1. Introduction

Effective quality control of medicines is an obligatory component of the national security system of the state [1]. Laboratories for the quality control of pharmaceutical products bear a major responsibility for the results obtained and conclusions made on their basis on the conformity of the tested samples with the requirements of the specifications, because the success of the treatment of patients or even their life depends on the results of such studies [2]. On the other hand, the results of the medicines quality control determine for the manufacturer and distributor the possibility of implementing a series of medicines, and the error here may be due to significant direct and indirect financial losses, the loss of the image of a reliable supplier or even revocation of the license for the medicines production [3].

Reliability, correctness and accuracy of the obtained analytical results depend on many interconnected factors: laboratory management, document circulation, competence of specialists, correctness of application and relevance of analytical methods, materials and reagents, metrological characteristics and state of service of measuring instruments (devices, equipment), storage conditions and preparation of analytical samples, hardware and software etc. [4].

State laboratories for quality control of medicines should documented guarantee the correctness of the obtained results, prove their competence not only to their customers, but also to regulatory bodies [5]. Today is

FORMATION OF THE QUALITY MANAGEMENT SYSTEMS AT STATE LABORATORIES FOR A MEDICINES CONTROL

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Abstract: The article reviews the regulatory framework in the field of regulating the activities of laboratories for quality control of medicines at the world and national levels. Taking into account the harmonization of the new version of ISO/IEC 17025 "General requirements for the competence of testing and calibration laboratories" and ISO 9001:2015 "Quality management systems. Requirements", the necessity of wide implementation of the process approach and implementation of risk-oriented thinking in the activities of laboratories has been substantiated. The general approaches to implementation of quality management systems (QMS) in the activity of testing pharmaceutical laboratories are offered. In particular, a typical list of QMS processes of the laboratory for quality control of medicines has been developed, and the division of such processes into three groups is proposed: management processes, resource provision processes, main (analytical testing) processes. It is substantiated that these groups of processes should be described in the Quality Manual with a mandatory graphic representation of the QMS process model structure with a description of the processes interaction conditions.

The use of the PDCA Cycle within each of the processes has been proven to promote systematic measurement, analysis of activities and the development of effective corrective and preventive actions (CAPA). The formation of effective QMS in state and private laboratories for quality control of medicines will help to reduce the number and significance of inconsistencies and errors in analytical work, and to provide proper guarantees for obtaining reliable results, to increase the awareness of staff in quality management methods and continuous improvement.

Keywords: quality management system, laboratory, process approach, standards, ISO 9001, ISO 17025, PDCA Cycle, medicines, quality control.

market conditions, developments in the field of information technology, changes to the ISO 9001 standard, have led to the need for changes of ISO/IEC 17025, the revision of which began in 2015 and conducted jointly with the International Accreditation Community (ILAC) and the South African Bureau of Standards (SABS). At present, the revision of the standard has reached the stage of the "Final Draft International Standard" (FDIS) [7], which is the last stage until the publication of the international standard.

According to ISO / IEC FDIS 17025:2016 (E) [7], paragraph 8, "Management System", laboratories should harmonize their work in accordance with the principles of ISO 9001 [8]. In this regard, the main changes in the standard concern:

– use of the process approach provided by the updated standards ISO 9001 [8], ISO 15189 [9] and ISO / IEC 17021-1 [10];

– application of computerized systems, electronic records, electronic results preparation procedures and reports [11];

– implement risk-oriented thinking (paragraph 8.5) in accordance with the provisions of ISO 9001:2015 [8].

Taking into account the upcoming innovations in ISO / IEC 17025 [8] and the lack of experience with the staff of domestic pharmaceutical laboratories regarding the implementation of effective QMS in accordance with current requirements, the issue of developing a methodology for laboratories QMS constructing remains open and requires research.

recognized that the status of an accredited laboratory does not provide such a guarantee: the necessary condition for the proof of the tests results is the introduction and constant maintenance of an effective quality assurance system in the working state [6].

For the unification and standardization of the requirements for the operation of national laboratories for the quality control of medicines at the international level, the World Health Organization (WHO) has developed official guidelines "Good practices for pharmaceutical quality control laboratories" [1], which is based on requirements of the standard ISO/IEC 17025 [2].

These recommendations, with some minor changes, are applied as the basis of their national rules by many countries of the world.

The ISO/IEC 17025 standard has become an international standard for the development of laboratory QMS. The current version of ISO/IEC 17025 was published in 2005. Changes in

One of the main directions of these studies is the definition of the principles of the construction and processes of the created QMS. The aim of the work was to analyze the initial measures for the formation of a QMS model, which implemented based on domestic state laboratories for quality control of medicines, as well as the development of applied proposals for the definition of processes and the formation of an optimal structure of the laboratory QMS.

2. Methods

The theoretical and methodological basis of the work is provisions on the formation of QMS on the basis of modern concepts of standardization and quality management. The information base of the research consists of scientific publications of Ukrainian and foreign scientists and practitioners devoted to problems of the formation, implementation and improving of

QMS, as well as official statistical data and provisions of normative documents concerning the above-mentioned questions. At the paper used: historical, logical and system-analytical methods (to find out the level of development of the problem in foreign and domestic literature); the method of structural-logical modeling (to describe the conceptual approaches to the formation and development of QMS); the method of comparative analysis (used to generalize existing approaches to the formation of QMS in accordance with international standards).

3. Results

The analysis of the QMS implementation in the pharmaceutical laboratories showed the similarity of the approaches used, despite differences in the number of personnel, assortment of methods of analysis, material resources, infrastructure [5]. The similarity of approaches involves a similar classification of processes and the structure of the QMS, as well as a similar set of documents and forms of records. This is due to a fundamentally similar type of laboratory and the similarity of the main activities. The organization of laboratories, especially state-owned, non-commercial laboratories, has distinct peculiarities that require a serious adaptation of approaches to the creation of QMS.

Firstly, to assess the degree of accuracy and reliability of the main result of the work of laboratories is more difficult than to evaluate the results of activities of manufacturing enterprises or distributors. For this purpose, there are rounds of professional testing programs of laboratories, internal "cross-checks", when one and the same sample is analyzed by several analysts to reveal discrepancies in results and their causes [3, 9].

Secondly, the lack of a competitive environment for state laboratories leads to a loss of incentive to improve the quality of services provided. This problem has recently been aggravated by modest government funding and the recent significant cuts in personnel.

To solve the first problem, an effective QMS is needed, it can minimize or even eliminate risk factors for the quality of test results. Process-oriented management provides for a clear allocation of responsibilities, the regulation of all types of activities that affect the final result, as well as the establishment of indicators and criteria for assessing the effectiveness of all processes for the possibility of their continuous improvement.

The solution of the second problem is impossible without the actions of the central governing body, which must develop and implement not only a system of continuous monitoring and control of the activities of laboratories, but also take measures to motivate employees.

Having analyzed the requirements of the standard ISO 9001:2015 [8], the general procedure for developing QMS can formulated as follows:

a) to determine the processes necessary for the QMS, as well as their application throughout the organization;

b) to determine the sequence and interaction of these QMS processes;

c) to define the criteria and methods necessary to ensure the effectiveness of the operation of these processes and their management;

d) to ensure the availability of the resources and information necessary to support the operation and monitoring of these processes;

e) to carry out monitoring, measurement and analysis of processes;

f) to take measures necessary to achieve the planned results and continuous improvement of the QMS processes.

Implementation of the process-oriented approach to the organization of laboratory activities and the creation of a process model of the QMS lies in the area of responsibility of the management of the laboratory. At this stage, it is necessary to define the processes of the QMS, to appoint their managers, to develop algorithms for the implementation of the processes and the conditions of interaction between them, as well as to define the inputs, outputs, resources, necessary management actions and means of measurement, monitoring and analysis of all processes of QMS.

An approximate list of QMS processes developed for a laboratory with a small state and limited resources is proposed:

1. Processes of management activity (management processes):

– management of QMS (quality policy development, strategic and operational planning, responsibility and authority allocation, information exchange, systematic monitoring of all processes, critical analysis of QMS by management, actions in case of discrepancies, development and implementation of corrective and preventive actions with the purpose of continuous improvement of activity);

– implementation of internal audits of the QMS.

2. Resource provision processes (providing processes):

– provision of human resources (recruitment, training, attestation etc.);

– provision of infrastructure (ensuring the proper condition of premises, equipment, communications etc., including cleaning);

– provision of the production environment (assurance and control of conditions for performing analytical and auxiliary works);

– management of documents and records (development, approval, updating, revision, storage, removal and disposal of documents and records, as well as control of documents circulation, including analytical normative documentation, pharmacopoeia etc.);

– metrological provision of tests (purchase, installation and adjustment of devices, control of verification and calibration procedures, qualification of measuring equipment etc.);

– provision of reagents, materials, tools and standard samples (purchase and control of circulation of used reagents, standard pharmacopoeia samples, auxiliary materials, tools, utensils etc.);

– Provision of activities and facilities for personnel safety.

3. Main process (analytical testing processes):

– ensuring communication with interested parties (contact with customers of analytical tests, supervisory bodies etc.);

– control of the test cycle (all stages of the test, from the receipt and registration of samples to the interpretation of analytical data and the formation of reports on the results of tests, if necessary – the development and validation of analytical techniques);

– actions in the case of receiving abnormal (unusual, unexpected) results, or outcomes beyond the specifications;

– registration and storage of arbitration samples.

The following groups of processes should be described in the Quality Manual, where it is also necessary to bring the graphic structure of the QMS process model and specify the conditions for the interaction of processes (their inputs and outputs), their monitoring, analysis, distribution of responsibility for each process (for example, using the "responsibility matrix"). Also needs to refer to lower level documents, such as Standard Operation Procedures (SOP) and instructions of various kinds (e. g. operating instructions for analytical equipment use, etc.).

The systematic measurement, analysis and adoption of corrective and preventive actions (implementation of the Deming-Shewhart Cycle, PDCA) within each individual process for small laboratories are not rational because they take a considerable amount of time. It believed that it is better to implement the PDCA Cycle in each of these process group data. The conditions for implementing these actions should also described in the Quality Manual. The monitoring and analysis procedures should documented in the relevant SOP.

By determining the required amount of document flow, the depth and accuracy of SOPs that describe a particular process, a registered quality person may use a methodology for assessing the risk by the quality of the test result. Using the internal classification of the criticality of the QMS processes, it is noted that some of the most critical processes require more detailed documentation and more extensive training of staff. For example, the FMEA method or other common methods and tools can used to establish a measurable characteristic of the criticality risk of each process.

These relatively new types of activities for laboratories such as internal audits, corrective and preventive actions, critical analysis by management, monitoring and analysis of processes, etc., need to be regulated in the documents of the laboratory QMS, applying the requirements of the relevant sections of the ISO 9001 standard. Recommendations for the implementation of internal audits are described in the standard ISO 19011:2011 [12]. In addition, it makes sense to use other ISO standards, such as 10012 (for metrological support) [13], 10013 (for QMS documentation) [14], 10015 (for personnel training) [15], and others.

4. Discussion

The analysis of the literature has shown that the construction of QMS of quality control laboratories is considered as recommendations for the development of regulatory documents of the QMS [16] and corrective and preventive actions [17] without describing the QMS processes and justifying the rationality of using the PDCA Cycle. The QMS of the laboratory, the approaches to formation of which are described above, will be a certain hierarchical system of those processes that influence the results of tests, with clear regulation and distribution of responsibility, mechanisms of self-evaluation and self-regulation. The construction of effective QMS in state laboratories for quality control of medicines will help to reduce the number and significance of inconsistencies and errors, to increase the probability of reliable results, to increase the awareness of staff. These measures should definitely be considered progressive both for the national quality control system for medicines and for the entire domestic pharmaceutical market.

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