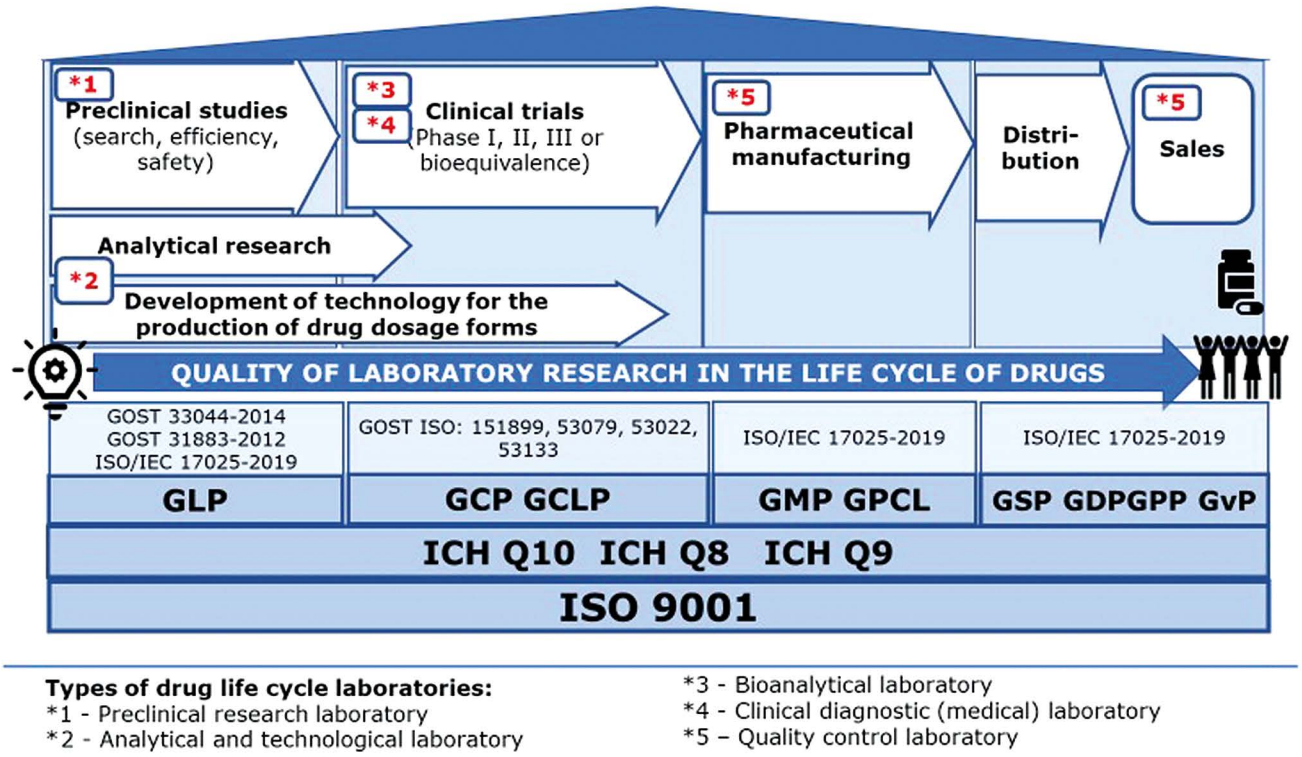

Figure 5. Model of an integrated quality management system for laboratories of drug life cycle laboratories.
Types of drug life cycle laboratories: *1 – preclinical research laboratory; *2 – analytical and technological laboratory; *3 – bioanalytical laboratory; *4 – clinical diagnostic laboratory; *5 – quality control laboratory

The most of the regulatory documents described above were developed and implemented for over 10 years ago. The professional society often asks why normative regulation of quality of drug laboratory studies is not yet clear enough.

As described by Zh. I. Aladysheva et al in their monograph "Industrial pharmacia. The method for product development" [21], there is the mechanism described by GMP specialist J. Sharpe – the rule of the ascending spiral or "Sharpe spiral" (figure 6) [21]. In accordance with the principle, the innovations in drug quality assurance are initially used by separate organizations on a voluntary basis. Later, the most useful of them being widely accepted, become mandatory. It is how the practice is reflected in regulatory requirements.

CONCLUSION

In accordance with the Russian requirements: "Drug quality – compliance of a drug product to the requirements of a compendial monograph or, if it is absent, regulatory documents" [6]. However, determinations of term, as a rule, are based on clinical value of drugs.

The final goal of laboratory studies as other stages of drug life cycle is assurance of drug quality and safety in humans. An error made in one of laboratories studies may cause large financial losses and may turn into a catastrophe for human health or life which is shown by examples from the history of pharmaceuticals [65].

Laboratory research quality system serves a basic instrument for the achievement of a final target – clinical value of drugs – and is committed to ensure risk minimization for patients. Each stage of drug life cycle provides a solution for a certain task towards the goal which should be considered in QMS formation in each of the types of laboratories. The range of regulatory documents and external assessment systems (accreditation, certification, inspection control, etc.) in national laboratory research is rather variable. Due to

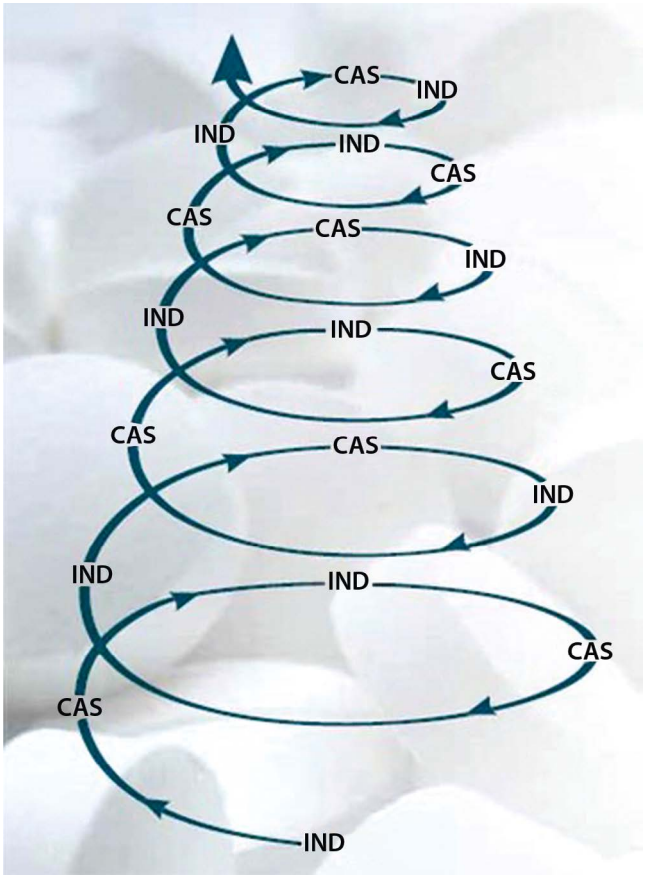

Figure 6. "Sharpe Spiral".
Where IND – industry, CAS – control and authorization system [21]

that, it is appropriate for laboratories to build a harmonic quality management system based on priorities in accordance with goals and tasks. The model of integral management system is the most efficient method for formation of such system.

REFERENSES

1. *Federal'nyy zakon Rossiyskoy Federatsii № 184-FZ ot 27.12.2002 "O tekhnicheskom regulirovanii"* [Federal Law of Russian Federation № 184-FZ of 27 December 2002 "On Technical Regulation"]. Available at: http://www.consultant.ru/document/cons_doc_LAW_40241/ Accessed: 26.07.2021. (In Russ.)
2. *SDA-06-2009 "Terminy i opredeleniya, ispol'zuemye v edinoy sisteme otsenki sootvetstviya v oblasti promyshlennoy, ekologicheskoy bezopasnosti, bezopasnosti v energetike i stroitel'stve"* [System of documents for accreditation SDA-06-2009 "Terms and definitions used in the unified conformity assessment system in the field of industrial, environmental safety, safety in energy and construction"]. Available at: https://docs.cntd.ru/document/902356361. Accessed: 26.07.2021. (In Russ.)
3. *SDA-15-2009. "Trebovaniya k ispytatel'nym laboratoriyam"* [System of documents for accreditation SDA-15-2009. "Requirements for testing laboratories"] Available at: http://www.normacs.ru/Doclist/doc/VJFV.html. Accessed: 26.07.2021. (In Russ.)
4. *GOST ISO/IEC 17025-2019 "Obshchie trebovaniya k kompetentnosti ispytatel'nykh i kalibrovochnykh laboratoriy"* [State standard GOST ISO/IEC 17025-2019 "General requirements for the competence of testing and calibration laboratories"]. Available at: https://docs.cntd.ru/document/1200166732. Accessed: 26.07.2021. (In Russ.)
5. *GOST ISO/IEC 17000-2012 "Otsenka sootvetstviya. Slovar' i obshchie printsipy"* [State standard GOST ISO/IEC 17000-2012 "Conformity assessment. Vocabulary and general principles"]. Available at: https://docs.cntd.ru/document/1200100949. Accessed: 26.07.2021. (In Russ.)
6. *Federal'nyy zakon Rossiyskoy Federatsii № 61-FZ ot 12.04.2010 "Ob obrashchenii lekarstvennykh sredstv"* [Federal Law of Russian Federation № 61-FZ of 12.04.2010 "On the Circulation of Medicines"]. Available at: http://www.consultant.ru/document/cons_doc_LAW_99350/ Accessed: 26.07.2021. (In Russ.)
7. *Reshenie Soveta Evraziyskoy ekonomicheskoy komissii ot 03.11.2016 № 81 "Ob utverzhdenii Pravil nadlezhashchey laboratornoy praktiki Evraziyskogo ekonomicheskogo soyuza v sfere obrashcheniya lekarstvennykh sredstv"* [Decision of the Council of the Eurasian Economic Commission dated 03.11.2016 No. 81 "On approval of the Rules of good laboratory practice of the Eurasian Economic Union in the field of circulation of medicines"]. Available at: https://docs.cntd.ru/document/456026101. Accessed: 26.07.2021. (In Russ.)
8. Feofilova A. E., Foteeva A. V., Rostova N. B. The Modern Concepts of Pharmaceutical Development in the Context of the Transition to a Uniform Regulation of Medicinal Products Circulation. *Razrabotka i registratsiya lekarstvennykh sredstv = Drug development & registration*. 2020;9(4):171-179. (In Russ.) DOI: 10.33380/2305-2066-2020-9-4-171-179.
9. Rozhnova S. A., Tsypkina A. V. Analysis of the system organization of pharmaceutical drug development. *Razrabotka i registratsiya lekarstvennykh sredstv = Drug development & registration*. 2017;(3):170–176. (In Russ.)
10. Singh H., Khurana L. K., Singh R. Chapter 3. Pharmaceutical development. In: Pharmaceutical Medicine and Translational Clinical Research. London: Academic Press; 2018. P. 33–46.
11. Torres M. Challenges in implementing quality by design: An industry perspective. *Bioprocess International*. 2015. Available at: https://bioprocessintl.com/analytical/downstream-development/challenges-in-implementing-quality-by-design-an-industry-perspective/ Accessed: 26.07.2021.
12. Singh L., Sharma V. Quality by Design (QbD) approach in pharmaceuticals: status, challenges and next steps. *Drug Delivery Letters*. 2015;5(1):2–8.
13. Guideline I. C. H. H. T. Pharmaceutical Development Q8 (R2). Current step 4. 2009. Available at: https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf. Accessed: 26.07.2021.

14. Guideline I. C. H. H. T. Quality risk management Q9. Current step 4. 2005. Available at: https://database.ich.org/sites/default/files/Q9_Guideline.pdf. Accessed: 26.07.2021.
15. Guideline I. C. H. H. T. Pharmaceutical quality system Q10. Current Step 5. 2008. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human_en.pdf. Accessed: 26.07.2021.
16. Lawrence X. Yu., Amidon G., Khan M. A., Hoag S. W., Polli J., Raju G. K., Woodcock J. Understanding pharmaceutical quality by design. *The AAPS journal*. 2014;16(4):771–783. DOI: 10.1208/s12248-014-9598-3.
17. Politis S. N., Colombo P., Colombo G., M. Rekkas D. M. Design of experiments (DoE) in pharmaceutical development. *Drug development and industrial pharmacy*. 2017;43(6):889–901. DOI: 10.1080/03639045.2017.1291672.
18. *GOST 7.32-2017 SIBID "Otchet o nauchno-issledovatel'skoy rabote. Struktura i pravila oformleniya"* [State standard GOST 7.32-2017 SIBID "Report on research work. Structure and design rules"]. Available at: https://docs.cntd.ru/document/1200157208. Accessed: 26.07.2021. (In Russ.)
19. Bespalov A., Michel M. C., Steckler T. Good research practice in non-clinical pharmacology and biomedicine. Basingstoke: *Springer Nature*; 2020. 423 p.
20. Guillén J., Steckler T. Good Research Practice: Lessons from Animal Care and Use. *Good Research Practice in Non-Clinical Pharmacology and Biomedicine*. 2019:367–382. DOI: 10.1007/164_2019_292.
21. Aladysheva Zh. I., Belyaev V. V., Beregovykh V. V., Brkich G. E., Greybo S. V., Demina N. B., Dzhurko Yu. A., Ivanovskiy S. A., Nikolenko N. S., Komissarova V. A., Korsakov M. K., Lavrent'eva L. I., Meshkovskiy A. P., Miroshnikov A. E., Onegin S. V., Parfenov A. A., Pozdnyakov N. O., Poroykov V. V., Pyatigorskaya N. V., Pyatigorskiy A. M., Rakov A. A., Sidorov A. V., Spitskiy O. R., Trubnikov A. A., Khokhlov A. A., Khokhlov A. L., Chikina I. V., Shabalina M. M., Shabrov V. N., Shitov L. N., Yaichkov I. I. *Promyshlennaya farmatsiya. Put' sozdaniya produkta* [Industrial pharmacy. Product creation path]. Moscow: Rossiyskaya akademiya nauk; 2019. 393 p. (In Russ.)
22. *GOST R ISO 9001-2015 "Sistemy menedzhmenta kachestva. Trebovaniya"* [State standard GOST R ISO 9001-2015 "Quality management systems. Requirements"]. Available at: https://docs.cntd.ru/document/1200124394. Accessed: 26.07.2021. (In Russ.).
23. OECD series on principles of good laboratory practice and compliance monitoring-ENV/MC/CHEM-98-17. Organisation for Economic and Co-Operation Development-OECD. 1998. Available at: https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en. Accessed: 26.07.2021.
24. Smirnov V. A., Goryachkin V. V., Shestakov V. N., Abramovich R. A. Guidelines for Promoting the Implementation of Pharmaceutical Quality Systems at EAEU Enterprises Through the Management of the Engagement of Production Personnel. *Razrabotka i registratsiya lekarstvennykh sredstv = Drug development & registration*. 2021;10(1):136–141. (In Russ.) DOI: 10.33380/2305-2066-2021-10-1-136-141.
25. Zaytseva M. A., Ivanov M. B., Verveda A. B., Lyanginen L. V. Risk Management in Preclinical Trials as Part of an Overall Integrated Quality Management System. *Bezopasnost' i risk farmakoterapii = Safety and Risk of Pharmacotherapy.* 2020;8(1):36–42. (In Russ.) DOI: 10.30895/2312-7821-2020-8-1-36-42.
26. Narkevich I. A., Flisyuk E. V., Shigarova L. V., Moskvin A. V. *Rasprostranenie sistemy menedzhmenta kachestva na nauchnuyu deyatel'nost'* [Extension of the quality management system to scientific activity]. *Ekonomika kachestva*. 2016;4(16):1–8. (In Russ.)
27. Narkevich I. A., Flisyuk E. V., Moskvin A. V., Shigarova L. V., Ivkin D. Yu., Ivkina A. S. Certification for the conformity of iso 9001 equirements as a first phase of implementation of good laboratory practice in the center of experimental pharmacology. *Razrabotka i registratsiya lekarstvennykh sredstv = Drug development & registration*. 2018;1:226–230. (In Russ.)
28. *GOST 33044-2014 "Printsipy nadlezhashchey laboratornoy praktiki"* [State standard GOST 33044-2014 "Principles of Good Laboratory Practice"]. Available at: https://docs.cntd.ru/document/1200115791. Accessed: 26.07.2021. (In Russ.)
29. *GOST 31883-2012 "Printsipy nadlezhashchey laboratornoy praktiki (GLP). Obespechenie kachestva v sootvetstvii s Printsipami GLP"* [State standard GOST 31883-2012 "Principles of Good Laboratory Practice (GLP). Quality assurance in accordance with the GLP Principles]. Available at: https://docs.cntd.ru/document/1200101517. Accessed: 26.07.2021. (In Russ.).
30. Burova E. D., Khodko S. V., Gushchina S. V., Makarova M. N., Makarov V. G. Risk management for quality assurance of preclinical research. *Vedomosti Nauchnogo tsentra ekspertizy sredstv meditsinskogo primeneniya = The Bulletin of the Scientific Centre for Expert Evaluation of Medicinal Products*. 2017;7(1):25–31. (In Russ.)
31. Knight L. A., Cree I. A. Quality assurance and good laboratory practice. *Methods in Molecular Biology*. 2011:115–124. DOI: 10.1007/978-1-61779-080-5_10.
32. *Reshenie Soveta Evraziyskoy ekonomicheskoy komissii № 79 ot 3.11.2016 "Ob utverzhdenii Pravil nadlezhashchey klinicheskoy praktiki Evraziyskogo ekonomicheskogo soyuza"* [Decision of the Council of the Eurasian Economic Commission No. 79 dated November 3, 2016 "On approval of the Rules for Good Clinical Practice of the Eurasian Economic Union"]. Available at: https://docs.cntd.ru/document/456026110. Accessed: 26.07.2021. (In Russ.)
33. *Reshenie Soveta Evraziyskoy ekonomicheskoy komissii № 85 ot 3.11.2016 "Ob utverzhdenii Pravil provedeniya issledovaniy bioekvivalentnosti lekarstvennykh preparatov v ramkakh Evraziyskogo ekonomicheskogo soyuza"* [Decision of the Council of the Eurasian Economic Commission No. 85 dated November 3, 2016 "On approval of the Rules for conducting bioequivalence studies of medicinal products within the framework of the Eurasian Economic Union"]. Available at: https://docs.cntd.ru/document/456026107. Accessed: 26.07.2021. (In Russ.)

34. *Perspektivy razvitiya sistemy GLP v Rossii i EAES* [Prospects for the development of the GLP system in Russia and the EAEU]. Available at: https://gxpnews.net/2020/10/perspektivy-razvitiya-sistemy-glp-v-rossii-i-eaes/ Accessed: 26.07.2021. (In Russ.)
35. Haidar S. H., Scheibner K. A. Bioanalytical Inspections: organizational changes and regulatory perspectives. *Bioanalysis*. 2016;8(10):999–1002. DOI: 10.4155/bio-2016-0052.
36. Kazey V. I. *K voprosu ob obespechenii prozrachnosti i kontrolya KI/BE dzhenerikov. V sb.: Mezhdunarodnaya nauchno-prakticheskaya konferentsiya "Razrabotka i registratsiya lekarstvennykh sredstv. Issledovanie preparatov po pravilam EAES"* [To the question of the danger of transparency and control of CI/BE of generics. In: International Scientific and Practical Conference "Development and Registration of Medicines. Research of drugs according to the rules of the EAEU"]. 6 December 2020. Moscow. 2020. (In Russ.).
37. Podpruzhnikov Yu. V. *Provedenie bioanaliticheskikh issledovaniy v sootvetstvii s trebovaniyami GLP* [Conducting bioanalytical research in accordance with the requirements of GLP]. *Visnik farmakologii ta farmatsii*. 2009;2:33–39. (In Ukrain.)
38. EMA Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples, EMA/INS/GCP/532137/2010. February 2012.
39. Khokhlov A. L., Lileeva E. G. Analysis of the quality of bioequivalence and pharmacokinetics studies in Russian Federation. *Kachestvennaya klinicheskaya praktika*. 2016;(2):64–70. (In Russ.)
40. Patel S., Huang Q. M., Jian W., Edom R., Weng N. Overview: Fundamentals of a Bioanalytical Laboratory. *Handbook of LC-MS Bioanalysis*. 2013:15–27. DOI: 10.1002/9781118671276.ch2.
41. Stevens W. Good clinical laboratory practice (gclp): the need for a hybrid of good laboratory practice and good clinical practice guidelines/standards for medical testing laboratories conducting clinical trials in developing countries. *Quality Assurance*. 2003; 10(2):83–89. DOI: 10.1080/10529410390262727.
42. WHO Good Clinical Laboratory Practice (GCLP). Available at: https://www.who.int/tdr/publications/documents/gclp-web.pdf. Accessed: 26.07.2021.
43. Todd C. A., Sanchez A. M., Garcia A. Thomas N. Denny, Sarzotti-Kelsoe M. Implementation of Good Clinical Laboratory Practice (GCLP) guidelines within the External Quality Assurance Program Oversight Laboratory (EQAPOL). *Journal of Immunological Methods*. 2014;409:91–98. DOI: 10.1016/j.jim.2013.09.012.
44. *GOST R ISO 15189-2009 "Laboratorii meditsinskie. Chastnye trebovaniya k kachestvu i kompetentnosti"* [State standard GOST R ISO 15189-2009 "Medical laboratories. Particular requirements for quality and competence"]. Available at: https://docs.cntd.ru/document/1200077769. Accessed: 26.07.2021. (In Russ.)
45. GOST R ISO 53022 *"Tekhnologii laboratornye klinicheskie. Trebovaniya k kachestvu klinicheskikh laboratornykh issledovaniy"* [State standard GOST R ISO 53022 "Technologies for laboratory clinical cues. Requirements for the quality of clinical laboratory research"]. Part 1–4. Available at: https://docs.cntd.ru/document/1200068114. Accessed: 26.07.2021. (In Russ.)
46. *GOST R ISO 53079-2008 "Tekhnologii laboratornye klinicheskie. Obespechenie kachestva klinicheskikh laboratornykh issledovaniy* [State standard GOST R ISO 53079-2008 "Clinical laboratory technologies. Quality assurance of clinical laboratory research"]. Part 1–4. Available at: https://docs.cntd.ru/document/1200068744. Accessed: 26.07.2021. (In Russ.)
47. *GOST R 53133.2-2008 "Tekhnologii laboratornye klinicheskie. Kontrol' kachestva klinicheskikh laboratornykh issledovaniy"* [State standard GOST R 53133.2-2008 "Technologies for laboratory clinical cues. Quality control of clinical laboratory tests"]. Part 1–4. Available at: https://docs.cntd.ru/document/1200072567. Accessed: 26.07.2021. (In Russ.)
48. Dolgikh T. I. The system of quality management in medical laboratory: the problematic issues of implementation of GOST RKS 9001-2008,GOST R ISO 15189-2009 and GOST R ISO 53079-2008. *Klinicheskaya laboratornaya diagnostika = Russian Clinical Laboratory Diagnostics*. 2013;4:49–51. (In Russ.)
49. Utarbaeva I. K., Tungishbaev M. *Sistema menedzhmenta kachestva v kliniko-diagnosticheskikh laboratoriyakh* [Quality management system in clinical diagnostic laboratories]. *Vestnik Kazakhskogo Natsional'nogo meditsinskogo universiteta.* 2015;4:364–365. (In Russ.)
50. Lyang O. V., Chernichuk O. V., Rysenkova E. Yu., Zhirova I. A., Kochetov A. G. Problems of quality management of laboratory tests in Russia. *Laboratornaya sluzhba = Laboratory Service*. 2017;6(2):33–37. (In Russ.)
51. *Zadachi chetyrekh etapov instrumenta PVKL* [Tasks of the four stages of the PVCL tool]. Available at: https://extranet.who.int/lqsi/ru/content/задачи-четырех-этапов-инструмента-пвкл.
52. *Upravlenie kachestvom* [Quality control]. Available at: Available at: https://extranet.who.int/lqsi/ru/node/526. Accessed: 26.07.2021. (In Russ.)
53. *Reshenie Soveta Evraziyskoy ekonomicheskoy komissii № 77 ot 03.11.2016 "Ob utverzhdenii Pravil nadlezhashchey proizvodstvennoy praktiki Evraziyskogo ekonomicheskogo soyuza"* [Decision of the Council of the Eurasian Economic Commission № 77 dated 03.11.2016 "On Approval of the Rules of Good Manufacturing Practice of the Eurasian Economic Union"]. Available at: https://docs.cntd.ru/document/456026099. Accessed: 26.07.2021. (In Russ.)
54. *Federal'nyy zakon RF № 2300-1 ot 07.02.1992 "O zashchite prav potrebiteley"* [Federal Law of the Russian Federation № 2300-1 of 07.02.1992 "On Protection of Consumer Rights"]. Available at: http://www.consultant.ru/document/cons_doc_LAW_305/ Accessed: 26.07.2021. (In Russ.)
55. *Pravila proizvodstva i kontrolya kachestva lekarstvennykh sredstv i sistema udostovereniya kachestva farmatsevticheskikh preparatov v mezhdunarodnoy torgovle* [Rules for the production and quality control of medicines and the system of certification of the quality of pharmaceuticals in international trade]. Available at: https://

apps.who.int/iris/handle/10665/101206. Accessed: 26.07.2021. (In Russ.)

56. WHO Technical Report Series No. 1003, 2017. Available at: https://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_1003_full-version.pdf?ua=1. Accessed: 26.07.2021.
57. WHO Technical Report Series, No. 957, 2010. Available at: https://www.who.int/medicines/publications/TRS957_2010.pdf. Accessed: 26.07.2021.
58. Hulebak K. L., Schlosser W. Hazard analysis and critical control point (HACCP) history and conceptual overview. *Risk analysis*. 2002;22(3):547–552. DOI: 10.1111/0272-4332.00038.
59. Shestakov V. N., Podpruzhnikov Yu. V. *Chto takoe khorosho i chto takoe plokho v farmatsevticheskom proizvodstve* [What is good and what is bad in pharmaceutical production]. Moscow: FBU «GILS i NP»; 2017. 180 p. (In Russ.)
60. Korčok D., Tršić-Milanović N., Mitić B., Karadžić N. The importance of integrated management systems in pharmacy. *Tehnika*. 2020;75(1):120–124. DOI: 10.5937/tehnika2001120k.
61. Yaremchuk A. A., Aleksandrov A. V. *Aktual'nost' vnedreniya integrirovannykh sistem menedzhmenta na farmpredpriyatiyakh* [Relevance of the implementation of integrated management systems at pharmaceutical enterprises]. *Remedium*. 2007;7:37–39. (In Russ.)
62. DallingI. Integrated Management Definition. CQIIMSIG. 2007. N.2.1.
63. PAS B. S. Specification of common management system requirements as a framework for integration. 2012.
64. Aleksandrov A. V. *Faktor sub"ektivnosti pri otsenke riska po kachestvu* [The factor of subjectivity in assessing risk by quality]. *Farmatsevticheskaya otrasl'*. 2001;5(28):116–119. (In Russ.)
65. Kim J. H., Scialli A. R. Thalidomide: the tragedy of birth defects and the effective treatment of disease. *Toxicological sciences*. 2011;122(1):1–6. DOI: 10.1093/toxsci/kfr088.