UDC 658.562.6.012

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THE ANALYSIS OF CHANGED REQUIREMENTS CONCERNING QUALITY MANAGEMENT OF THE UPDATED VERSION OF NATIONAL GUIDELINES OF GOOD DISTRIBUTION PRACTICE OF MEDICINAL PRODUCTS

The article describes and analyzes the guidelines of the updated version of the National Guideline СТ-Н МОЗУ 42-1.0:2014 "Medicinal Products. Good Distribution Practice" (GDP Guidelines) as to implementation of the quality management requirements in the operation of a distribution company. Rational progressive innovations are highlighted, in particular those concerning the top management activity in the quality field, quality risk management, quality manual and monitoring of the quality systems functioning, management of outsourced activities, activity of a responsible person of the distribution company, change control systems and management of change systems with respect to all critical processes, corrective and preventive actions (CAPA), etc. Specific terms and requirements are also identified. According to the authors these terms and requirements need to be reviewed, clarified or harmonized with other industry standards.

Key words: Good Distribution Practice of Medicinal Products (GDP), GDP Guidelines, Quality Management, Quality Assurance, Distribution Company.

PROBLEM STATEMENT

In February 2014 the State Administration of Ukraine on Medicinal Products reported on the development of new regulations – Guideline СТ-Н МОЗУ 42-1.0:2014 "Medicinal Products. Good Distribution Practice" (hereinafter GDP Guideline), which is approved by the order of the Ministry of Healthcare of Ukraine on 05.02.14 № 100 [1]. This document was designed to update and harmonize according to EU regulatory document "Guidelines of 7 March 2013 on Good Distribution Practice of Medicinal Products for Human Use (2013/C 68/01)".

GDP National Guideline is recommended for organization of good distribution of medicinal products (MP) for human use in accordance with the principles and rules of Good Distribution Practice and for the development of quality systems by wholesalers including those that produce MP. It can be used for audit, certification and conformance inspection of enterprises to the principles and rules of GDP, licensing of MP wholesale and so on. This guideline applies to entities that distribute MP in Ukraine, including companies that produce MP, regardless of subordination and type of ownership. The updated version of Ukrainian GDP is substantially amended compared with the previous version – the Guideline СТ-Н МОЗУ 42-5.0:2008, approved by the order of the Ministry of Healthcare of Ukraine from 16.02.2009 № 95. Thus, one of the key aspects of the new wording is a significant expansion of the chapter "Quality Management", which now includes the following paragraphs: 1.1 "Principle", 1.2 "Quality System", 1.3 "Management of outsourced activities", 1.4 "Management review and monitoring" and 1.5 "Quality Risk Management" [1]. The spectrum of requirements as to the operation of distribution pharmaceutical companies (DPC) expanded significantly.

ANALYSIS OF RECENT RESEARCH AND PUBLICATIONS

A number of publications highlights the approaches to the implementation of specific requirements for the pharmaceutical industry (GMP, GDP and other practices [8, 10], but they do not touch upon a question of the QMS formation at DPC. Some authors explain the poor performance of implemented QMS at domestic DPC by mistakes at the early stages of QMS formation project: incorrectness of definition and poor processes regulation,

absence or inadequacy of indicators and methods of performance monitoring, formality of rules of corrective and preventive actions, lack of staff training and motivation, etc. In general information about the implementation of the QMS at pharmaceutical companies is contained in the regulations (Guidelines on good practices – GMP, GDP, GPP, etc.) [2, 4, 7, 9]. Publications, which explains in detail the implementation of QMS for pharmaceutical companies (especially – for DPC), are very few and they have a local character [1].

EMPHASIZING OF UNSOLVED EARLIER ASPECTS OF THE COMMON ISSUE

The reason of GDP Guideline is the detailed regulation of quality management activities. Obviously, this is a consequence of global trends observed in recent years in the regulatory area of the pharmaceutical sector, and at the level of other industries in the developed countries – even in recent decades. The main thesis of the modern concept of pharmaceutical companies activity is moving the focus from quality control at the certain points of the production process (in fact – from the conformance inspection of the measured parameters prescribed at the regulations tolerance range) to the ensured stability, reproducibility and readiness of all processes which affect the conformity of product to determined requirements anyway. It is referred to creating a so-called *Quality Assurance System* (*QAS*), which is a network of interrelated processes that create the conditions for the production of proper quality goods (services). In its turn, such a system, including planning, process control and continuous improvement actions is called *Quality Management System* (*QMS*). In recent decades the world's only standard that regulates the formation of such systems is ISO 9001 [5]. Implementation of QMS according to ISO 9001 was very popular: at the beginning of 2013 there were certified over 1.2 million of QMS in 185 countries.

It should be noted that although the main objective of government regulators is to control the QAS operation during the recent years industry standards have become closer to the universal requirements of ISO 9001 designed for QMS development, constant improvement of customer and consumer satisfaction and increase of the effectiveness of companies. Some of the ideas of ISO 9001 quality management are in the basis of the updated versions of guidelines of good practice, including GDP.

FORMULATION OF THE ARTICLE OBJECTS

In the context of a new version of the GDP Guideline and significant changes in regulatory requirements for QMS of MP distribution companies we consider important to analyze the new requirements of GDP Guideline (particularly the quality management) and development of proposals as to the practical implementation.

STATEMENT OF BASIC MATERIAL OF THE RESEARCH

Let's analyze the main point of new GDP Guideline requirements.

In the paragraph "Quality Management" the GDP National Guideline requires the support of quality system operation with setting out responsibilities, processes and principles of risk management according to the activity types of MP distribution company. GDP Guideline requires to clearly define and systematically review all distribution activities [2, p. 1]. There is the issue in this fragment – the term "quality system" (QS) which is interpreted in the guideline as «the complex of all aspects of the system that implements the quality policy and ensures the achievement of the quality.» However, the term has not been used in international standards (including ISO 9000) and other documents of such level for more than 10 years and is an anachronism, because there is generally accepted term *quality management system* or *quality assurance system* (depending on the application) at the present level of development of the science of quality. Thus, in the standard ISO 9000:2007 [6, § 3.2.3] quality management system is treated as a «management system to direct and control an organization with regard to quality» and the term quality assurance [6, § 3.2.11] – as «part of quality management focused on providing confidence that quality requirements will be fulfilled». So, it is more correctly to use the term QAS in the Guideline on good practice in general and GDP in particular as it fully conveys the concept of these practices. However, the new version of the GDP Guidelines does not even contain any links to ISO 9000 standards, which took place in the previous version.

Later in the chapter «Quality Management» the GDP Guideline includes the requirement that also deserves special attention: «all critical steps of distribution processes and significant changes should be justified and where relevant validated» [2, p. 1]. Again, for unknown reasons the term «validation» is not listed in the chapter «Terms and Definitions» and it is not specified how to understand the concept of «critical steps of the distribution process» and what changes should be considered significant. Obviously, it is understood that through the quality risk identification and evaluating a distributor company has to identify the most critical processes in their activity and validate them. But there may

be a misunderstanding and double-meanings about setting the boundaries of criticalness of such processes, the overrun of which should be considered as a pretext for carrying out the validation work. We believe that the Guideline should contain more detailed explanation on this. However, referring to ISO 9000 an interpretation of the term validation can be found [6, § 3.8.5] «validation – this is a confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled». It is also noted that the conditions for validation can be real or simulated – it could be a significant factor for a distribution company. Standard ISO 9001 includes even more important information which specifies validation objects in p. 7.5.2: «The organization shall validate any processes for production and service provision where the resulting output cannot be verified by subsequent monitoring or measurement and, as a consequence, deficiencies become apparent only after the product is in use or the service has been delivered. Validation shall demonstrate the ability of these processes to achieve planned results» [5, § 7.5.2].

The next key innovation in the GDP Guideline is to determine the leading role of the top management of the enterprise because now it is emphasized that QS is their responsibility and requires their active participation in the management system [2, § 1.1]. This provision is consistent with the relevant requirements of ISO 9001, where a certain chapter [5, p 5] is dedicated to the issue of top management liability. However, unlike to ISO 9001, the GDP Guidelines does not include more or less specific requirements to the top management activity; there are only general provisions.

Chapter 1.2 «Quality System» of the GDP Guideline explains the scope of distributor quality system: «The quality managing system should encompass the organizational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the product delivered maintains its quality and integrity and remains within the legal supply chain during storage and/or transportation». The term QMS (in EU GDP Guideline – system for managing quality) named in the paragraph of the Guideline in general reflects the content of the paragraph, but looks strange as it is found only a few times more in the text of the document mixed with the term QS (for example, in paragraph 1.3, in part III of paragraph 1.4 and in some more).

The same paragraph 1.2 states that «The quality system must be fully documented and its *efficiency* must be verified (in EU GDP Guideline – *effectiveness*!). In our opinion, the application of the term efficiency in relation to QS looks inappropriate in such document as a Guideline because this term as opposed to *effectiveness* (used in all ISO 9000 texts) includes not just "extent to which planned activities are realized and planned results achieved", but also the establishment of "the relationship between the result achieved and the resources used" [6, §. 3.2.14-3.2.15]. It is a questionable assumption that representatives of regulatory authorities or other parties can somehow determine the amount of resources spent to achieve the quality objectives because these resources include the staff and infrastructure (equipment and facilities, premises, means of communication), documentation and much more. Moreover, the cost of these resources is not a one-time thing: it occurs during the continuing organization activity. In addition to determine the effectiveness of QS it is necessary to compare the ratio «cost-benefit» for various periods of time.

Paragraph 1.2 of the new GDP Guideline also requires that the distributor ensures that all components of QS are provided with the necessary resources: «a sufficient number of competent personnel, appropriate and adequate facilities, equipment and technical means». Similar requirements in more details are included in the standard ISO 9001, which distinguishes three categories of resources: personnel (human resources), the infrastructure and working environment [4, p 6]. We consider a defect of the new Guideline is the lack of requirements for the working environment (the conditions under which the work performed including physical, environmental, social and other factors, such as noise, temperature, humidity, lighting or weather conditions, motivation and encouragement systems that create microclimate in the team, etc.). Parameters of the working environment are one of the key factors influencing the quality of MP and the customer service throughout all processes of distribution.

There is another innovation in the Guideline: «A *quality manual* or equivalent documentation approach should be established". We would like to note that the previous versions of the GDP Guideline did not include any requirements for such document as a quality guideline. This is a reasonable requirement dictated by the need to describe the available quality system as a document approved by top management. ISO 9001 contains the same request, which sets out comprehensive information about the purpose of quality manual development and its components [5, § 4.2.2].

Another GDP Guideline thesis agreed-on with ISO 9001 is the need for the appointment of an *Responsible Person* (*RP*), who should have clearly defined powers and responsibilities to ensure that

QS implemented and maintained [2, § 1.2]. The role and functions of the RP stated in paragraph 2.2 «Responsible Person", where among other things it is stated that RP "must have appropriate experience and competence, must be trained with GDP and have appropriate knowledge": without any specification that would be highly desirable. Moreover, it is stated that "it is desirable for RP to have a degree in pharmacy" – this recommendation also raises many questions.

We should note that emphasizing requirements for the RP in a separate paragraph of the GDP Guideline and its specification is a certainly expected and progressive measure, because the issue of the RP`s activity at the pharmaceutical companies is still one of the urgent problems of practical pharmacy. It is also can be stated that the concept of the RP is somewhat different in case with ISO 9001 and GDP Guideline. For example, ISO 9001 in paragraph 5.5.2 [5] suggests that Management representative should be from among the top management of the organization and the Guideline does not include such a requirement. GDP Guideline requires RP to ensure the functioning of virtually all critical processes of distributor company (permitting activities, functioning of initial and continuing personnel training programs, MP withdrawal operations, consideration of customers complaints, suppliers and recipients approval, approval of any contracting (outsourcing) works that may affect GDP, self-inspection and implementation of necessary corrective actions, storage of all duty delegation protocols, deciding on the final disposition of returned, rejected, recalled or falsified products, etc.). On the other hand, the standard 9001 provides that the Management representative (authorized person) should analyze the performance of QMS processes, inform the management about the obtained results and the need to take corrective actions and resources. Therefore, we believe it appropriate to organize activities of the RP subject to the ISO 9001.

A major innovation in the new GDP Guideline is the use of concepts - *change control system* and *management of change system* in respect of all critical processes. Such a system should "incorporate quality risk management principles, and be proportionate and effective". However, there is no mention of how it is possible to determine this effectiveness.

Final guidelines of the paragraph 1.2 stipulates all the aspects that QS must guarantee including: ensuring conditions of purchase, maintenance, MP supply, specification of management responsibility, products are delivered to the right recipients within a satisfactory time period, documentation and investigation of deviations from approved procedures, appropriate corrective and preventive actions (commonly known as CAPA) are taken to correct deviations and prevent them in line with the principles of quality risk management. As can be seen from the above, the new version of the GDP Guideline stipulates systemic aspects of the distributor company operation wider than the last.

Another innovation in the Guideline is the paragraph 1.3 "Management of outsourced activities". This activity is related to the purchasing, storage, supply or export of MP and it must be covered by the QMS and should include assessment of compliance and competence of a performer, the responsibilities and processes of information of parties involved in activities relating to quality, regular monitoring and observation of the performer`s actions, and the definition and implementation of all improvements needed on a regular basis. We consider this is a progressive innovation that meets modern concepts of quality management. These requirements are also consistent with ISO 9001 [5, § 4.1].

The GDP Guideline in paragraph 1.4 «Management review and monitoring», which implies the existence of the quality system review procedures, agreed upon with the requirements of ISO 9001 [5, § 5.6]. This review, among other things, should include evaluation of the achieved goals of QS, assessment of performance indicators (quality indicators) that can be used to monitor the effectiveness of processes within the quality system, feedback on outsourced activities, risk assessments and audits, inspections, conclusions and audits by customers, changes in regulatory requirements that may affect the QMS, changes in business conditions and goals. It is assumed to promptly document the results of each inspection and inform the personnel of an enterprise about the results.

Paragraph 1.5 "Quality Risk Management" of the new Guideline is dedicated to the requirements as to the quality risk management as a systematic process for the assessment, control, communication and review of risks to the quality of medicinal products. It can be applied both proactively and retrospectively. Noted: "Quality risk management should ensure that the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient. The level of effort, formality and documentation of the process should be commensurate with the level of risk". In general, these requirements are also expected, as the concept of risk management is increasingly being implemented at pharmaceutical, food and other areas. However, it should be noted that the term "quality

risks" also needs clarification: the current Guideline СТ-Н МОЗУ 42-4.2:2011 "Medicinal Products. Quality Risk Management (ICH Q9)" includes the term "quality risks" as in a number of other standards [3].

CONCLUSIONS AND PROSPECTS FOR FURTHER RESEARCH

All other requirements of the new GDP Guideline are not significant in comparison with the previous version of this document, and therefore do not require detailed analysis. As for the changes examined the following conclusions can be made:

1) as a whole, the new version of the GDP Guideline compares favorably with the previous one, because includes more advanced requirements and regulations;

2) some of the terms used in the Guideline СТ-Н МОЗУ 42-1.0:2014 require coordination with similar terms used in original english version and other guidelines on good practices and international standards. One of the key terms to be altered is a "quality system", as in other GxP Guidelines the term "pharmaceutical quality system" is applied (Pharmaceutical Quality System, PQS) – management system that directs and controls the activity of the pharmaceutical company as to quality [3];

3) some new requirements of the Guideline 42-1.0:2014 (in particular regarding quality management) are too general and non-specific and therefore may cause misunderstanding or ambiguous interpretation by a MP distribution companies;

4) developing QMS a distribution company can use the requirements of ISO 9001 as a basis, which should be complemented with the more specific requirements of GDP Guideline. Based on the combination of the requirements, the QMS formation may become more productive. This particularly applies to the implementation of the process approach that is not required by the GDP Guideline, but it is the basis for the construction of any modern management systems.

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УДК 658.562.6.012

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АНАЛІЗ ОНОВЛЕНИХ ВИМОГ ЩОДО УПРАВЛІННЯ ЯКІСТЮ НАЦІ-ОНАЛЬНОЇ НАСТАНОВИ З НАЛЕЖНОЇ ПРАКТИКИ ДИСТРИБУЦІЇ ЛІКАРСЬКИХ ЗАСОБІВ

У статті розглянуті та проаналізовані положення нової версії національної Настанови СТ-Н МОЗУ 42-1.0:2014 «Лікарські засоби. Належна практика дистрибуції». Виділені раціональні і прогресивні нововведення, що стосуються діяльності керівництва у сфері забезпечення й управління якістю; визначення, оцінювання, аналізування й управління ризиками для якості ЛЗ; настанови з якості як основоположного документу системи якості; систематичного огляду і моніторингу функціонування системи якості вищим керівництвом; аутсорсингової діяльності дистриб'ютора ЛЗ; функцій уповноваженої особи компанії-дистриб'ютора; системи контролю змін і системи управління змінами відносно всіх критичних процесів дистрибуції лікарських засобів; коригувальних і запобіжних дій (CAPA) та деякі інші положення. Також визначені окремі терміни і вимоги Настанови СТ-Н МОЗУ 42-1.0:2014, які, на думку авторів, потребують перегляду з метою уточнення чи виправлення формулювання, або ж узгодження з іншими галузевими нормативами.

Ключові слова: належна практика дистрибуції лікарських засобів (GDP), Настанова з GDP, управління якістю, забезпечення якості, дистриб'ютор лікарських засобів.

УДК 658.562.6.012

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АНАЛИЗ ОБНОВЛЕННЫХ ТРЕБОВАНИЙ К УПРАВЛЕНИЮ КАЧЕСТВОМ НАЦИОНАЛЬНОГО РУКОВОДСТВА ПО НАДЛЕЖАЩЕЙ ПРАКТИКЕ ДИСТРИБУЦИИ ЛЕКАРСТВЕННЫХ СРЕДСТВ

В статье рассмотрены и проанализированы положения новой версии национального Руководства СТ-Н МОЗУ 42-1.0:2014 «Лекарственные средства. Надлежащая практика дистрибуции», касающиеся реализации требований к управлению качеством в функционировании компании-дистрибьютора. Выделены рациональные прогрессивные нововведения, в частности, касающиеся деятельности руководства в области качества, управления рисками для качества, Руководства по качеству, обзора и мониторинга функционирования системы качества со стороны руководства, управления договорной (аутсорсинговой) деятельностью, деятельности Уполномоченного лица компании-дистрибьютора, системы контроля изменений и системы управления изменениями в отношении всех критических процессов, корректирующих и предупреждающих действий (CAPA) и некоторых других. Также определены отдельные термины и требования, по мнению авторов требующие пересмотра, уточнения или согласования с другими отраслевыми нормативами.

Ключевые слова: надлежащая практика дистрибуции лекарственных средств (GDP), Руководство по GDP, управление качеством, обеспечение качества, дистрибьютор лекарственных средств.

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Надійшла до редакції:
28.03.2014