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ODESA NATIONAL MEDICAL UNIVERSITY

Faculty of Pharmacy

Department of General and Clinical Pharmacology and Pharmacognosy

APPROVE

Vice-rector for scientific and pedagogical Work

_____Eduard BUTYACHKIVSKY

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METHODOLOGICAL RECOMMENDATIONS FOR LECTURES ON THE ACADEMIC DISCIPLINE QUALITY SYSTEM IN PHARMACY

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Head of the Department  (Yaroslav ROZHKOVSKY)

Developers:

Rozhkovsky Yaroslav Volodymyrovych Doctor of Medical Sciences, Professor, Head of the Department of General and Clinical Pharmacology and Pharmacognosy

Eberle Lidia Viktorivna Candidate of Biological Sciences, Associate Professor

Karpova Olga Viktorivna Assistant

Lecture No. 1

Topic 1. The evolution of the global development of quality management science and its role in pharmacy.

Relevance of the topic. The pharmaceutical industry in developed countries is among the most dynamic and profitable sectors. However, it also functions as a unique market segment regulated by governmental authorities and controlled by insurance medicine. Enterprises that successfully restructure and withstand intense competition will be able to compete in international markets.

Objective: to form theoretical knowledge of the evolution of the global development of quality management science and its role in pharmacy among higher education students.

Key concepts: quality, quality management, quality management system, quality loop/circle, individual quality control, workshop quality control, acceptance quality control, statistical quality control, total quality management.

Lecture plan and organizational structure:

1. Key terms in quality management.
2. Stages of development in quality management worldwide.
3. Fundamental concepts of quality management.

Lecture content

Key terms in quality management

The category of "quality" has a multifaceted nature in terms of its origin and existence, applicable in various spheres of societal activity. Therefore, it can be considered a philosophical, social, and economic category, among others.

According to the international standard ISO 9000:2000, *quality* is understood as the degree to which a set of inherent characteristics of an object (product or service) meets the requirements established in regulatory documents.

Quality management refers to the actions carried out during the development, production, and realization of an object to form, ensure, and maintain the specified level of quality.

Quality management is implemented within the framework of a quality management system. *A quality management system* (*quality system*) is a management system for directing and controlling an organization concerning quality.

The quality loop/cycle is a conceptual model of interdependent activities that affect quality at various stages of the product or service lifecycle.

Stages of development in quality management worldwide

The stages of quality management development in the world began with *individual quality control*, which was prevalent in production until the late 19th century. In this form of management, one worker or a small group of workers were responsible for manufacturing products. Each worker had the opportunity to fully control the quality of their work, thereby ensuring the quality of the product.

The development of industrial production and the deepening of internal work division led to the emergence of *workshop quality control* in the early 20th century. In this form of management, functions, and responsibilities for quality were distributed among individual workers and workshop supervisors. Workshop control was based on the principles of scientific quality management developed by the renowned American expert Frederick Taylor. Taylor's methodology aimed to set tolerances for quality indicators, measure their values, and classify production as acceptable or defective based on whether the indicator fell within the tolerance. However, the concepts of "quality standard", "tolerance" and "defect" were only applied to individual products (components and parts) and did not extend to batches (flows) of production and technological processes.

Acceptance quality control. During the Second World War, the development of mass production in industrial enterprises and the increase in production volumes led to the separation of technical control from production operations. Independent technical control services with staff controllers headed by a chief were established in industrial enterprises, who were subordinate to the enterprise's management.

Statistical quality control. The most significant characteristic of the spread of statistical quality control was the transition from 100 % inspection to sampling inspection, where control data are systematically sampled during the production process according to a predetermined plan and processed using mathematical statistical methods. The industrial application of statistical quality control methods is associated with the work of Walter Shewhart, an expert from an American company. In 1924, he developed *Statistical Quality Control* (*SQC*). Shewhart demonstrated that all types of products and services, as well as the processes where they are formed, are subject to deviations from specified values, which he termed variations. For continuous monitoring of the situation, he proposed using control charts with control limits – Shewhart charts. Thus, the main idea of W. Shewhart's quality management model was to improve quality by reducing process variability.

Total quality control. This concept was introduced by Armand Feigenbaum back in 1957. He proposed making total quality control the responsibility of a special administrative department solely dedicated to quality control. Feigenbaum's main idea was to implement quality at the early stages of product creation rather than merely inspecting the quality of the finished product. Based on the general methodology of total quality control, Feigenbaum put forward the concept of *Total Quality Control* (*TQC*). Within this concept, quality was regarded as the singular and most significant force in organizational success and company growth. Feigenbaum's main objectives for TQC included:

1) predictive elimination of potential discrepancies in the production process at the design stage,

2) quality control of incoming products (incoming quality control),

3) production management,

4) supervision of compliance with specified quality requirements.

The implementation and development of the TQC concept varied unevenly across different countries. Despite originating from the USA and Europe, this system gained the most widespread adoption in Japan.

It was in Japan that the ideas of TQC were met with enthusiasm, and they received further development thanks to Professor Kaoru Ishikawa. Ishikawa advocated for involving all employees of the company in the quality improvement process. Therefore, the Japanese approach became known as *Company Wide Quality Control* (*CWQC*). According to this new approach to quality management, companies focused on the following goals:

1) Quality above short-term profits.

2) People in the management system – involving all employees in the quality management process.

3) Consumer-centricity – shifting the mindset towards the perspective of the consumer.

4) Wide implementation of statistical control methods.

The pioneers of quality management concepts contributed to the transition to the era of total quality management.

The concept of product quality assurance based on international standards ISO 9000

The international standards in the field of quality management, ISO 9000 series, are based on the principles of the modern concept of *Total Quality Management* (*TQM*). The ISO standards concept answers the question of what needs to be done to ensure quality, while the TQM concept addresses how to do it.

The primary philosophy of TQM is based on the principle of "continuous improvement." Regarding quality, the guiding principle is "striving for zero defects", for costs – "zero non-productive costs" and for supplies – "just in time".

12 principles underlying TQM:

1. All organization activities are oriented towards satisfying the needs and expectations of customers, upon which its success in the market economy depends.
2. Viewing production relationships among employees as customer-supplier relationships.
3. Continuous improvement of production and quality activities.
4. Comprehensive and systematic solutions for quality assurance tasks at all stages of an object's life cycle.
5. Shifting the main efforts in quality towards human resources (emphasis on employee attitudes towards work, on leadership style).
6. Involvement of all personnel in addressing quality problems (quality is everyone's business).
7. Continuous improvement of organization employees' competence.
8. Focus not on detecting, but on preventing non-conformities.
9. Approach to quality assurance as a continuous process, where the quality of the object at the final stage is a result of achieving quality at all previous stages.
10. Optimization of the relationship in the triad "quality – costs – time".
11. Ensuring the accuracy of quality data through the use of statistical methods.
12. Continuous quality improvement.

Fundamental concepts of quality management

The concept of Walter Shewart

W. Shewart first proposed a cyclical model that divides quality management into 4 stages. The idea of this cycle was later developed, refined, and recommended for use by his student Edward Deming. In memory of the joint work of these outstanding scholars, the cycle is also called the Deming – Shewart cycle.

The concept of Edward Deming

E. Deming first justified and formulated the necessity to abandon the control of production as a management principle, focusing on managing production processes instead, and demonstrated the advantage of investing in preventive actions. Deming's principle of continuous improvement suggests that the process of quality management, assurance, and further improvement occurs continuously. According to Deming, the quality management model (Deming cycle) is implemented based on the following actions:

- Planning (Plan)
- Execution (Do)
- Check (Check)
- Action (Action)

This cycle became the basis of the Total Quality Management (TQM) concept.

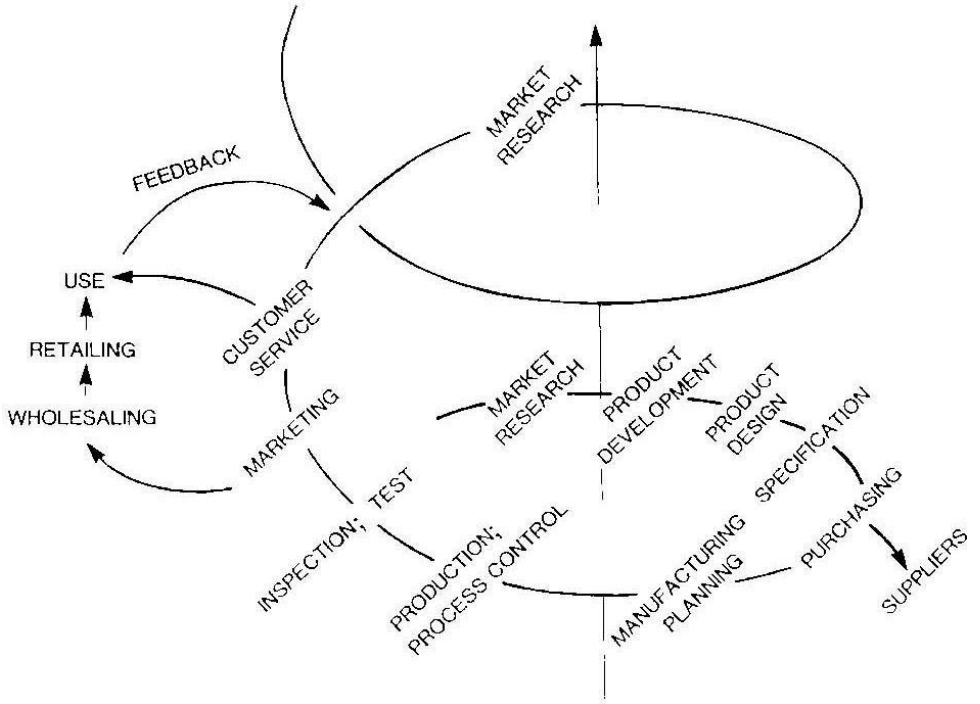
In his book "Out of the Crisis," published in 1986, E. Deming formulates 14 key principles of quality management and considers them as the basis for transforming American industry. Deming's postulates orient companies toward long-term and sustainable work, urging managers to create conditions for continuous improvement of enterprise activities, prioritizing the interests and aspirations of people.

An illustrative example of Deming's philosophy, expressed in his 14 postulates, can be the "Joiner Triangle" proposed by Brian Joiner, the leader of the American company "Joiner Associates Inc.". All vertices of the triangle have a direct connection with Deming's postulates:

- passion for quality,
- all as one team,
- scientific approach.

Joseph Juran's Concept

J. Juran was the first to justify the transition from quality control to quality management. He developed the famous "Juran's Quality Spiral" (or "Juran's Spiral"). This timeless spatial model defines the main stages of quality management work.



Juran's Spiral

Joseph Juran is the author of *the concept of Annual Quality Improvement* (*AQI*).

The most important principles of AQI are:

1) planning by management of quality improvement measures at all levels and in all areas of enterprise activity;

2) development of measures aimed at preventing errors in quality management;

3) transition from administration (top-down orders) to systematic management of all activities in the quality sphere.

Armand Feigenbaum's Concept

A. Feigenbaum developed a five-level model of quality management system.

The basic first level involves preparing for the design of the quality assurance system.

The second level entails designing the quality assurance system.

The third level is the activation stage of the system.

The fourth level involves implementing the system.

The final fifth level is comprehensive quality control.

The Ettinger – Sittig Concept

Among the quality management models developed in the 1950s, the Ettinger – Sittig model stands out. Unlike Feigenbaum's model, this model takes into account the need to manage functional quality and the influence of demand on product quality. According to this model, the first stage of each quality management cycle is studying demand.

Kaoru Ishikawa's Concept

K. Ishikawa formulated the basic principles of the role of quality management in the Japanese economy. In the early 1950s, he began a campaign to train top-level managers of firms in statistical control methods. Ishikawa introduced an original graphical method for analyzing cause-and-effect relationships to world practice, which became known as his "Ishikawa diagram" and became part of the seven tools of quality control.

Genichi Taguchi's Concept

G. Taguchi named his *concept "quality engineering"*. The key principle of Taguchi's concept is managing deviations from the nominal value. Taguchi's methods allow for designing products and processes that are insensitive to the influence of "noise", which are variable factors causing dispersion of parameter values that are difficult, impossible, or expensive to change. From an economic standpoint, even minor "noises" reduce profits because they increase production costs and warranty expenses. Taguchi emphasizes the stages preceding product design, as it is at these stages that the task of achieving robustness is addressed.

Philip Crosby's Concept

In his *"Zero Defects" concept*, Philip Crosby argues that improving quality does not require significant expenses because, in reality, improving quality simultaneously increases productivity. This is because many cost items associated with eliminating detected defects and reworking defective products are reduced. Therefore, the key to the success of the "Zero Defects" program is the principle of not accepting any initial level of acceptability for defects (zero defect level).

Crosby's 14 principles ("absolutes") outlining the sequence of actions to ensure quality in enterprises also gained wide popularity.

1. Clear definition of the organization's management commitment to quality, as well as their responsibility in decision-making.
2. Form a team that will implement the quality assurance program.
3. Determine methods for assessing quality at all stages of its formation, as well as current and potential quality problems.
4. Organize accounting and determination of costs associated with quality assurance.
5. Communicate the management's quality policy to all employees of the enterprise, ensuring conscious employee attitudes towards quality. Define the costs of poor-quality work and convey this information to subordinates.
6. Develop procedures for corrective actions in quality assurance.
7. Develop a program for defect-free production (the "zero defects" system).
8. Organize training for mentors who will implement the zero-defect program.
9. Organize regular quality days (zero defects days).
10. Motivate employees to set personal goals that imply quality improvement.
11. Develop procedures to eliminate the causes of defects.
12. Develop a program for the moral encouragement of employees for meeting quality requirements.
13. Create a task force (special committee) consisting of quality professionals to implement the zero-defect program.
14. Organize ongoing training for personnel in the field of quality.

So, starting from the 1920s until the early 1980s, the main problem of quality was perceived and addressed by experts primarily as an engineering-technical issue of controlling and managing the variability of production and manufacturing processes, while the management problem was seen mainly as an organizational and even socio-psychological issue. In the 1950s-1980s, there was an active convergence of quality assurance methods with the concepts of general management. Quality systems began to widely incorporate the toolkit of management science. Addressing quality challenges required the creation of an adequate organizational structure. This structure should include all departments, and moreover, every employee of the company, at all stages of the product life cycle or quality loop. From these considerations, the concept of TQM logically emerged. The implementation of TQM into the activities of modern enterprises has become one of the most significant innovations in ensuring a proper level of quality and competitiveness in recent years.

General material and educational support for the lecture: presentation materials for the lecture.

Self-assessment questions:

1. The combination of organizational structure, methods, processes, and resources necessary for quality management is:

A) quality loop
B) quality system
C) quality management
D) quality circle
E) quality management

2. The achievement of the required product quality was accomplished through the use of means and methods of technical control at such stages of the evolution of quality management science as:

A) workshop quality control
B) acceptance quality control
C) statistical quality control
D) overall quality control
E) total quality management

3. The most comprehensive disclosure of subordinates' abilities and the elimination of coercion is one of the main principles of the concept:

A) F. Taylor
B) W. Shewhart
C) F. Crosby
D) A. Feigenbaum
E) K. Ishikawa

4. Managing deviation from nominal value is a fundamental principle of the quality management concept:

A) K. Ishikawa
B) G. Taguchi
C) J. Juran
D) W. Shewhart
E) E. Deming

List of references:

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2. Nalezhni praktiki u farmatsiyi: navch. posib. dlya studentiv visch. navch. zakl. / V. O. Lebedinets, O. V. Tkachenko, Yu. I. Gubin ta in. Harkiv: NFaU: Zoloti storinki, 2017. 296 s. [in Ukrainian]

Lecture No. 2

Topic 2. Regulatory framework for quality management of medicinal products.

The relevance of the topic. Since the 1990s, various industry-specific versions of international quality standards have been emerging. Establishing effective and efficient quality management systems in enterprises that comply with the provisions of international standards is a guarantee of meeting consumer requirements and, consequently, the economic success of the enterprise.

Objective: to form theoretical knowledge of higher education students on the application of general principles and basic methods of development, implementation, maintenance, and improvement of quality management systems of pharmaceutical enterprises/organisations in accordance with the provisions of international standards.

Key concepts: standard, international standard, international standardization organization, national standard, national standardization body, mandatory certification, voluntary certification, social responsibility.

Lecture plan and organizational structure:

1. Basic types of standards.
2. ISO 9000 series standards.
3. ISO 10000 series standards.
4. ISO 13485 standard.
5. ISO 14000 series standards.
6. ISO 19011 standard.
7. ISO 22000 standard.
8. Standards for social responsibility.
9. ISO 27000 series standards.
10. ISO 31000 series standards.
11. ISO 37001 standard.
12. Standards for health and safety management systems.

Lecture content

Basic types of standards

Since the 1990s, various sectoral versions of international quality standards have been developed.

A standard is a regulatory document based on consensus (general agreement of the majority of interested parties), adopted by a recognized body, establishing rules, guidelines, or characteristics for general and repeated use, aimed at achieving an optimal level of orderliness in a certain area.

An international standard is a standard adopted by an international standardization organization and available for a wide range of users.

An international standardization organization is an organization engaged in standardization, membership in which is open to the relevant national bodies of all countries. One such organization is the *International Organization for Standardization* (*ISO*).

A national standard is a standard adopted by the national standardization body and available to a wide range of users.

A national standardization body is a standardization body recognized at the national level, with the right to be a national member of relevant international and regional standardization organizations.

International standards do not have mandatory status for all participating countries. Any country in the world has the right to apply or not apply them. The decision to apply the ISO international standard is mainly related to the country's level of participation in international division of labor and the state of its foreign trade.

International standards are adopted as national standards provided they are accepted by the national standardization body.

Types of Certification:

1. *Mandatory Certification*. Certification for compliance with requirements that are classified by regulatory documents as mandatory and must be complied with, as well as requirements provided for by current legislative acts; conducted only by state certification bodies.

2. *Voluntary Certification*. Certification for compliance with requirements that are not classified by regulatory documents as mandatory requirements.

ISO 9000 Series Standards

ISO 9000:2015 Quality management systems — Fundamentals and vocabulary

This standard contains basic concepts, principles, and terminology of quality management systems, as well as the basis for other quality management system standards. Every organization intending to establish and implement a quality system should refer to this standard.

ISO 9001:2015 Quality management systems — Requirements

The standard contains a comprehensive list of quality system elements relevant to all stages of the product lifecycle and corresponding measures, from which an organization can select and apply elements according to its needs. All requirements are generic and intended for application in any organization, regardless of its type or size, as well as the type of products and services it produces or provides.

ISO/TS 9002:2016 Quality management systems — Guidelines for the application of ISO 9001:2015

The standard provides guidance on implementing the requirements of ISO 9001:2015, including examples. It is useful both in preparing a quality management system for certification and for further development.

ISO 9004:2018 Quality management — Quality of an organization — Guidance to achieve sustained success

This standard contains guiding principles for enhancing an organization's ability to achieve sustained success through evaluation and improved effectiveness. It is useful for organizations already certified that strive to achieve the best results beyond basic requirements.

ISO 10000 Series Standards

The ISO 10000 series standards are companion standards that support the ISO 9000 series of standards.

ISO 10001:2018 Quality management — Customer satisfaction — Guidelines for codes of conduct for organizations

The standard for codes of corporate ethics in customer interaction covers issues such as product delivery and service provision, product returns, handling of customer information, advertising, and after-sales service conditions.

ISO 10002:2018 Quality management — Customer satisfaction — Guidelines for complaints handling in organizations

The standard for handling customer complaints provides guidance for organizations in planning, designing, developing, implementing, supporting, and improving an effective process for handling complaints related to any type of activity associated with products and services.

ISO 10003:2018 Quality management — Customer satisfaction — Guidelines for dispute resolution external to organizations

The standard for resolving disputes outside the organization helps organizations plan, maintain, and improve an effective process for resolving disputes outside the organization. It also assists in selecting service providers for dispute resolution and developing recommendations to avoid similar situations in the future by increasing customer satisfaction.

ISO 10004:2018 Quality management — Customer satisfaction — Guidelines for monitoring and measuring

The standard for monitoring customer satisfaction provides recommendations for identifying and implementing processes for monitoring and assessing customer satisfaction.

ISO 10005:2018 Quality management — Guidelines for quality plans

The standard contains guiding principles for the development and implementation of action plans to ensure proper quality – quality programs.

ISO 10006:2017 Quality management — Guidelines for quality management in projects

This standard provides guidelines for quality management in projects.

ISO 10007:2017 Quality management — Guidelines for configuration management

The purpose of this standard is to enhance the overall understanding of the subject matter and promote the use of configuration management.

ISO 10012:2003 Measurement management systems — Requirements for measurement processes and measuring equipment

This standard establishes general requirements and provides guidance on managing measurement processes and metrological confirmation of suitability for measuring equipment used to maintain and demonstrate compliance with metrological requirements.

ISO 10013:2021 Quality management systems — Guidance for documented information

This standard provides guidance on the development and maintenance of documentation necessary to ensure the effective functioning of a quality management system tailored to the specific needs of the organization.

ISO 10014:2021 Quality management systems — Managing an organization for quality results — Guidance for realizing financial and economic benefits

This standard is intended for top management. It provides guidance on realizing financial and economic benefits through effective implementation of the eight quality management principles outlined in ISO 9000:2005.

ISO 10015:2019 Quality management — Guidelines for competence management and people development

ISO 10018:2020 Quality management — Guidance for people engagement

This standard provides guidance on involving personnel in the implementation of a quality management system within the organization and enhancing their participation, as well as increasing their competence within the organization.

ISO 10019:2005 Guidelines for the selection of quality management system consultants and use of their services

This standard is intended to assist organizations in selecting a consultant for their quality management system.

ISO 13485 Standard

EN ISO 13485:2016/A11:2021 Medical devices — Quality management systems — Requirements for regulatory purposes (ISO 13485:2016)

This standard establishes the requirements for a quality management system when an organization needs to demonstrate its ability to consistently provide medical devices and related services that consistently meet customer and applicable regulatory requirements.

ISO 14000 Series Standards

International ISO 14000 series standards are designed for companies and organizations of any type that need practical tools to manage their environmental responsibilities.

The main standards in this series include:

ISO 14001:2015 Environmental management systems — Requirements with guidance for use

The standard establishes the requirements that enable any organization to develop, implement, maintain, and improve an environmental management system.

ISO 14004:2016 Environmental management systems — General guidelines on implementation

The standard is of a recommendatory nature and contains guidelines for the creation, implementation, operation, and improvement of an environmental management system, as well as its interaction with other management systems of the organization.

ISO 14050:2020 Environmental management — Vocabulary

The standard defines the main concepts related to the environmental activities of organizations, as published in the ISO 14000 series of international standards.

ISO 19011 Standard

Стандарт ISO

ISO 19011:2018 Guidelines for auditing management systems

The standard contains guidelines for planning and conducting management system audits.

ISO 22000 Standard

ISO 22000:2018 Food safety management systems — Requirements for any organization in the food chain

The standard establishes requirements for a food safety management system that enables an organization, directly or indirectly involved in the food chain, to plan, implement, maintain, and update its food safety management system. This ensures that products and services are safe when used as intended.

Standards for social responsibility

ISO 26000 Standard

ISO 26000:2010 Guidance on social responsibility

Social responsibility is the ability of an organization or enterprise to assess the social consequences of its activities.

ISO 26000 standard provides instructions on the basic principles of social responsibility and ways to integrate socially responsible behavior into existing strategies, systems, practices, and processes of the organization.

The International Standard SA 8000:2014 (Social Accountability 8000)

Standard defines requirements for social protection, enabling organizations to develop, implement, and maintain policies and management methods for social protection issues.

The United Nations Global Compact

The idea of the United Nations Global Compact was proposed at the 1999 World Economic Forum. It is a special initiative of UN Secretary-General Kofi Annan, whose mission is to call on companies to build their activities and strategies based on the 10 Principles in the areas of human rights, labor relations, environmental protection, and anti-corruption efforts.

ISO 27000 Series Standards

ISO/IEC 27000:2018 Information technology — Security techniques — Information security management systems — Overview and vocabulary

The standard contains terms and definitions used in the standards of information security management systems.

ISO/IEC 27001:2022 Information security, cybersecurity and privacy protection — Information security management systems — Requirements

The standard establishes requirements for an information security management system to demonstrate an organization’s ability to protect its information resources.

ISO/IEC 27002:2022 Information security, cybersecurity and privacy protection — Information security controls

The standard provides the best practical advice on information security management for those responsible for creating, implementing, or maintaining information security management systems.

ISO 31000 Series Standards

ISO 31000:2018 Risk management — Guidelines

The standard contains descriptions of the principles and processes upon which risk management is based.

ISO/TR 31004:2013 Risk management Guidance for the implementation of ISO 31000 Status : Withdrawn

IES 31010:2019 Risk management — Risk assessment techniques

The standard presents modern methodologies for selecting and applying general risk assessment methods, considering their application scope, advantages, and disadvantages for each.

ISO 37001 Standard

ISO 37001:2016 Anti-bribery management systems – Requirements with guidance for use

As of the current period, a new version of the ISO/DIS 37001 standard is being developed to replace ISO 37001:2016.

The standard defines requirements and provides guidance on the development, implementation, maintenance, and improvement of anti-corruption management systems.

Standards for the health and safety management system

OHSAS 18001 Standard

OHSAS 18001:2007 Occupational Health and Safety Management Systems. Requirements.

The OHSAS 18001 standard sets forth requirements for occupational health and safety management systems in the workplace and is designed to assist organizations in controlling the health and safety of employees in the workplace.

OHSAS 18002:2008 Occupational health and safety management systems — Guidelines for the implementation of OHSAS 18001:2007

ISO 45001 Standard

ISO 45001:2018 Occupational health and safety management systems – Requirements with guidance for use

The ISO 45001 standard is based on the guiding principles of the International Labour Organization (ILO) and the British standard OHSAS 18001. It is expected that ISO 45001 will replace OHSAS 18001.

This standard establishes requirements for an occupational health and safety management system and provides guidelines for their implementation, enabling organizations to create safe and healthy working conditions, preventing injuries and ill-health associated with work, and actively improving their performance in occupational health and safety.

General material and educational support for the lecture: presentation materials for the lecture.

Self-assessment questions:

1. International standards have mandatory status for all member countries:

A) Yes

B) No

C) Yes, if provided for by current legislative acts in the member country

2. The standard that contains a complete list of elements of the quality system related to all stages of the product life cycle and corresponding measures:

A) all ISO 9000 series standards

B) ISO 9004:2018

C) ISO/TS 9002:2016

D) ISO 9001:2015

E) ISO 9000:2015

3. By adhering to this standard, organizations can guarantee that they take preventive measures to minimize their impact on the environment, can ensure compliance with relevant legal requirements, and achieve their environmental goals:

A) UN Global Compact

B) ISO 14001:2015

C) ISO 9001:2015

D) ISO 10012:2003

E) ISO 14050:2020

4. The standard that defines requirements for social protection:

A) ISO 26000:2010

B) ISO 9001:2015

C) UN Global Compact

D) OHSAS 18001

E) SA 8000:20141.

List of references:

1. ISO 9000:2015 Quality management systems — Fundamentals and vocabulary.
2. ISO 9001:2015 Quality management systems — Requirements.
3. ISO/TS 9002:2016 Quality management systems — Guidelines for the application of ISO 9001:2015.
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5. ISO 10001:2018 Quality management — Customer satisfaction — Guidelines for codes of conduct for organizations.
6. ISO 10002:2018 Quality management — Customer satisfaction — Guidelines for complaints handling in organizations.
7. ISO 10003:2018 Quality management — Customer satisfaction — Guidelines for dispute resolution external to organizations.
8. ISO 10004:2018 Quality management — Customer satisfaction — Guidelines for monitoring and measuring.
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14. ISO 10014:2021 Quality management systems — Managing an organization for quality results — Guidance for realizing financial and economic benefits.
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34. ISO 45001:2018 Occupational health and safety management systems – Requirements with guidance for use.
35. International Organization for Standardization (ISO): Global standards for trusted goods and services – URL: https://www.iso.org/home.html
36. Legislation of Ukraine – URL: https://zakon.rada.gov.ua/laws/

Lecture No. 3

Topic 2. Regulatory framework for quality management of medicinal products.

The relevance of the topic. WHO, in developing the national medical strategy, emphasizes that pharmaceuticals must be of high quality, safe, and effective. Ensuring the quality of pharmaceuticals is a comprehensive concept that must be guaranteed at all stages of the pharmaceutical product life cycle—from initial development, market placement, to cessation of production and medical use of the products. This is achieved through industry quality management standards in pharmaceuticals, which encompass Good Practices (GxP).

Objective: to form theoretical knowledge of higher education students on the application of general principles and basic methods of development, implementation, maintenance and improvement of quality management systems of pharmaceutical enterprises/organisations in accordance with the rules of Good Pharmaceutical Practice and other industry standards.

Key concepts: pharmaceutical development, good laboratory practice, good clinical practice, bioavailability, bioequivalence, good regulatory practice, good manufacturing practice, good storage practice, good distribution practice.

Lecture plan and organizational structure:

1. The concept of Good Pharmaceutical Practices (GxP) and their role in ensuring quality at all stages of the life cycle of medicines.
2. ICH Q8.
3. Good Laboratory Practice.
4. Good Clinical Practice.
5. Good Regulatory Practice.
6. Good Manufacturing Practice.
7. Good Storage Practices.
8. Good Distribution Practices.

Lecture content

The concept of Good Pharmaceutical Practices (GxP) and their role in ensuring quality at all stages of the life cycle of medicines

In Ukraine, Good Practices are implemented at the level of standards of the Ministry of Health of Ukraine. Currently, to ensure the quality control of pharmaceuticals, the Ministry of Health of Ukraine has approved the following guidelines:

Guideline ST-N MOH of Ukraine 42-3.1:2004 Quality Guideline. Pharmaceuticals. Pharmaceutical Development

Guideline ST-N MOH of Ukraine 42-3.0:2011 Pharmaceuticals. Pharmaceutical Development (ICH Q8)

Guideline ST-N MOH of Ukraine 42-6.0:2008 Pharmaceuticals. Good Laboratory Practice

Guideline ST-N MOH of Ukraine 42-6.0:2014 Pharmaceuticals. Preclinical Safety Studies as a Basis for Human Clinical Trials and Drug Registration (ICH M3(R2))

Guideline ST-N MOH of Ukraine 42-7.0:2008 Pharmaceuticals. Good Clinical Practice

Guideline ST-N MOH of Ukraine 42-7.4:2022 Pharmaceuticals. Bioequivalence Studies

Guideline ST-N MOH of Ukraine 42-1.1:2013 Pharmaceuticals. Good Regulatory Practice

Guideline ST-N MOH of Ukraine 42-4.0:2020 Pharmaceuticals. Good Manufacturing Practice

Guideline ST-N MOH of Ukraine 42-5.1:2011 Pharmaceuticals. Good Storage Practice

Guideline ST-N MOH of Ukraine 42-5.0:2014 Pharmaceuticals. Good Distribution Practice

Good Pharmacy Practice: Quality Standards for Pharmacy Services (WHO/UNICEF Joint Statement on GPP) WHO; Standard, International Document as of 01.01.2011

Guideline ST-N MOH of Ukraine 42-8.7:2018 Pharmaceuticals. Pharmacovigilance Practices

Guideline ST-N MOH of Ukraine 42-4.2:2011 Pharmaceuticals. Risk Management for Quality (ICH Q9)

Guideline ST-N MOH of Ukraine 42-4.3:2011 Pharmaceuticals. Pharmaceutical Quality System (ICH Q10)

The guidelines listed are standards of the Ministry of Health of Ukraine, compliance with which is not mandatory according to the Law of Ukraine "On Standardization". However, when an indication of the mandatory nature of certain standards is contained in other regulatory legal acts, such a standard becomes imperative. An example of this is the Guideline "Pharmaceuticals. Good Manufacturing Practice" (GMP).

Guideline ST-N MOH of Ukraine 42-3.1:2004 Quality Guideline. Pharmaceuticals. Pharmaceutical Development

This guideline corresponds to the documents:

CPMP/QWP/155/96 Note for Guidance on Development Pharmaceutics, 1998

CPMP/QWP/054/98 Decision Trees for the Selection of Sterilisation Methods. Annex to Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/98), 2000

This guideline applies to medicinal products for human use and establishes recommendations regarding the structure of pharmaceutical development studies and the information from these studies to be included in the registration dossier for the finished medicinal product.

Guideline ST-N MOH of Ukraine 42-3.0:2011 Pharmaceuticals. Pharmaceutical Development (ICH Q8)

The guideline is in line with the EMA and ICH documents:

EMEA/CHMP/167068/2004 – ICH. – Part I: Note for Guidance on Pharmaceutical Development (ICH Topic Q 8 (R2) Pharmaceutical Development). – Part II: Annex to Note for Guidance on Pharmaceutical Development (ICH Topic Q 8 Annex Pharmaceutical Development), June 2009

The goal of pharmaceutical development is to develop a high-quality drug and its manufacturing process to consistently produce products with specified functional characteristics. According to the guideline, quality cannot be tested in drugs; that is, quality must be built in during development.

This guideline applies to medicinal products developed, registered, and manufactured in Ukraine for sale on the domestic market and for export purposes or imported into Ukraine.

Guideline ST-N MOH of Ukraine 42-6.0:2008 Pharmaceuticals. Good Laboratory Practice

This guideline corresponds to the document:

Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances

Good Laboratory Practice (*GLP*) is a quality system related to the organizational process and conditions under which preclinical safety studies for human health and the environment are planned, conducted, controlled, documented, reported, and stored in archives.

This guideline establishes principles and rules for conducting preclinical safety studies of medicinal products, which are most often synthetic chemical substances but may have natural or biological origins, and in some cases, be living organisms. The purpose of preclinical studies of these substances is to obtain data on their safety for human use.

Guideline ST-N MOH of Ukraine 42-6.0:2014 Pharmaceuticals. Preclinical Safety Studies as a Basis for Human Clinical Trials and Drug Registration (ICH M3(R2))

This guideline corresponds to the document:

EMA/CPMP/ICH/286/1995 (ICH M3(R2)) Guideline on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals – December 2009

This guideline defines provisions (recommendations) for conducting studies that should not be considered as a sequence of specific individual tests, but rather should be closely linked to the planned clinical trial program and implemented in the overall drug development process. This guideline promotes safety, enhances ethical principles (including reducing the use of laboratory animals), and accelerates the introduction of new drugs into medical practice. It applies to the planning and conduct of preclinical safety studies of medicinal products in accordance with the clinical trial phase and drug registration, as well as the assessment of registration dossier materials.

Guideline ST-N MOH of Ukraine 42-7.0:2008 Pharmaceuticals. Good Clinical Practice

This guideline corresponds to the documents:

CPMP/ICH/135/95 (E 6) Note for Guidance on Good Clinical Practice, 2002

Integrated Addendum to: Guideline For Good Clinical Practice E6(R2), 2017

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the planning and conduct of clinical trials of medicinal products for use in humans, as well as for the documentation and reporting of their results.

This standard applies to all types of medicinal products for human use and establishes general requirements for the planning, organization, conduct, and documentation of the results of clinical trials of medicinal products for human use.

Guideline ST-N MOH of Ukraine 42-7.4:2022 Pharmaceuticals. Bioequivalence Studies

This guideline corresponds to the documents:

CPMP/QWP/EWP/1401/98 Rev.1/Corr** Guideline on the Investigation of Bioequivalence, 2010

EMA/CHMP/600958/2010/Corr.* Appendix IV of Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev.1): Presentation of Biopharmaceutical and Bioanalytical Data in Module 2.7.1, 2011

Bioavailability refers to the speed and extent to which the active substance or its active component is absorbed into the systemic circulation and becomes available at the site of action.

Bioequivalence means that, based on properly conducted studies, the absence of a significant difference in the speed and extent to which the active substance or its active component in pharmaceutically equivalent or pharmaceutically alternative preparations becomes available at the site of action of the drug upon administration at the same molar dose under similar conditions.

This guideline applies to the planning, conduct, and evaluation of tests and studies on the bioavailability and bioequivalence of drugs at the stages of pharmaceutical development, manufacturing, compilation of registration dossiers and registration, as well as making changes to registration dossier materials and during audits or inspections of institutions conducting relevant studies.

According to the Procedure for Conducting Clinical Trials of Medicinal Products and Expertise of Materials of Clinical Trials and the Model Regulation on Ethics Committees, approved by the Order of the Ministry of Health of Ukraine dated September 23, 2009, No. 690:

1. Planning, conducting, and reporting of all clinical trials, including studies on bioequivalence assessment, shall be carried out in accordance with the requirements and principles of Good Clinical Practice (GCP).

2. The laboratory conducting pharmacokinetic studies involved in clinical trials must comply with the requirements of Good Laboratory Practice (GLP).

3. The production and storage of the investigational medicinal product, as well as handling it, shall be carried out in accordance with the requirements of Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) as stipulated by the legislation.

Guideline ST-N MOH of Ukraine 42-1.1:2013 Pharmaceuticals. Good Regulatory Practice

The guideline corresponds to the recommendations of the World Health Organization (WHO) outlined in the document for National Medicines Regulatory Authorities (NMRAs) titled "Marketing authorization of pharmaceutical products with special reference to multisource (generic) products – 2nd ed."

Good Regulatory Practice (*GRP*) in the field of pharmaceuticals refers to the principles and rules of regulatory activity applied by the central executive authority in the field of health care or other authorized bodies, expert institutions aimed at ensuring the effectiveness, safety, quality, and availability of medicinal products.

The primary goal of Good Regulatory Practice is to enhance the effectiveness, consistency, and transparency of the activities of the central executive authority in the field of health care, authorized bodies, and expert institutions performing regulatory functions.

Guideline ST-N MOH of Ukraine 42-4.0:2020 Pharmaceuticals. Good Manufacturing Practice

This guideline corresponds to the document:

The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use

This guideline establishes the provisions of Good Manufacturing Practice (GMP) for medicinal products for human use, including active substances used in medicinal products. It applies to the production of medicinal products manufactured in Ukraine for sale on the domestic market and for export purposes, as well as to medicinal products imported into Ukraine.

The guideline is suitable for organizing the production of medicinal products in accordance with GMP principles and rules, as well as for use in audits, inspections, certification of production areas for compliance with GMP, and licensing of medicinal product manufacturing.

Industrial production of medicinal products and the production of investigational medicinal products in Ukraine must comply with the requirements of the Guideline on Good Manufacturing Practice. The procedure for confirming compliance with the conditions of medicinal product manufacturing with GMP requirements is approved by the Ministry of Health of Ukraine by order No. 1130 dated December 27, 2012 (as amended on March 22, 2022). The confirmation of compliance by the State Service of Ukraine on Medicines and Drugs Control with the conditions of medicinal product manufacturing with GMP requirements is carried out by issuing a certificate of compliance with the conditions of medicinal product manufacturing with GMP requirements (for residents) or a conclusion on confirming compliance with GMP requirements for medicinal product manufacturing (for non-residents).

Guideline ST-N MOH of Ukraine 42-5.1:2011 Pharmaceuticals. Good Storage Practice

This guideline corresponds to the documents:

Guide to good storage practices for pharmaceuticals (Annex 9). WHO Expert Committee on Specifications for Pharmaceuticals Preparations. Thirty-seventh Report. Geneva, World Health Organization, 2003: 125-136 (WHO Technical Report Series, № 908)

CPMP/QWP/609/96/Rev 2 Guideline on declaration of storage conditions: A: in the product information of medicinal products; B: for active substances. Annex to note for guidance on stability testing of new drug substances and products. Annex to note for guidance on stability testing of existing active substances and related finished products, 2007

This guideline establishes the rules of Good Storage Practice (GSP) for medicinal products for human use. It is applicable for managing the proper storage of medicinal products for human use during their manufacturing, wholesale distribution, and retailing.

This guideline is used in conjunction with existing guidelines on Good Manufacturing Practice and Good Distribution Practice.

It is employed for auditing, inspecting, and certifying organizations, as well as for licensing the manufacturing, wholesale, and retail trade of medicinal products.

Guideline ST-N MOH of Ukraine 42-5.0:2014 Pharmaceuticals. Good Distribution Practice

This guideline corresponds to the document:

Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use (Text with EEA relevance) (2013/C 343/01)

This guideline is used to organise the proper distribution of human medicinal products in accordance with the principles and rules of the GDP and to build quality systems by wholesale trade enterprises, including those that manufacture medicinal products.

This guideline applies to the distribution of medicinal products manufactured in Ukraine for sale on the domestic market and for export, as well as medicinal products imported to Ukraine.

This guideline is suitable for use for the purpose of auditing, inspection, certification of relevant enterprises for compliance with the principles and rules of Good Distribution Practice, licensing of wholesale trade in medicinal products.

As of the current period, certification for compliance with the requirements of good distribution practice in Ukraine is carried out on a voluntary basis.

Self-assessment questions:

1. At the stages of pharmaceutical development of a medicinal product, the industry standard is applied:

A) ICH Q8

B) Guidance on bioequivalence studies

C) GCP

D) options A) and B) are correct

E) options A) and C) are correct

2. The principles and rules for conducting preclinical safety studies of medicinal products are established by the guideline:

A) GCP

B) Guidance on bioequivalence studies

C) GLP

D) ICH M3(R2)

E) options C) and D) are correct

3. Production and storage of investigational products, as well as handling with them, must be carried out in accordance with the rules of the industry standard:

A) GMP

B) GCP

C) ICH M3(R2)

D) GSP

E) all options are correct, except option C)

4. Compliance with the rules of this good practice helps trading companies to prevent counterfeit medicines from entering the legal supply chain:

A) GMP

B) GDP

C) GSP

D) GRP

E) GLP

List of references:

1. CPMP/QWP/155/96 Note for Guidance on Development Pharmaceutics, 1998.
2. CPMP/QWP/054/98 Decision Trees for the Selection of Sterilisation Methods. Annex to Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/98), 2000.
3. EMEA/CHMP/167068/2004 – ICH. – Part I: Note for Guidance on Pharmaceutical Development (ICH Topic Q 8 (R2) Pharmaceutical Development). – Part II: Annex to Note for Guidance on Pharmaceutical Development (ICH Topic Q 8 Annex Pharmaceutical Development), June 2009 (EMEA/CHMP/167068/2004 – ICH.
4. Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances.
5. EMA/CPMP/ICH/286/1995 (ICH M3(R2)) Guideline on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals – December 2009.
6. CPMP/ICH/135/95 (E 6) Note for Guidance on Good Clinical Practice, 2002.
7. Integrated Addendum to: Guideline For Good Clinical Practice E6(R2), 2017.
8. CPMP/QWP/EWP/1401/98 Rev.1/Corr** Guideline on the Investigation of Bioequivalence, 2010.
9. EMA/CHMP/600958/2010/Corr.* Appendix IV of Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev.1): Presentation of Biopharmaceutical and Bioanalytical Data in Module 2.7.1, 2011.
10. National Medicines Regulatory Authorities (NMRAs): Marketing authorization of pharmaceutical products with special reference to multisource (generic) products – 2nd ed.
11. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use.
12. Guide to good storage practices for pharmaceuticals (Annex 9). WHO Expert Committee on Specifications for Pharmaceuticals Preparations. Thirty-seventh Report. Geneva, World Health Organization, 2003: 125–136.
13. CPMP/QWP/609/96/Rev 2 Guideline on declaration of storage conditions: A: in the product information of medicinal products; B: for active substances. Annex to note for guidance on stability testing of new drug substances and products. Annex to note for guidance on stability testing of existing active substances and related finished products, 2007.
14. Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use (Text with EEA relevance) (2013/C 343/01).
15. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) – URL: https://www.ich.org/
16. European Medicines Agency (EMA) – URL: https://www.ema.europa.eu/en/
17. Legislation of Ukraine – URL: https://zakon.rada.gov.ua/laws/
18. Regulatory and directive documents of the Ministry of Health of Ukraine – URL: https://moz.gov.ua/
19. The State Expert Center of the Ministry of Health of Ukraine – URL: https://www.dec.gov.ua/
20. The State Service of Ukraine on Medicines and Drugs Control – URL: https://www.dls.gov.ua/

Lecture No. 4

Topic 2. Regulatory framework for quality management of medicinal products.

The relevance of the topic. WHO, in developing the national medical strategy, emphasizes that pharmaceuticals must be of high quality, safe, and effective. Ensuring the quality of pharmaceuticals is a comprehensive concept that must be guaranteed at all stages of the pharmaceutical product life cycle—from initial development, market placement, to cessation of production and medical use of the products. This is achieved through industry quality management standards in pharmaceuticals, which encompass Good Practices (GxP).

Objective: to form theoretical knowledge of higher education students on the application of general principles and basic methods of development, implementation, maintenance and improvement of quality management systems of pharmaceutical enterprises/organisations in accordance with the rules of Good Pharmaceutical Practice and other industry standards.

Key concepts: good pharmacy practice, pharmacovigilance, pharmaceutical quality system, integrated quality management systems, State Pharmacopoeia of Ukraine.

Lecture plan and organizational structure:

1. Good Pharmacy Practice.
2. Good Pharmacovigilance Practices.
3. ICH Q9.
4. ICH Q10.
5. Integrated quality management systems of pharmaceutical organisations.
6. State Pharmacopoeia of Ukraine.

Lecture content

Good Pharmacy Practice: Quality Standards for Pharmacy Services (WHO/UNICEF Joint Statement on GPP) WHO; Standard, International Document as of 01.01.2011

By the Order of the Ministry of Health of Ukraine dated May 30, 2013, No. 455 "On the WHO and FIP Guideline Good Pharmacy Practice: Quality Standards for Pharmacy Services", with the aim of improving the provision of quality medical care in healthcare facilities, the joint guideline of the World Health Organization and the International Pharmaceutical Federation "Good Pharmacy Practice: Quality Standards for Pharmacy Services" is recommended for implementation.

Good Pharmacy Practice (*GPP*) is the principles and rules of retail dispensing of medicinal products, their storage, control, manufacturing in pharmacy conditions, dispensing, compliance with which ensures the quality of the medicinal product at the retail trade stage.

By the Order of the Ministry of Health of Ukraine dated January 5, 2022, No. 7, 36 pharmacist protocols were approved, which are recommended for use by the heads of pharmacy establishments of all forms of ownership in practical activities.

Guideline ST-N MOH of Ukraine 42-8.7:2018 Pharmaceuticals. Pharmacovigilance Practices

Pharmacovigilance is the science and activity aimed at detecting, assessing, understanding, and preventing adverse effects or any other problems associated with medicinal products.

This guideline corresponds to the documents:

EMA/541760/2011 Rev. 2* Guideline on good pharmacovigilance practices (GVP). Module I – Pharmacovigilance systems and their quality systems.

EMA/816573/2011 Rev. 2* Guideline on good pharmacovigilance practices (GVP). Module II – Pharmacovigilance system master file.

EMA/119871/2012 Rev. 1* Guideline on good pharmacovigilance practices (GVP). Module III – Pharmacovigilance inspections.

EMA/228028/2012 Rev. 1* Guideline on good pharmacovigilance practices (GVP). Module IV – Pharmacovigilance audits.

EMA/838713/2011 Rev. 2* Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems.

EMA/873138/2011 Rev. 1* Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products.

EMA/816292/2011 Rev. 1* Guideline on good pharmacovigilance practices (GVP). Module VII – Periodic safety update report.

EMA/813938/2011 Rev 2* Corr** Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies.

EMA/827661/2011 Guideline on good pharmacovigilance practices (GVP). Module IX – Signal management.

EMA/169546/2012 Guideline on good pharmacovigilance practices (GVP). Module X – Additional monitoring.

EMA/118465/2012 Guideline on good pharmacovigilance practices (GVP). Module XV – Safety communication.

EMA/204715/2012 Rev 2* Guideline on good pharmacovigilance practices (GVP). Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators.

EMA/168402/2014 Corr* Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products.

This guideline applies to medicinal products registered and marketed in Ukraine. It also extends to the establishment and maintenance of pharmacovigilance systems, conducting audits, inspections, and audits of the pharmacovigilance system by an authorized institution in Ukraine. It involves creating an updated risk management system for medicinal products, exchanging safety data, analyzing safety data obtained during the post-registration period, signal management, generating and submitting regularly updated safety reports, and communicating safety issues with healthcare professionals and patients.

Structurally, the guideline consists of separate modules corresponding to Module I, II, III, IV, V, VI, VII, VIII, IX, X, XV, XVI, and Part XIII of the Guideline on Good Pharmacovigilance Practices (GVP) adopted in the EU.

Guideline ST-N MOH of Ukraine 42-4.2:2011 Pharmaceuticals. Risk Management for Quality (ICH Q9)

This guideline corresponds to the document:

EMA/INS/GMP/79766/2011 Quality Risk Management (ICH Q9), 31 January 2011

This guideline establishes principles and provisions for a systematic approach to risk management for quality within the pharmaceutical quality system and quality management in the pharmaceutical industry. It presents a range of internationally recognized alternative methods and tools for quality risk management along with a list of possible application areas.

This guideline is applied in the pharmaceutical industry and regulatory activities during audits and inspections of organizations by regulatory authorities. It is also used for certifying the pharmaceutical quality system of drug manufacturers on a voluntary basis.

Guideline ST-N MOH of Ukraine 42-4.3:2011 Pharmaceuticals. Pharmaceutical Quality System (ICH Q10)

This guideline corresponds to the document:

EMA/INS/GMP/79818/2011 Pharmaceutical Quality System (ICH Q10), 31 January 2011

This guideline establishes provisions for a quality management system for the pharmaceutical industry (pharmaceutical quality system).

The document ICH Q10 provides an example of a pharmaceutical quality system designed for the entire lifecycle of a drug.

This guideline is used to assess the effectiveness of the pharmaceutical quality system during audits and inspections of organizations by regulatory authorities. It is also used for certifying the pharmaceutical quality system of drug manufacturers on a voluntary basis.

Integrated quality management systems for pharmaceutical organizations

Due to the development of systems that meet the requirements of several international standards for systems, the practice of creating integrated quality management systems has been increasingly widespread in recent years. For manufacturing pharmaceutical enterprises, a typical example is an integrated management system developed based on the requirements of GMP (Good Manufacturing Practice) and international standards such as ISO 9001 (Quality Management System), ISO 14001 (Environmental Management System), OHSAS 18001 (Occupational Health and Safety Management), and SA 8000 (Social Responsibility Management System).

In practice, there are two main approaches to forming an integrated quality management system:

1) Construction of an additive model, which involves the step-by-step addition of other management systems to the main quality management system model.

2) Development of a simultaneous integration model, which involves the simultaneous integration of multiple management systems into a single complex. The second model has significant organizational and economic advantages, requires less implementation time, but due to the complexity of its formation, it is used much less frequently.

It should be noted that a significant number of quality experts believe that the organizational and methodological basis for implementing an integrated management system in a pharmaceutical enterprise should not be GxP rules, but rather the ISO 9001 standard. Its universal methodology and principles, including process and system approaches, leadership, and employee involvement, most closely align with the principles of general management and allow for the integration of standards of other management systems without significant problems. The basic standards upon which the integrated management system is built can be strengthened and supplemented by recommendations from other standards and guidelines. These include ISO 9004 (management for sustainable success), ISO 14004 (guidelines for implementing an environmental management system), OHSAS 18002 (implementation principles for OHSAS 18001 requirements), ISO 26000 (alternative standard for social responsibility management system), ICH Q9 guideline (quality risk management), referenced in the GDP guideline (Good Distribution Practice), and the ICH Q10 guideline (pharmaceutical quality system).

The process of implementing a management system based on each individual standard is recommended to be carried out in four main stages: planning, implementation, verification, and correction, which corresponds to the implemented Deming – Shewhart cycle (PDCA) concept of ISO standards. This approach can be applied both to achieve continuous improvement of the entire integrated management system and to each of its individual elements.

Certification can be carried out for individual management systems as well as for the entire integrated management system.

The State Pharmacopoeia of Ukraine

The State Pharmacopoeia of Ukraine (*SPU*) is a legal document that contains general requirements for medicinal products, pharmacopoeial articles, and methods for quality control of medicinal products.

The developer of the SPU is the State Enterprise "Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines" under the assignment of The State Service of Ukraine on Medicines and Drugs Control.

The State Pharmacopoeia of Ukraine has legislative force. Its requirements for medicinal products are mandatory for all enterprises and institutions in Ukraine, regardless of their ownership form, that manufacture, store, control, distribute, and use medicinal products.

Ukraine was the first among the CIS countries to develop and implement its national Pharmacopoeia. The first edition of the State Pharmacopoeia of Ukraine (SPU) was introduced on October 1, 2001. Four supplements to the first edition of the SPU were issued during the period from 2001 to 2011. The SPU 2.0 was introduced by Order No. 830 dated January 1, 2016. All articles of the SPU 1.0 and its supplements were updated in the SPU 2.0 based

on the current edition of the European Pharmacopoeia (EP) – EP edition 8.0 with Supplements 8.1 and 8.2 at that time.

SPU 2.0 includes the following types of articles:

1. Translations of corresponding EP articles. This category comprises the majority of individual articles (monographs) on substances for pharmaceutical use and some medicinal products, including insulin and immunoglobulins, as well as some monographs on medicinal plant materials and herbal medicinal products.

2. Translations of corresponding EP articles supplemented by national parts reflecting the experience of standardization of medicinal products in Ukraine. This category includes a significant number of general articles and monographs on medicinal plant materials.

3. Purely national general and specific articles that are absent in the EP but are mandatory. This category includes monographs on finished medicinal products, medicinal plant materials, herbal medicinal products, as well as articles on medicinal products prepared in pharmacies.

4. Purely national articles absent in the EP and of a recommendatory and informational nature. This category includes articles on dietary supplements, statistical analysis of results, and validation of analytical methods and tests.

SPU 2.0 consists of three volumes. The contents of SPU 2.0 are as follows:

Volume 1

General remarks

Analytical methods

Materials and containers

Reagents

General texts

General monographs

General articles on medicinal forms

Volume 2

Monographs on substances

Volume 3

Monographs on vaccines for human use

Monographs on immunosera for human use

Monographs on immunosera for veterinary use

Radiopharmaceutical medicinal products

Suture materials for human use

Suture materials for veterinary use

Medicinal plant materials and herbal medicinal products

Homeopathic medicinal products

Monographs on finished medicinal products

Medicinal products prepared in pharmacies

Dietary supplements

To maintain harmonization with the European Pharmacopoeia, which is updated annually, supplements to SPU 2.0 are issued. Supplement 1 to the second edition of SPU (SPU 2.1) came into force on January 1, 2017, SPU 2.2 – on March 16, 2018, SPU 2.3 – on July 1, 2018, SPU 2.4 – on July 1, 2020, SPU 2.5 – on April 1, 2021, and SPU 2.6 – on March 1, 2023.

The main focus of the supplements to SPU is:

- on the development of objects absent in the EP (primarily monographs on finished medicinal products), and
- on the development of objects that require consideration of national specifics in their application, primarily medicinal plant materials and herbal medicinal products.

It is envisaged that the State Enterprise "Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines" will continue to pay considerable attention to the development

of pharmacopoeial standards for finished medicinal products, medicinal plant materials, herbal medicinal products, medicinal products prepared in pharmacies, and dietary supplements.

General conclusion on the topic

The harmonious combination of mandatory quality requirements outlined in pharmacopoeias, requirements of good practices, and ISO standards, which have a recommended nature, ensures the quality and safety of medicinal products or medical devices throughout all stages of their lifecycle most effectively.

Self-assessment questions:

1. The principles and recommendations for quality risk management within the pharmaceutical quality system are established by the guideline:

A) ICH Q8
B) ICH Q9
C) ICH Q10
D) ICH M3(R2)
E) all options are correct

2. The principles and rules for creating a risk management system associated with the use of medicinal products are established by the guideline:

A) GVP
B) GCP
C) Guidance on bioequivalence studies
D) ICH Q10
E) all options are correct, except option D)

3. For manufacturing pharmaceutical companies, a typical example is an integrated management system developed on the basis of requirements:

A) GMP, ISO 45001:
A) GMP, ISO 45001
B) GVP, ISO 9004
C) GMP, ISO 9001
D) GDP, ISO 14001
E) GMP, SA 8000

4. The provisions regarding the pharmaceutical quality system are established by the guideline:

A) GPP
B) GMP
C) GVP
D) ICH Q10
E) ICH Q8

List of references:

37. Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services [Annex 8]. WHO Technical Report Series, No. 961, 2011.

38. EMA/541760/2011 Rev. 2* Guideline on good pharmacovigilance practices (GVP). Module I – Pharmacovigilance systems and their quality systems.

39. EMA/816573/2011 Rev. 2* Guideline on good pharmacovigilance practices (GVP). Module II – Pharmacovigilance system master file.

40. EMA/119871/2012 Rev. 1* Guideline on good pharmacovigilance practices (GVP). Module III – Pharmacovigilance inspections.

41. EMA/228028/2012 Rev. 1* Guideline on good pharmacovigilance practices (GVP). Module IV – Pharmacovigilance audits.

42. EMA/838713/2011 Rev. 2* Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems.

43. EMA/873138/2011 Rev. 1* Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products.
44. EMA/816292/2011 Rev. 1* Guideline on good pharmacovigilance practices (GVP). Module VII – Periodic safety update report.
45. EMA/813938/2011 Rev 2* Corr** Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies.
46. EMA/827661/2011 Guideline on good pharmacovigilance practices (GVP). Module IX – Signal management.
47. EMA/169546/2012 Guideline on good pharmacovigilance practices (GVP). Module X – Additional monitoring.
48. EMA/118465/2012 Guideline on good pharmacovigilance practices (GVP). Module XV – Safety communication.
49. EMA/204715/2012 Rev 2* Guideline on good pharmacovigilance practices (GVP). Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators.
50. EMA/168402/2014 Corr* Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products.
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54. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) – URL: https://www.ich.org/
55. European Medicines Agency (EMA) – URL: https://www.ema.europa.eu/en/
56. European Directorate for the Quality of Medicines and HealthCare (EDQM) – URL: https://www.edqm.eu/en/
57. Legislation of Ukraine – URL: https://zakon.rada.gov.ua/laws/
58. Regulatory and directive documents of the Ministry of Health of Ukraine – URL: https://moz.gov.ua/
59. The State Expert Center of the Ministry of Health of Ukraine – URL: https://www.dec.gov.ua/
60. The State Service of Ukraine on Medicines and Drugs Control – URL: https://www.dls.gov.ua/
61. Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines – URL: https://sphu.org/viddil-dfu

Lecture No. 5

Topic 3. Regulatory authorities of Ukraine in the field of quality management of medicinal products.

The relevance of the topic. The central executive authority in the field of healthcare, along with other authorized bodies and expert institutions, employs good regulatory practices in the circulation of medicines to ensure their efficacy, safety, quality, and accessibility.

Objective: to form theoretical knowledge of the structure of the state system of regulation of medicines circulation in Ukraine among higher education students.

Key concepts: central executive authority in the field of healthcare, specialized expert organization authorized by the central executive authority in the field of healthcare in the sphere of medicine circulation, state registration of a medicinal product, state re-registration of a medicinal product, applicant, full dossier medicinal product, generic medicinal product, hybrid medicinal product, similar biological medicinal product, medicinal product with well-established medical use, fixed combination, informed consent, traditional medicinal product, ―i*n bulk*‖ product, orphan product, registration dossier, state register of medicinal products, benefit/risk ratio of a medicinal product, unexpected adverse reaction, expected adverse reaction, non-serious adverse reaction, serious adverse reaction, central executive authority in the fields of quality control and safety of medicinal products, certification of quality systems, certificate for a company's quality system.

Lecture plan and organizational structure:

1. The Ministry of Health of Ukraine.
2. The State Expert Centre of the Ministry of Health of Ukraine.
3. The Directorate of Pharmaceutical Support of the Ministry of Health of Ukraine.
4. The State Service of Ukraine on Medicines and Drugs Control.
5. Certification and licensing as components of the quality system in pharmacy.

Lecture content

Structure of the state system for regulating the circulation of medicines

The State Expert Centre of the Ministry of Health of Ukraine

The Ministry of Health of Ukraine (*MOH*) is the central executive authority whose activities are directed and coordinated by the Cabinet of Ministers of Ukraine.

The MOH is the main body in the system of central executive authorities responsible for forming and implementing state policy in the field of healthcare, protecting the population from infectious diseases, combating HIV/AIDS and other socially dangerous diseases, and preventing and controlling non-communicable diseases. It also ensures the formation and implementation of state policy in the following areas:

- epidemiological surveillance, immunoprophylaxis, prevention and reduction of tobacco use and its harmful effects on public health, food safety, creation of a national blood system, quality system management in blood safety, biological safety and biological protection, combating antimicrobial resistance, ensuring the formation of state policy in the areas of sanitary and epidemiological well-being of the population;
- technical regulation of medical devices, medical devices for *in vitro* diagnostics, active implantable medical devices, and cosmetic products;
- providing the population with high-quality, effective, and safe medicinal products; ensuring the development, production, quality control, and distribution of medicinal products, medical immunobiological preparations, circulation of narcotic drugs, psychotropic substances, their analogs, and precursors, combating their illegal circulation, as well as ensuring the safety of medical devices and cosmetic products.

The structure of the Ministry of Health includes the following departments:

- Directorate of Strategic Planning and Coordination
- Department of Public Health
- Department of Medical Services

- Department of Digital Transformations in Healthcare
- Department of High-Tech Medical Care and Innovations
- Pharmaceutical Management
- Department of International Cooperation and European Integration.

The State Enterprise "State Expert Center of the Ministry of Health of Ukraine"

The State Enterprise "State Expert Center of the Ministry of Health of Ukraine" (*SEC MOH of Ukraine*) is an organization authorized by the Ministry of Health of Ukraine. It specializes in the preclinical study, clinical trials, and state registration of medicinal products within the framework defined by the laws of Ukraine "On Medicinal Products" and "On the Protection of the Population from Infectious Diseases". It is also the leading organization in the field of pharmacovigilance, standardization of medical care, and medical, including pharmaceutical, services. This includes the development of relevant medical and technological documents and draft regulatory acts. The SEC MOH of Ukraine is state-owned and falls under the jurisdiction of the Ministry of Health of Ukraine.

Structure of the State Expert Center of the Ministry of Health of Ukraine (main divisions):

- Department of Registration Materials Expertise
- Department of Preclinical and Clinical Trials Materials Expertise
- Department of Pharmaceutical Activities
- Department of Coordination of Expert Materials
- Department of Health Technology Assessment and Price Monitoring
- Department of Pharmacovigilance
- Audit Office
- Office of Bioavailability and Bioequivalence Materials Expertise
- State Registers Administration Division

According to the Law of Ukraine "On Medicines," medicinal products are allowed for use in Ukraine after their state registration.

State registration of a medicinal product is a procedure conducted in accordance with the requirements of current legislation aimed at substantiating the efficacy, safety, and quality of a medicinal product and is a prerequisite for its circulation and medical use.

State re-registration of a medicinal product is a procedure carried out in accordance with the requirements of current legislation with the aim of extending the authorization for medical use of the medicinal product in Ukraine.

The Ministry of Health of Ukraine conducts state registration/re-registration based on the results of expertise performed by the State Expert Center of the Ministry of Health of Ukraine.

Applicant (holder of registration certificate) is a legal entity or a natural person responsible for efficacy, quality, and safety of a medicinal product according to the procedure established by the acting legislation, and having resources to perform pharmacovigilance in Ukraine, and being responsible for reliability of information included in registration dossier submitted by him.

During the registration of a medicinal product, the applicant must specify the grounds for choosing the type of medicinal product that the set of registration documents corresponds to.

Types of medicinal products

Full dossier medicinal product (innovative/original medicinal product) is a medicinal product containing a new active substance.

Generic medicinal product is a medicinal product whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. This type of medicinal product envisages that the registration dossier contains references to the registration information contained in the dossier for the reference product.

If a medicinal product has such differences from the reference medicinal product as changes in the salt form of the active substance, therapeutic indications, dosage, dosage form, or route of administration, it is classified as a hybrid medicinal product.

Similar biological medicinal product (biosimilar) is a biological medicinal product which is similar in terms of quality, efficacy and safety to the registered reference biological product, which patent protection period expired.

Medicinal product with well-established medical use is a medicinal product for which the applicant can demonstrate that the active substance of the medicinal product with well-established therapeutic properties within the EU and/or Ukraine for at least 10 years has been recognized as effective and has an acceptable level of safety in any medicinal form.

Fixed combination is a combination of several active substances in one medicinal form for therapeutic purposes.

Informed consent. The holder of registration for a medicinal product may allow another applicant to use the documentation of the registration dossier for their registered medicinal product for the registration of other medicinal products with the same qualitative and quantitative composition of active substances and the same pharmaceutical form.

Traditional medicinal product is a medicinal product for which the applicant can prove that the respective preparation has been used in medical practice for a period of not less than 30 years preceding the date of submission of the traditional medicinal product for registration, including at least 15 years in the EU and/or Ukraine.

―In bulk‖ product – any medicinal product, which passed all stages of manufacturing process, except for pre-packaging and/or final packaging and labelling.

Product of limited use (orphan product) – a medicinal product which is intended for the diagnosis, prevention or treatment of a rare life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons by the time of submission of the application for state registration.

Structure of the registration dossier for a medicinal product:

Module 1. Administrative information

Module 2. Summary of the Common Technical Document

Module 3. Quality. Chemical, pharmaceutical, and biological information about medicinal products containing chemical and/or biological active substances

Module 4. Non-clinical Study Reports

Module 5. Clinical Study Reports

Procedure for the state registration of medicinal products in Ukraine:

1. Expertise of the registration dossier. The registration dossier for a medicinal product is reviewed by the State Expert Center of the Ministry of Health of Ukraine.

2. Preparation of motivated conclusions. Based on the results of the expert evaluation, the State Expert Center of the Ministry of Health of Ukraine prepares motivated conclusions regarding the efficacy, safety, and quality of the medicinal product. These conclusions form the basis for the recommendation to the Ministry of Health of Ukraine regarding the state registration of the medicinal product or refusal of registration.

3. State Registration/Re-registration. The Ministry of Health of Ukraine makes the decision on the state registration or re-registration of the medicinal product. Confirmation of registration is the issuance of a registration certificate for the medicinal product.

Information about registered medicinal products in Ukraine and instructions for their medical use can be obtained from the State Register of Medicinal Products of the State Expert Center of the Ministry of Health of Ukraine.

It should be noted that proper quality of medications is not an absolute guarantee that pharmacotherapy will not have adverse effects. The use of medicinal products implies that their therapeutic effect should occur, but adverse reactions may occur.

Pharmacovigilance, which involves monitoring the safety of medicinal products during their medical use, is one of the primary directions in implementing national drug policies in all countries worldwide.

The pharmacovigilance system is a mechanism used by the state and pharmaceutical manufacturers to monitor the safety and efficacy of medicines and determine any changes in the balance between benefit and risk. The pharmacovigilance system is established within the healthcare system at the state level and by pharmaceutical manufacturers.

The benefit-risk ratio of a medicinal product is an assessment of the positive therapeutic effects of the medicinal product compared to any risks related to its quality, safety, or efficacy that affect patient or public health.

Unexpected adverse reaction is an adverse reaction whose nature or severity is not consistent with the information provided in the drug's instruction for medical use.

Expected adverse reaction is an adverse reaction whose nature or severity is consistent with the information provided in the drug's instruction for medical use of the registered medicinal product.

Non-serious adverse reaction is any adverse reaction that does not result in death, does not pose a threat to life, does not require hospitalization or prolongation of existing hospitalization, does not result in persistent or significant disability or incapacity, does not cause congenital anomalies or developmental defects, and does not have any other significant medical condition.

Serious adverse reaction is any adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, causes congenital anomalies or developmental defects, or has any other significant medical condition.

The Directorate of Pharmaceutical Provision of the Ministry of Health of Ukraine

The Directorate of Pharmaceutical Provision of the Ministry of Health of Ukraine (the Directorate) is an independent structural unit of the Ministry of Health of Ukraine responsible for shaping state policy in the pharmaceutical sector of the healthcare industry.

The Directorate comprises 5 expert groups:

Expert Group on Rational Use of Medicines

The main priority tasks of this expert group include:

- developing regulatory acts for the full functioning of the "Accessible Medicines" reimbursement program and systematic review and approval of the Register of Medicinal Products subject to reimbursement, as well as the Register of Maximum Prices for Medicinal Products subject to reimbursement according to data from 5 reference countries;
- reviewing the National List of Essential Medicines;
- approving the Register of maximum wholesale and retail prices for certain medicinal products purchased with budgetary funds and included in the national list, as well as the Register of reference prices for insulin products.

Expert Group on Medical Devices and Cosmetic Products

The main directions of work of this group include ensuring the formation and implementation of state policy in the field of technical regulation of the circulation of medical devices and cosmetic products.

Expert Group on the Quality and Accessibility of Medicinal Products

The main tasks of this expert group include:

- coordinating the development and approval of rules for preclinical studies and clinical trials of medicinal products and ensuring compliance with them;
- preparation of notifications for the import of unregistered medicinal products, reagents, standards, etc., into the territory of Ukraine in cases provided for by legislation.

Expert Group on the Circulation of Narcotic Drugs

One of the main tasks of the Expert Group is to ensure the formation and implementation of state policy on the circulation of narcotic drugs, psychotropic substances, and precursors, as well as to counter their illegal circulation.

Expert Group on the Registration of Medicinal Products and Disinfectants

The main directions of work of the Expert Group include:

- formulation of state policy in the field of circulation of medicinal products and disinfectants in accordance with the directions of state registration (re-registration) of medicinal products, including medical immunobiological preparations in Ukraine;
- registration of disinfectants and formation of a registry of disinfectants.

The State Service of Ukraine on Medicines and Drugs Control

The State Service of Ukraine on Medicines and Drugs Control (SMDC) is the central executive body, whose activities are directed and coordinated by the Cabinet of Ministers of Ukraine through the Minister of Health, who implements state policy in the fields of quality and safety control of medicinal products, including medical immunobiological preparations (hereinafter – medicinal products), medical equipment and devices (hereinafter – medical devices), as well as the circulation of narcotic drugs, psychotropic substances, and precursors, and counteracting their illegal circulation.

Department of Licensing of Production of Medicines, Blood and Certification of the State Service of Ukraine on Medicines and Drugs Control

The main functions of the Department include:

- ensuring the licensing of business activities related to the manufacturing of medicinal products;
- ensuring the licensing of business activities related to the collection and testing of donor blood and blood components;
- managing the formation and maintenance of the licensing register for the manufacturing of medicinal products.

Department of Quality Control of Medicines and Blood of the State Service of Ukraine on Medicines and Drugs Control

The main functions of the Department include:

- ensuring the licensing of business activities related to the import of medicinal products;
- ensuring state control over compliance with legal requirements regarding the quality and safety of medicinal products, donor blood, and its components at all stages of circulation;
- conducting sector-specific certification of laboratories for quality control of medicinal products and laboratories within the blood system.
- organizing and implementing measures to detect, withdraw, and prevent the circulation of falsified, substandard, unregistered medicinal products, as well as medicinal products that do not meet established regulatory requirements, within the Department's competence.

Department of State Regulation and Control in the Sphere of Circulation of Narcotic Drugs, Psychotropic Substances, Precursors and Counteraction to Their Illegal Circulation of the State Service of Ukraine on Medicines and Drugs Control

The main functions of the Department include:

- ensuring the licensing of all types of business activities in the circulation of narcotic drugs, psychotropic substances, and precursors;
- organizing the submission of proposals to determine:
  - the maximum permissible quantities of narcotic drugs, psychotropic substances, and precursors contained in medicinal products;

- the list of tools and equipment used for the production and manufacture of narcotic drugs, psychotropic substances, and precursors that are subject to control, as well as the rules for conducting operations with them;
- the procedure for transporting narcotic drugs, psychotropic substances, and precursors within Ukraine and the documentation required for such transport;
- the volume of quotas within which the production, manufacture, storage, import, and export of narcotic drugs and psychotropic substances for medical and scientific purposes, as well as medicinal products containing narcotic drugs, psychotropic substances, and precursors in quantities exceeding the permissible limits, are carried out.

➢ ensuring, in coordination with the Security Service of Ukraine (SBU), the issuance of permits to business entities for the import and transit of narcotic drugs, psychotropic substances, and precursors;

➢ controlling compliance by business entities with the procedure for the destruction of narcotic drugs, psychotropic substances, and precursors.

Department of Wholesale and Retail Trade of Medicinal Products of the State Service of Ukraine on Medicines and Drugs Control

Main functions of the Department:

➢ conducting the examination of documents submitted for obtaining, amending, and renewing licenses for conducting business activities related to the production of medicinal products in pharmacy settings, and the wholesale and retail trade of medicinal products;

➢ forming and maintaining a database of entities certified for compliance with Good Distribution Practice (GDP) requirements;

➢ implementing state control over the compliance of business entities with the licensing conditions for the specified types of business activities; this includes organizing and conducting planned and unplanned inspections of entities engaged in the specified business activities.

State enterprise under the management of the State Service of Ukraine on Medicinal Products and Drug Control:

1. State Enterprise "Central Laboratory for Quality Analysis of Medicinal Products and Medical Products"

The State Enterprise "Central Laboratory for Quality Analysis of Medicinal Products and Medical Products" is a reference laboratory of the State Service of Ukraine on Medicines and Drugs Control with the following main activities:

➢ conducting quality analysis of finished medicinal products;

➢ qualifying analytical instruments and equipment;

➢ performing technical expertise and inspections of the production conditions of medicinal products as directed by the State Service of Ukraine on Medicines and Drugs Control to determine compliance with Good Manufacturing Practice (GMP) requirements.

2. State Enterprise "Ukrainian Pharmaceutical Quality Institute"

The main activities of the State Enterprise "Ukrainian Pharmaceutical Quality Institute" include:

➢ providing training for specialists from enterprises, institutions, and organizations, including public servants, on the rules and standards of Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) for the production of medicines and medical devices in accordance with European and international standards;

➢ conducting scientific and technical examinations and inspections to confirm the compliance of the manufacturing conditions of medicinal products with the requirements of good manufacturing and distribution practices of enterprises, institutions and organisations regardless of ownership form, conducting certification of production of medicinal products, organizations engaged in wholesale distribution of medicinal products, conducting accreditation

of quality control laboratories of medicinal products, conducting audits, inspections, surveys, etc.;

- conducting specialized examinations to issue expert opinions for the importation into and exportation from Ukraine of narcotic drugs, psychotropic substances, and precursors.

3. State Enterprise "Ukrainian Scientific Pharmacopoeial Centre for the Quality of Medicines"

The main tasks and directions of work of the State Enterprise "Ukrainian Scientific Pharmacopoeial Centre for the Quality of Medicines":

- Development, maintenance, and publication of the State Pharmacopoeia of Ukraine (SPU).
- Development and maintenance of the National System of Pharmacopoeial Reference Standards of SPU.
- Quality control of medicinal products under the task of the State Service of Ukraine on Medicinal Products and Drug Control.

The laboratory, at the request of the State Service of Ukraine on Medicinal Products and Drug Control, carries out laboratory analysis of the quality of samples of medicinal products imported into the customs territory of Ukraine or available on the market of Ukraine, and provides conclusions on the results of this analysis regarding the conformity of the quality of medicinal products to the requirements of relevant pharmacopoeial monographs or current methods of quality control. The laboratory conducts arbitral analysis of medicinal products at the request of the State Service of Ukraine on Medicinal Products and Drug Control and at the request of business entities.

- Organization and conduct of the Program of Professional Testing of Quality Control Laboratories.
- International cooperation.

Certification

In 1970, the Eighth Session of the ISO General Assembly adopted a resolution to transition to the development of international standards instead of recommendations. At the same time, the session decided to establish the Committee for Certification of Conformity of Products to International Standards, renamed the ISO Committee for Conformity Assessment (CASCO) in 1985. It was during this period that national certification systems and networks of independent testing laboratories were established. To ensure a unified approach to certification issues and prevent differences in national certification systems from hindering trade expansion between countries, it was decided to assign this body the task of developing international recommendations for countries on all aspects of certification. An important area of CASCO's activities is to facilitate mutual recognition and acceptance of national certification systems, as well as the use of international standards in the field of conformity assessment.

The Ukrainian Technical Committee for Standardization (TC 89) is a full member of ISO/CASCO.

According to the decree of the Cabinet of Ministers of Ukraine dated November 26, 2014, No. 1163 "On the designation of a state enterprise performing the functions of a national standardization body," the functions of the national standardization body are performed by the state enterprise "Ukrainian Scientific Research and Training Center for Standardization, Certification, and Quality Issues".

In accordance with the Law "On Standardization," the main powers of the national standardization body include organizing and coordinating activities related to the development, adoption, verification, review, cancellation, and restoration of the effect of national standards.

The State Enterprise "Ukrainian Scientific Research and Training Center for Standardization, Certification, and Quality Issues" represents the interests of Ukraine in the International Organization for Standardization (ISO).

Certification of quality systems is the process of verification, assessment, and certification by an accredited certification body that the quality management system of the evaluated enterprise complies with the requirements of a national or international quality management standard.

A certificate for a company's quality system is a document issued in accordance with the certification system's rules, which certifies that the quality management system of the evaluated enterprise meets the requirements of a national or international quality management standard.

After the economic part of the Association Agreement between Ukraine and the EU came into force, in accordance with the requirements of EU legislation in the field of conformity assessment, changes were made to the Cabinet of Ministers of Ukraine Decree "On Standardization and Certification" dated May 10, 1993, No. 46-93. According to these changes, as of January 1, 2018, the operation of the Decree and the state certification system UkrSEPRO ceased. Thus, from January 1, 2018, Ukraine fully transitioned to conformity assessment procedures and certification of products and services according to European principles.

However, considering the existing needs of Ukraine's industry for competent conformity assessment of products by a third-party independent body, as well as society's need for reliable information on the quality and safety of goods and services, the State Enterprise "UKRMETRTESTSTANDART" has created the "Voluntary UkrSEPRO System", giving manufacturers the freedom to find the optimal way to confirm the quality of their products. The Voluntary UkrSEPRO System involves the participation of certification bodies with a positive reputation acquired during their work in the state certification system, high technical competence, and extensive experience in conformity assessment activities.

General material and educational support for the lecture: presentation materials for the lecture.

Self-assessment questions

1. The specialized organization in the field of preclinical studies and clinical trials of medicinal products, authorized by the Ministry of Health of Ukraine, is:

A) The State Service of Ukraine on Medicines and Drug Control

B) The State Enterprise ―Ukrainian Scientific Pharmacopoeia Center for Medicinal Products Quality‖

C) The State Enterprise ―Ukrainian Pharmaceutical Quality Institute‖

D) The State Enterprise ―State Expert Center of the Ministry of Health of Ukraine‖

E) The State Enterprise ―Ukrainian Scientific Research and Training Center for Standardization, Certification and Quality Problems‖

2. The list of tasks of the State Service of Ukraine on Medicines and Drug Control does not include the following task:

A) Licensing of the import of pharmaceuticals

B) Maintenance of a licensing register for pharmaceutical production

C) Issuance of permits to import narcotic drugs to economic entities

D) Monitoring compliance with licensing conditions for wholesale and retail trade in pharmaceuticals

E) Revision of the National List of Essential Medicines

3. The adverse reaction, the nature or severity of which corresponds to the available information about the medicinal product in the instructions for medical use, which poses a threat to life, requires patient hospitalization, can be characterized as:

A) expected non-serious

B) unexpected serious

C) expected serious

D) unexpected non-serious

E) this side effect cannot be classified

4. A medicinal product for which the applicant can demonstrate that the active substance of the medicinal product with well-established therapeutic properties within the EU for at least 10 years had recognized efficacy and an acceptable level of safety in any pharmaceutical form belongs to such type of medicinal products:

A) biosimilar

B) hybrid

C) generic

D) medicinal product with well-established medical use

E) traditional medicinal product

List of references:

1. International Organization for Standardization (ISO): Global standards for trusted goods and services – URL: https://www.iso.org/home.html

2. Legislation of Ukraine – URL: https://zakon.rada.gov.ua/laws/

3. Regulatory and directive documents of the Ministry of Health of Ukraine – URL: https://moz.gov.ua/

4. The State Expert Center of the Ministry of Health of Ukraine – URL: https://www.dec.gov.ua/

5. The State Service of Ukraine on Medicines and Drugs Control – URL: https://www.dls.gov.ua/

6. Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines – URL: https://sphu.org/viddil-dfu

Lecture No. 6

Topic 4. Statistical methods of quality control.

The relevance of the topic. Today, high product quality is regarded as one of the important conditions for economic development, which determines the pace of industrial growth in the country, the efficiency of labor resource utilization, the success of foreign trade, and national prestige. Striving to enter global markets with intense competitive battles, domestic enterprises are actively implementing quality management systems that meet recognized international requirements and stimulate continuous product improvement. Effective management of production process quality is impossible without the use of statistical methods that can timely, promptly, and objectively reflect changes in the process.

Objective: to provide higher education students theoretical knowledge regarding statistical methods of quality control.

Key concepts: quality analysis, process analysis, process control, statistical acceptance control, checklist, Pareto diagram, Ishikawa cause-and-effect diagram, histogram, scatter diagram, control chart, stratification.

Lecture plan and organizational structure:

1. The essence of statistical methods of quality control.
2. Checklist.
3. Pareto diagram.
4. Ishikawa cause-and-effect diagram.
5. Histogram.
6. Scatter diagram.
7. Control chart.
8. Stratification.

Lecture content

The essence of statistical methods of quality control

The main task of statistical methods in the quality management of production processes is to guarantee and maintain quality at all stages of production to obtain high-quality end products. Therefore, statistical process management and fact-based decision-making are the main requirements of the international standards ISO 9000 series for quality systems, which can be met through the implementation of statistical methods at enterprises.

The terminological basis for the use, selection and implementation of statistical methods is laid down in the international standard ISO/TR 10017:2021 Quality management – Guidance on statistical techniques for ISO 9001:2015.

Statistical methods help to optimize the process of finding the causes of nonconformities, increase the accuracy and reliability of conclusions, and the effectiveness of measures developed to eliminate the identified causes of failures and defects. The use of statistical methods in production practice leads to a significant reduction in costs and an increase in product quality, which is associated with production and quality analyses, process analyses, process control, and acceptance sampling:

Quality analysis is based on the premise that if it is impossible to achieve perfect quality, a certain level of defects is acceptable, for which selective control methods can be created.

Process analysis is an analysis that allows understanding the relationship between causal factors and outcomes such as quality, cost, productivity, etc.

Process control involves identifying the causal factors that affect the uninterrupted functioning of the production process.

Acceptance sampling is a selective quality control of products based on the application of mathematical statistics methods to check the compliance of product quality with the established requirements.

Among the statistical methods of quality control, the most common are the so-called seven elementary quality control tools:

1) Checklist;
2) Pareto diagram;
3) Ishikawa cause-and-effect diagram;
4) Histogram;
5) Scatter diagram;
6) Control chart;
7) Stratification.

Checklist

Whatever the task of the quality management system, which combines the sequence of application of statistical methods, always begins with the collection of initial data.

A control sheet is a form for recording data during control, on which the controlled parameters are applied.

The purpose of the control sheet is to

– to facilitate the process of collecting data on controlled parameters and identifying defects,

– automatically organize data to facilitate its further use.

Pareto diagram

A Pareto diagram is a bar graph that helps identify the primary causes (factors) of losses.

A Pareto diagram is created as follows:

1. Collect data on defects and their number.

2. Determine the total number of defects of each type that occurred over a certain period of time.

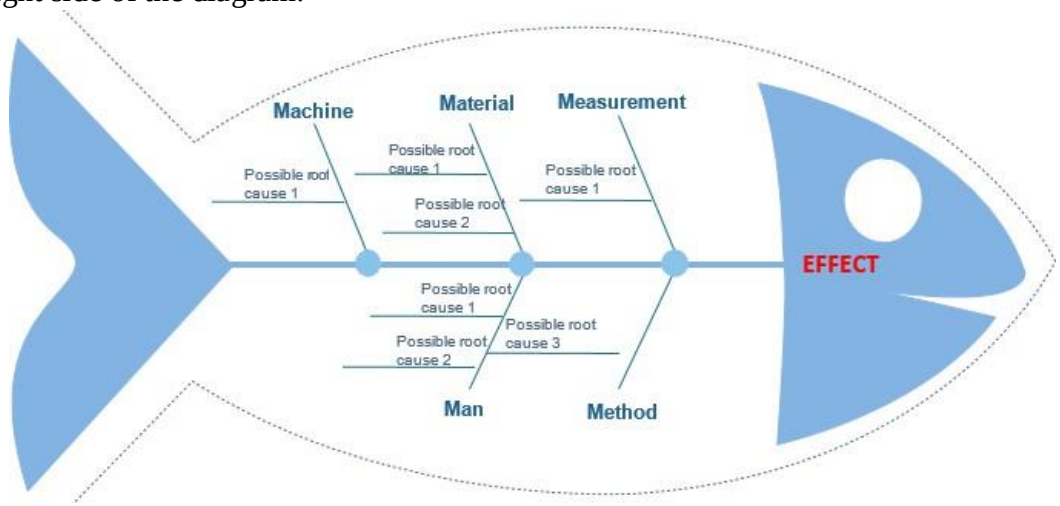
3. A bar graph is created in which the height of each column corresponds to the number of defects of a certain type. The columns are arranged in descending order of the number of defects from left to right. The main task of creating a diagram is to identify those few types of defects that have an absolute and relative majority. The elimination of these defects will ultimately result in increased product quality and the best economic effect.

Often, a Pareto diagram reveals a pattern based on the Pareto principle (the 80 % to 20 % rule), according to which most effects are caused by relatively few causes.

Ishikawa cause-and-effect diagram

The Ishikawa diagram is a graphical method of studying the most significant cause-and-effect relationships between factors and consequences in a situation or problem under study.

The Ishikawa diagram ("fish skeleton") is used when it is necessary to investigate and depict all potential causes with effects that arise during the production process. The diagram is visually based on a clear relationship between causes and effects, quality indicators and factors that influence them. "Causes" are labeled on the left side of the diagram, and effects are labeled on the right side of the diagram.



Building a cause and effect diagram.

1. When constructing a K. Ishikawa diagram, a horizontal line with an arrow ("spine") is drawn in the center, at the end of the arrow, on the right side, a quality indicator is written in the frame – this is the object of analysis / quality indicator (consequence).

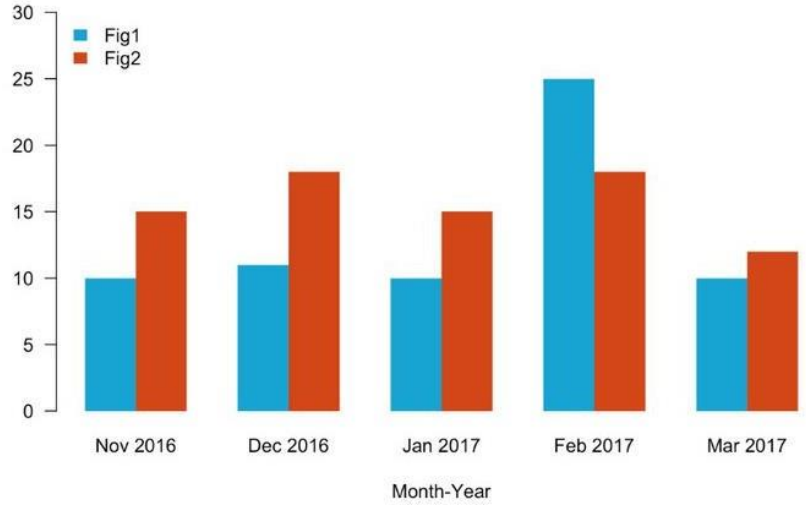
2. Large primary arrows ("big bones") are drawn to the central horizontal line representing the object of analysis. The main causes (of the first level) are placed on the "big bones" and connected with the "spine" by sloping arrows. When structuring the diagram at the level of primary arrows, in many real situations, one can use the rule proposed by Kaoru Ishikawa himself, known as the "5Ms": materials, methods, measuring, men, and machines. This rule suggests that, in general, there are five possible main causes of certain effects.

3. Further, to each primary arrow, secondary-level arrows ("middle bones") are drawn, to which, in turn, tertiary-level arrows ("small bones") and so on are drawn until all arrows representing factors that have a significant impact on the object of analysis are included in the diagram.

Thus, Ishikawa's cause-and-effect diagram allows identifying key relationships between various factors and gaining a more thorough understanding of the analyzed process. It also helps determine the main factors contributing the most significant contribution to the problem under consideration and prevents or eliminates their effects.

Histogram

A histogram is a column chart that is used to graphically represent data grouped by the frequency of falling into a certain interval. The intervals are the bases of the columns into which the data set is divided. The height of the columns is proportional to the frequency of the observation results falling into the corresponding interval.



The histogram is created in the following sequence:

a) a table of initial data is compiled;

b) the range of the analyzed parameter is estimated;

c) the width of the range is determined;

d) the starting point of the first interval is set;

e) select the final number of intervals.

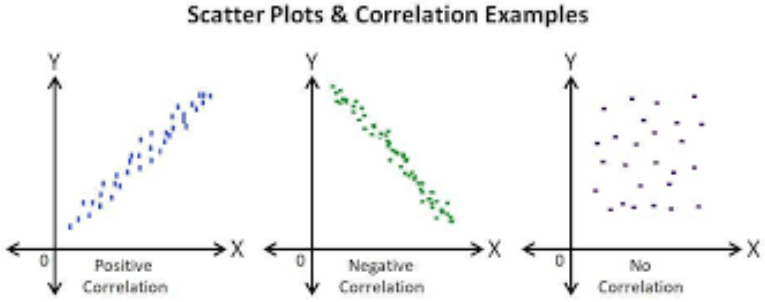
Therefore, constructing a histogram helps narrow down the search for problematic areas by demonstrating models of deviation from the desired mean level.

Scatter diagram

A scatter diagram is used to identify the dependence of one variable (product quality indicator, process parameters, etc.) on another. The diagram does not answer the question of whether one variable is the cause of another, but it can clarify whether a causal relationship exists in this case and what its strength is.

The most common statistical method for identifying such a relationship is correlation analysis, based on the estimation of the correlation coefficient. Correlations are described by the corresponding equations.

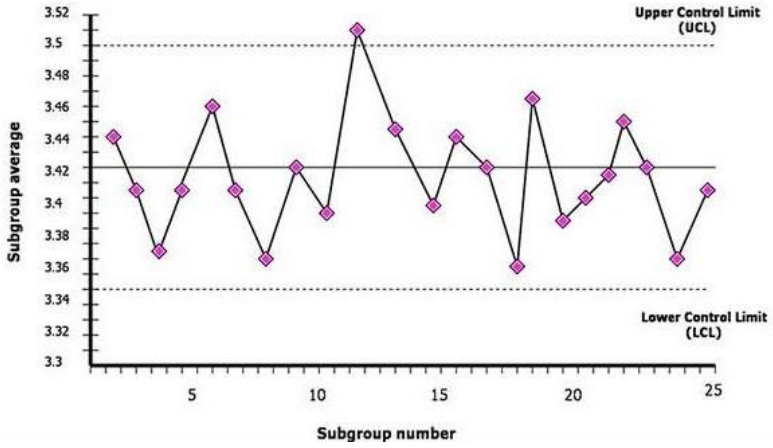
The data displayed by a scatter diagram form a correlation field. The relationship between related datasets is established based on the shape of the field. The closer the points are to the diagonal line, the greater the dependence between the two specified parameters.



Control chart

A control chart is a type of graph, but it differs from a regular graph by the presence of lines called dimensional control limits.

Any control chart consists of a center line, a pair of control limits, one above (upper limit) and one below (lower limit) the center line, and the values of product quality indicators plotted on the chart to determine suitability for use.



If all the points (values of product quality indicators) are within the control limits, the production process is considered to be in a quality state, and the products comply with the technological process and the standard. If there is an outlier point, this indicates the detection of deviations from the established norm, inconsistencies, defects and rejects, and the process is considered to be out of control. In this case, it is necessary to take corrective actions to return the quality system to the standard, or to find new conditions for manufacturing products.

The control chart helps to identify and subsequently take into account mistakes and compensate for shortcomings.

Stratification

Stratification is the division of the obtained data into separate groups depending on the selected stratifying factor. Any parameter that determines the specifics of the conditions of occurrence and receipt of data can be selected as a stratifying factor.

According to this method, statistical data are stratified, i.e., data are grouped depending on the conditions of their receipt, and each group of data is processed separately. Data divided into groups according to their characteristics are called layers (strata), and the process of dividing into layers (strata) is called stratification.

The method of stratification is often used in evidence-based medicine during clinical trials. The essence of the method lies in considering factors in the study that may influence the experiment's outcome. For example, in a clinical trial of a drug whose effect may vary depending on the age of the subject, patients are initially divided into subgroups based on age, and then randomization is conducted separately for each subgroup.

General material and educational support for the lecture: presentation materials for the lecture.

Self-assessment questions

1. What quality control tool allows to visualize the amount of loss depending on various defects, focusing on eliminating those defects that cause the most losses?

A) Scatter diagram

B) Pareto diagram

C) Cause-and-effect diagram

D) Control chart

2. Which quality control tool allows tracking the nature of process flow and influencing it to prevent deviations from the requirements set by the standard for the process?

A) Scatter diagram

B) Stratification

C) Ishikawa diagram

D) Control chart

3. Which quality control tool is used to identify the relationship between two parameters and provides the ability to determine the type and density of the relationship between them?

A) Scatter diagram

B) Pareto diagram

C) Cause-and-effect diagram

D) Control checklist

4. Which quality control tool enables the identification of the most significant factors affecting the final outcome?

A) Control checklist

B) Pareto diagram

C) Cause-and-effect diagram

D) Histogram

List of references:

1. ISO 9001:2015 Quality management systems — Requirements.

2. ISO/TR 10017:2021 Quality management – Guidance on statistical techniques for ISO 9001:2015.

Lecture No. 7

Topic 5. Regulation and documentation of pharmaceutical quality management processes.

The relevance of the topic. Document management processes for any pharmaceutical company are one of the cornerstone elements of the management system. The use of modern, effective methods and tools for document management is critical and necessary at all stages of the document flow. Implementation of a project to implement a quality management system at a pharmaceutical company requires the establishment of clear algorithms for performing document and record management activities as processes that achieve the planned results, as well as systematic tracking of the performance indicators of these processes and implementation of actions for their continuous improvement.

Objective: to provide higher education students with theoretical knowledge regarding the regulation and documentation of processes within the pharmaceutical quality system.

Key concepts: quality manual, quality policy, quality objectives, process execution methodologies, standard operating procedure, work instruction, protocol (as a record form), "inter-process" documents.

Lecture plan and organizational structure:

1. The essence of documenting the quality management system at a pharmaceutical enterprise.
2. Quality manual.
3. Process execution methodologies.
4. Third-level quality management system documents.
5. Fourth-level quality management system documents.
6. "Inter-process" documents.
7. Formulating the document control procedure.

Lecture content

The essence of documenting the quality management system at a pharmaceutical enterprise

According to the requirements of *ISO 9001:2015 Quality management systems. Requirements* the organization must document its quality management system, i.e. describe in the relevant documents all the processes of the system being established.

According to ISO 9001, at the most general level, the documentation of the quality management system should include:

a) documented quality policy and objectives;

b) quality manual;

c) documented methods and protocols required by the standard;

d) documents, including protocols, that the organization has identified as necessary to ensure the effective planning, operation and control of its processes.

The structure of the quality management system documentation is hierarchical.

Typical levels of quality management system documentation

First-level quality management system document: Quality manual

Quality manual is a conceptual document describing the quality management system. This document reflects all activities of the pharmaceutical company that affect the quality of products.

The quality manual may include the quality policy and objectives (but they may be in a separate document).

The quality policy should contain commitments to meet the requirements and continuously improve the performance of the quality management system.

Quality objectives are formed on the basis of the organization's quality policy and must be achievable.

Second-level quality management system documents: Process execution methodologies (Documented procedures)

Process execution methodologies describe the interrelated processes and activities necessary for implementing the quality management system, specifically detailing the execution of activities at the level of each individual process. Second-level methodologies may include graphical representations of activities in the form of flowcharts, which visually demonstrate the process flow, the order of interaction of internal subprocesses (operations), and the connections between them. They should contain references to accompanying documentation, define conditions for measurements, monitoring, and analysis of the process, include criteria for its effectiveness, references to reporting forms, and provide a detailed description of the distribution of responsibilities and authorities within the process, among other things. Process execution methodologies are usually developed by process owners (managers), coordinated among managers of all other processes within the quality management system, and approved by top management.

Third-level quality management system documents

The third level logically consists of specific instructions describing the algorithms for performing individual types of work (operations) within the quality management system processes, as well as documents containing requirements for the characteristics of raw materials, materials, equipment, facilities, products, personnel, etc. Such documents in a pharmaceutical company include:

- standard operating procedures (SOPs),
- work, technological, job-specific, and any other instructions,
- specifications,
- standards,
- technical conditions,
- analytical normative documentation, and more.

According to *ISO 10013:2021 Quality management systems. Guidance for documented information*, *work instructions* are detailed descriptions of how to perform tasks and record results. Work instructions can include detailed written descriptions, job sequence charts, templates, equipment operating instructions, drawings, or a combination of these.

The third level is the most numerous. Usually, such documents should be developed by individuals responsible for performing the described operation, and coordinated and verified by employees from standardization, quality management departments, and so on.

Fourth-level quality management system documents

This level may consist of record forms (*protocols*) that need to be maintained during or after the execution of processes and operations at various levels. Within the quality management system, protocols document the parameters of work execution and/or contain the characteristics of their results (e.g., test protocols, analysis reports, inspection records, validation and qualification work records, process control charts, product research results, system operation reports, etc.). These specific documents are necessary to confirm the proper execution of certain operations and processes and also provide information for their monitoring and analysis.

"Inter-process" documents

"Inter-process" documents can include provisions, internal standards, regulations, methodologies, and others that establish policies or general rules for performing certain tasks throughout the organization (e.g., "Rules for Documenting the Quality Management System"). These documents are not appropriately classified under any specific process, nor is it practical to create a separate process for the activities they regulate.

Quality management system documentation can be on any medium, such as paper or electronic.

The sequence of developing quality management system documentation does not necessarily have to follow the documentation hierarchy. Process execution methodologies and work instructions are often developed before the final version of the quality manual is completed.

Formulating the document control procedure

The ISO 9001 standard requires defining criteria and methods for all processes within the quality management system, including the document control process, to ensure their effective functioning and control. The standard also mandates the monitoring, measurement, and analysis of processes, as well as taking necessary actions to achieve planned results and ensure continuous improvement.

Based on this, it is necessary to:

1. Regulate all stages of the document lifecycle within the quality management system of the organization: from the initiation of their development, coordination, approval, distribution, and ensuring personnel awareness of their provisions, to updating, withdrawal, replacement, archiving, and destruction.

2. Clearly establish the objectives and tasks of the document control process, as well as all other "process" attributes: necessary resources and actions for managing it.

The resources of the process are determined by the organization and usually are not a problematic issue. The outputs of the process should be systematically evaluated and analyzed to identify discrepancies, take corrective actions, and continuously improve the process, which is the responsibility of the process manager. The set of managerial actions is typically described in the corresponding process execution methodology "Document Control within the Quality Management System". It is crucial that such a process execution methodology reflects all stages of the PDCA cycle during process regulation.

Therefore, it should be acknowledged that in establishing a quality management system at a pharmaceutical company, there are quite complex issues regarding the implementation of an effective document control system that complies with ISO 9001 and all other established requirements. Optimizing document control will ultimately have a positive impact on product quality, stability, and the effectiveness of all quality management system processes.

General material and educational support for the lecture: presentation materials for the lecture.

Self-assessment questions:

1. Which documents of a pharmaceutical company are managed in accordance with the requirements of ISO 9001?

A) All documents of the pharmaceutical company

B) Documents that regulate activities that affect the quality of products

C) Documents whose circulation is regulated by internal requirements of the pharmaceutical company

2. Which standard provides guidance on the development and maintenance of quality management system documentation?

A) EN ISO 9001:2015

B) ISO 9001:2015

C) ISO/TR 10013:2001

D) ISO 9004:2018

3. In which document does an organisation document its own quality management system?

A) Quality manual

B) Documented quality policy

C) Documented quality objectives

D) Process execution methodology

E) Work instruction

4. Which level of quality management system documents includes the organisation's documents that describe the distribution of responsibilities and authorities within the process?

A) To the first level

B) To the second level

C) To the third level

D) To the fourth level

E) These are "inter-process" documents

List of references:

1. ISO 9001:2015 Quality management systems — Requirements.

2. ISO 10013:2021 Quality management systems — Guidance for documented information.

3. Nalezhni praktiki u farmatsiyi: navch. posib. dlya studentiv visch. navch. zakl. / V. O. Lebedinets, O. V. Tkachenko, Yu. I. Gubin ta in. Harkiv: NFaU: Zoloti storinki, 2017. 296 s. [in Ukrainian]

Lecture No. 8

Topic 6. Risk assessment for the quality of medicinal products at all stages of their lifecycle.

The relevance of the topic. In the production of medicinal products, there is inevitably a certain level of risk involved. An effective approach to quality risk management can subsequently guarantee high product quality for the patient by implementing preventive measures to identify and control potential quality issues during development and manufacturing.

Objective: to provide higher education students with theoretical knowledge on assessing risks for the quality of medicinal products at all stages of their lifecycle.

Key concepts: risk, quality risk management, failure mode and effects analysis; failure mode, effects, and criticality analysis; fault tree analysis, hazard analysis and critical control points, hazard and operability analysis, preliminary hazard analysis, ranking and filtering of risks.

Lecture plan and organizational structure:

1. The process of quality risk management.
2. Failure Mode and Effects Analysis (FMEA).
3. Failure Mode, Effects, and Criticality Analysis (FMECA).
4. Fault Tree Analysis (FTA).
5. Hazard Analysis and Critical Control Points (HACCP).
6. Hazard and Operability Analysis (HAZOP).
7. Preliminary Hazard Analysis (PHA).
8. Ranking and filtering of risks.

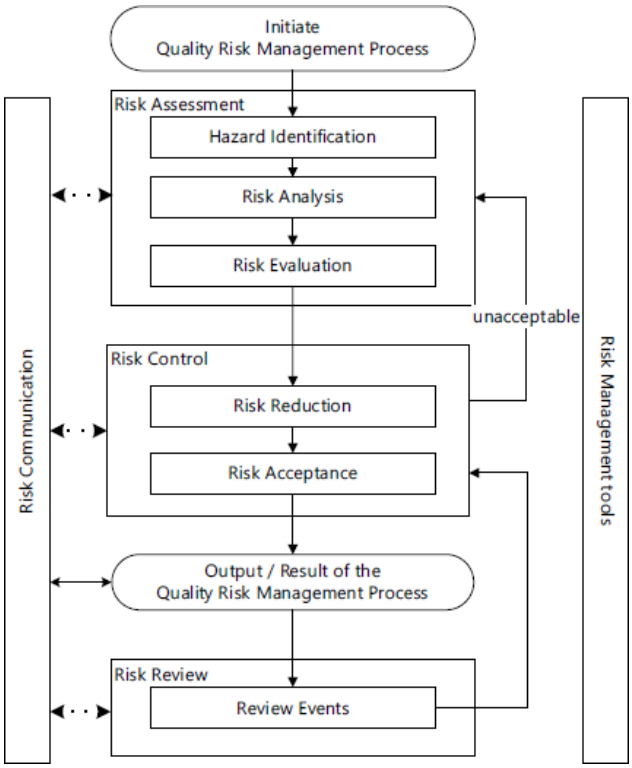
Lecture content

The process of quality risk management

Risk can be defined as the combination of the probability of an event occurring and the severity of its consequences.

ICH Harmonised Guideline Quality Risk Management Q9(R1) provides principles and examples of quality risk management tools that can be applied to various aspects of pharmaceutical quality.

A model for quality risk management process is outlined in the diagram.



Stage I: Initiating the Quality Risk Management Process

The possible steps used to initiate and plan the quality risk management process may include the following:

1. Defining the issue or risk question, including relevant assumptions that define the possibility of risk.

2. Gathering initial information and/or data regarding potential hazards, harm, or impact on human health relevant to general risk assessment.

3. Appointing a leader and defining necessary resources.

4. Establishing a schedule, expected outcomes, and appropriate level of decision-making regarding the risk management process.

Stage II: General Risk Assessment

The process of studying risk begins with a clear description of the problem associated with the risk. At this stage, risks are identified, analyzed, and assessed.

To clearly define risks, it is helpful to answer three fundamental questions:

1. What could go wrong? (*Risk identification*)

2. What is the likelihood that it will go wrong? (*Risk analysis*)

3. What are the consequences (severity)? (*Risk assessment*)

The outcome of the general risk assessment is either a quantitative risk assessment or a qualitative description of the risk range. If the risk is quantified, numerical probability is used. Alternatively, risks can be expressed using qualitative descriptors such as "high", "medium", or "low", which should be defined in as much detail as possible.

Stage III: Risk Control

The purpose of risk control is to reduce risk to an acceptable level. The amount of effort applied to risk control should be proportional to the significance of the risk.

Risk control should focus on the following issues:

1. Is the risk above an acceptable level?

2. What needs to be done to reduce or eliminate the risk?

3. What is the acceptable balance between benefits, risks, and resources?

4. Are new risks arising as a result of controlling established risks?

For certain types of harm, even the best practices in quality risk management may not completely eliminate the risk. In such cases, it may be decided that an appropriate quality risk management strategy is applied and that the quality risk is reduced to an established (acceptable) level.

Stage IV: Risk Review

Risk management should be part of an ongoing quality management process. A mechanism for event review or monitoring should be implemented.

The results of the risk management process should be reviewed considering new knowledge and experience. If the quality risk management process has been initiated, it should be continued to review events that may impact previous decisions within the quality risk management process, whether these events are planned or unplanned. The frequency of any review should be based on the level of risk.

The Risk Management Methodology

Representatives from the pharmaceutical industry and regulatory bodies can assess and manage risks using recognized risk management tools:

1. Basic auxiliary risk management methods: control charts, cause-and-effect diagrams, etc.

2. Failure Mode and Effects Analysis (FMEA)

3. Failure Mode, Effects, and Criticality Analysis (FMECA)

4. Fault Tree Analysis (FTA)

5. Hazard Analysis and Critical Control Points (HACCP)

6. Hazard and Operability Analysis (HAZOP)

7. Preliminary Hazard Analysis (PHA)

8. Risk ranking and filtering

9. Supporting statistical methods: control charts, histograms, Pareto diagrams, etc.

Failure Mode and Effects Analysis (FMEA)

FMEA provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance.

Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures.

Advantage of the method

FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

Disadvantage of the method

One of the main disadvantages of the method is its limited use to the identification of single failures rather than a combination of failures.

Potential Areas of Use

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process.

Failure Mode, Effects, and Criticality Analysis (FMECA)

Failure Mode, Effects, and Criticality Analysis (FMECA) is an expanded method derived from Failure Mode and Effects Analysis (FMEA). It includes an assessment of the severity of consequences. The result of FMECA is a relative "risk scale" for each type of failure, which is used to rank modes based on their relative risk.

Advantage of the method

FMECA can establish points where additional preventive measures are necessary to minimize risks.

Disadvantage of the method

As is the case with FMEA, one of the main disadvantages of the method is its limited use to the identification of single failures rather than a combination of failures.

Potential Areas of Use

FMECA is particularly useful in the pharmaceutical industry for addressing failures and risks associated with manufacturing processes.

Fault Tree Analysis (FTA)

FTA evaluates system failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes.

Advantage of the method

FTA is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes.

Disadvantage of the method

The disadvantage of the method is the static nature of the model, which does not take into account the time dependence factor.

Potential Areas of Use

FTA can be applied to investigate complaints or deviations to achieve a full understanding of their root causes and ensure that planned improvements fully resolve the issue without leading to other problems (i.e., solving one problem does not become the cause of another problem).

Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety. HACCP involves identifying critical control points in the production process.

HACCP consists of the following seven steps:

1) conduct a hazard analysis and identify preventive measures for each step of the process;

2) determine the critical control points;

3) establish critical limits;

4) establish a system to monitor the critical control points;

5) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;

6) establish system to verify that the HACCP system is working effectively;

7) establish a record-keeping system.

Advantage of the method

The output of a HACCP analysis is risk management information that facilitates monitoring of critical points. This allows to organize regular control at critical control points in the production process.

Disadvantage of the method

The disadvantage of HACCP is the application of measures only when the controlled parameters exceed the set limits, which does not always give effective results, because it does not allow to take into account the changes in the controlled parameter within the specified limits.

Potential Areas of Use

HACCP can be used to identify and manage risks associated with physical, chemical, and biological hazards (including microbial contamination).

Hazard and Operability Analysis (HAZOP)

HAZOP is based on the theory that risk events are the result of deviations from planned or operational parameters.

It is a systematic brainstorming technique for identifying hazards using so-called "guide-words". "Guide-words" (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or planned parameters.

Advantage of the method

As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

Disadvantage of the method

One of the main disadvantages of the method is that the method relies on expert judgement of designers, who may find it difficult to identify flaws in their own designs.

Potential Areas of Use

HAZOP can be applied to manufacturing processes, equipment, and technical means for producing active substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards.

Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm.

Advantages of the method

- It can be used in situations with limited information.
- It allows to investigate risk at early stages of the system’s life cycle.

Disadvantages of the method:

- It provides only preliminary information.
- It is not a comprehensive method and cannot provide detailed information about hazardous events and ways to prevent them.

Potential Areas of Use

PHA is most frequently used in the early stages of project development when there is limited information about the details of the plan or operational methods. PHA often serves as a preliminary tool for further investigations.

Risk ranking and filtering

The method involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. ―Filters‖, in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Advantages of the method

- The advantage of this method is the rapid acquisition of information.
- Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool.

Disadvantage of the method

The main disadvantage of the method is its relatively high level of subjectivity.

Potential Areas of Use

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry.

General material and educational support for the lecture: presentation materials for the lecture.

Self-assessment questions:

1. The purpose of risk control is:

A) Quantitative risk assessment

B) Qualitative description of the risk range

C) Reducing risk to an acceptable level

D) Gathering initial information related to risk

2. Which risk management method ensures the identification and monitoring of critical control points in the process?

A) Preliminary Hazard Analysis (PHA)

B) Fault Tree Analysis (FTA)

C) Hazard Analysis and Critical Control Points (HACCP)

D) Hazard and Operability Analysis (HAZOP)

E) The correct answers are C) and D)

3. Which risk management method allows identifying numerous system error factors by establishing causal chains?

A) Fault Tree Analysis (FTA)

B) Failure Mode and Effects Analysis (FMEA)

C) Hazard and Operability Analysis (HAZOP)

D) Preliminary Hazard Analysis (PHA)

4. Which risk management method is applied in the early stages of project development?

A) Hazard Analysis and Critical Control Points (HACCP)

B) Hazard Operability Analysis (HAZOP)

C) Preliminary Hazard Analysis (PHA)

D) Risk Ranking and Filtering Method

E) The correct answers are A) and B)

List of references:

1. ISO 31000:2018 Risk management — Guidelines.
2. IES 31010:2019 Risk management — Risk assessment techniques.

3. EMA/INS/GMP/79766/2011 Quality Risk Management (ICH Q9), 31 January 2011.

4. Nalezhni praktiki u farmatsiyi: navch. posib. dlya studentiv visch. navch. zakl. / V. O. Lebedinets, O. V. Tkachenko, Yu. I. Gubin ta in. Harkiv: NFaU: Zoloti storinki, 2017. 296 s. [in Ukrainian]

Lecture No. 9

Topic 7. Organization of activities for validating production processes and qualifying equipment and auxiliary systems in organizations that are pharmaceutical market entities.

The relevance of the topic. According to the requirements of good manufacturing practice, there must be a documented general policy of the manufacturer regarding intentions and approach to validation, as well as persons responsible for the development, verification, approval, and documentation of each stage of validation.

Objective: to provide higher education students with theoretical knowledge regarding the organization of activities related to the validation of manufacturing processes and the qualification of equipment and auxiliary systems in organizations within the pharmaceutical market.

Key concepts: validation, process validation, prospective validation, concurrent validation, re-validation, qualification, critical quality attribute, critical process parameter, acceptance criteria, specificity, accuracy, precision, detection limit, quantitation limit, linearity, range, robustness, cleaning validation, user requirements specification, design qualification, installation qualification, operational qualification, performance qualification, re-qualification.

Lecture plan and organizational structure:

1. Validation: definition of concepts, objects, types.
2. Validation staffing.
3. Validation documents.
4. Validation of analytical methods.
5. Cleaning validation.
6. Qualification: definition of concepts, objects.
7. Qualification stages.

Lecture content

Validation: definition of concepts, objects, types

Validation is the actions that, according to the principles of good manufacturing practice, demonstrate that a certain methodology, process, equipment, raw material, activity, or system actually yield the expected results.

Objects:

- technological process (for each name of medicinal product);
- methods of quality control (analytical methods);
- cleaning procedures;
- methods of in-process control testing;
- computerized systems.

Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

• *Prospective validation* is validation carried out before routine production of products intended for sale.

• *Concurrent validation* is validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches.

• *Re-validation* is the repetition of process validation to ensure that changes to the process/equipment made in accordance with change control procedures have not adversely affected process characteristics and product quality.

Qualification is actions that confirm that specific equipment is operating correctly and indeed producing the expected results. The concept of "validation" is broader and sometimes includes the concept of "qualification".

Validation staffing

At the enterprise, there should be a formed validation committee whose main task is to manage validation activities.

For each object, a validation group should be formed.

The main tasks of the validation groups are:

1) Preparation for testing (compilation of test protocols, etc.).

2) Conducting tests, documenting, recording deviations, changes, non-compliances.

3) Interpreting results, their formalization and analysis, preparation of conclusions and recommendations, preparation of a report.

Validation documents

1. Validation Master Plan

The Validation Master Plan establishes a list of objects subject to validation, defines personnel responsibilities, specifies the frequency of validation activities, and outlines documentation requirements.

The Validation Master Plan should include:

- the purpose of validation;
- an organizational scheme for validation activities;
- a list of all facilities, systems, equipment, and processes that require qualification/validation;
- the form of documentation to be used for protocols and reports;
- planning and execution schedule;
- changes control;
- references to existing documents.

2. Validation measurement protocol

This document describes the subject of qualification/validation, the type of validation being conducted (e.g., retrospective, prospective, concurrent), lists the measuring instruments to be used, the number of production cycles required for validation, critical process parameters, critical quality attributes, and associated acceptance criteria.

Critical quality attribute (CQA) is a physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality.

Critical process parameter (CPP) is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Acceptance criteria are numerical limits, intervals, or other relevant criteria for accepting the results of tests.

3. Validation Report

A document containing cross-references to the validation protocol and summarizing the obtained results, explaining any deviations identified with corresponding conclusions, including recommended changes to correct deficiencies. Any deviations from the validation protocol must be documented with appropriate justification.

Validation of Analytical Methods

If the analytical methods used are not included in the European Pharmacopoeia, or any other relevant pharmacopoeia, they must undergo validation.

The methodology for validation of analytical methods involves the determination of the following typical validation characteristics.

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

The precision of an analytical procedure expresses the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. The precision of an analytical method is usually characterized by the standard deviation or relative standard deviation for a series of measurements.

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

The linearity of an analytical procedure is its ability to obtain test results which are directly proportional to the concentration of analyte in the sample.

The range of an analytical procedure is the interval between the upper and lower concentration of analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

Cleaning validation

Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level.

Typically, cleaning validation should target stages of the process where contamination or carryover of materials pose the greatest risk to API quality. For example, validation of equipment cleaning procedures may not be necessary at the initial stages of the process if residues are removed in subsequent cleaning stages.

If different APIs or intermediate products are manufactured on the same equipment, cleaning validation takes into account the solubility data of residues and the complexity of equipment cleaning, as well as the maximum residue limits, considering their activity, toxicity, and stability.

Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used in a routine manufacturing process.

Qualification: definition of concepts, objects

Qualification is actions that confirm that specific equipment is operating correctly and indeed producing the expected results.

Objects:

- technical systems, including: premises, classified and non-classified according to cleanliness classes;
- main technological equipment;
- quality control equipment;
- engineering systems ensuring production operation (water for pharmaceutical purposes, clean steam, process gases).

Before commencing the process validation activities, it is necessary to complete the proper qualification of equipment and auxiliary systems.

Qualification stages

User requirements specification (URS)

The specification for equipment, facilities, utilities or systems should be defined in a URS. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level.

The URS should be a point of reference throughout the validation life cycle.

Design qualification (DQ)

It is the documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose. The requirements of the user requirements specification should be verified during the design qualification.

Compliance of the design with GMP should be demonstrated and documented at this stage.

Factory acceptance testing (FAT) / Site acceptance testing (SAT)

Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery.

Where appropriate and justified, documentation review and some tests could be performed at the FAT or other stages without the need to repeat on site if it can be shown that the functionality is not affected by the transport and installation.

FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.

Prior to installation, equipment should be confirmed to comply with the URS at the vendor site.

Installation qualification (IQ)

It is the documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Operational qualification (OQ)

It is the documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

OQ should include tests to confirm upper and lower operating limits, and/or "worst-case" conditions.

Performance qualification (PQ)

It is the documented verification that systems and equipment can perform effectively and reproducibly based on the approved process method and product specification.

PQ should include:

- Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions with worst case batch sizes.
- Tests should cover the operating range of the intended process.

Re-qualification

Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.

General material and educational support for the lecture: presentation materials for the lecture.

Self-assessment questions:

1. Validation, in which the batches produced during the validation protocol execution are allowed for sale, is:

A. Re-validation
B. Prospective validation
C. Qualification
D. Concurrent validation
E. Cleaning validation

2. The process parameter, the variability of which can affect a critical quality attribute, is:

A. Acceptance criteria
B. Critical process parameter
C. Critical quality attributes
D. Worst case
E. Range

3. Under the ability to identify the analyzed substance in the presence of other substances that may be in the sample, the following validation characteristic of the analytical method is understood:

A. Accuracy
B. Specificity
C. Reproducibility
D. Precision
E. Linearity

4. Documented verification that facilities, systems and equipment, when used together, can function with reproducible results based on an approved process method and product specification is:

A. Requalification
B. Design qualification
C. Installation qualification
D. Operational qualification
E. Performance qualification

List of references:

1. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use.

2. EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev 1 Guideline on process validation for finished products – information and data to be provided in regulatory submissions.

3. Nalezhni praktiki u farmatsiyi: navch. posib. dlya studentiv visch. navch. zakl. / V. O. Lebedinets, O. V. Tkachenko, Yu. I. Gubin ta in. Harkiv: NFaU: Zoloti storinki, 2017. 296 s. [in Ukrainian]

Lecture No. 10

Topic 8. Audits of pharmaceutical quality systems.

Relevance of the topic. A modern pharmaceutical enterprise represents a rather complex and, at the same time, well-organized system. One of the most common tools for assessing the functioning of this system is the conduct of audits, as this procedure is defined both by the rules of good manufacturing practice and the requirements of ISO 9001:2015.

Objective: to provide higher education students with theoretical knowledge about audits of pharmaceutical quality systems.

Key concepts: audit, audit object, audit group, internal audit, external audit, combined audit, joint audit, audit criteria, audit evidence, audit program.

Lecture plan and organizational structure:

1. Concept of audit, classification of audits, audit criteria and evidence.
2. Principles of auditing.
3. Process flow for the management of an audit programme, audit methods.
4. Process flow for the performing an audit.
5. Conducting audit follow-up.

Lecture content

Concept of audit, classification of audits, audit criteria and evidence

The procedure for conducting audits of the functioning of a pharmaceutical enterprise (systematic analysis of the system) is defined by GMP rules and the requirements of ISO 9001:2015 *Quality management systems. Requirements.* Guidelines for conducting management system audits and evaluating the competence of persons involved in the audit process are presented in the standard ISO 19011:2018 *Guidelines for auditing management systems*.

Audit is systematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled.

Classification of audits

Internal audits (first party audits) are conducted by the organization itself, or on its behalf, for management review and other internal purposes.

External audits include second and third party audits.

Second party audits are conducted by parties having an interest in the organization, such as customers, or by other persons on their behalf.

Third party audits are conducted by independent auditing organizations, such as regulators or those providing certification.

Combined audit is carried out together at a single auditee (organization as a whole or parts there of being audited) on two or more management systems.

Joint audit is conducted at a single auditee by two or more auditing organizations.

Audit criteria and evidence

Audit criteria are set of requirements used as a reference against which objective evidence is compared.

Audit evidence records, statements of fact or other information, which are relevant to the audit criteria and verifiable.

Audits are conducted to determine compliance with a range of audit criteria, either separately or in combination:

– requirements defined in one or more management system standards;
– policies and requirements defined by relevant interested parties;
– legal and regulatory requirements.

Principles of auditing

Conducting an audit is based on 7 principles:

1. Adherence to ethical norms — the foundation of professionalism.

Auditors and the person managing an audit programme should:

– perform their work with honesty, diligence, and responsibility;
– demonstrate their competence while performing their work;
– perform their work in an impartial manner, i.e. remain fair and unbiased in all their dealings;
– be able to withstand any pressure that could influence their judgments during the audit.

2. Honesty in reporting results — the obligation to report truthfully and accurately.

Audit findings, audit conclusions and audit reports should reflect truthfully and accurately the audit activities. Significant obstacles encountered during the audit and unresolved diverging opinions between the audit team and the auditee should be reported.

3. Due professional care — the demonstration of diligence and prudence during the audit.

Auditors should exercise due care in accordance with the importance of the task they perform and the confidence placed in them by the audit client and other interested parties. An important factor in carrying out their work with due professional care is having the ability to make reasoned judgements in all audit situations.

4. Confidentiality — protection of information.

Auditors should exercise discretion in the use and protection of information acquired in the course of their duties.

5. Independence — the principle of impartiality in auditing and objectivity of audit conclusions.

Auditors should be independent of the activity being audited wherever practicable, and should in all cases act in a manner that is free from bias and conflict of interest.

6. Evidence-based approach — a rational method for forming reliable and reproducible audit conclusions in a systematic audit process.

Records, factsheets, or other information related to audit criteria (*audit evidence*) should be verifiable.

7. Risk-based approach — an approach to auditing that considers risks and opportunities.

The risk-based approach significantly influences the planning, conduct of audits, and preparation of audit reports to ensure that audits focus on issues important to the audit client.

The diagram illustrates the process flow for the management of an audit programme, including performing an audit

Audit programme – the arrangements for a set of one or more audits planned for a specific time frame and directed towards a specific purpose.

1. Process flow for the management of an audit programme

1.1 Establishing the audit programme objectives

The audit client (*organization or person requesting an audit*) should ensure the establishment of the audit programme objectives.

These objectives can be based on consideration of the following:

- needs and expectations of interested parties, including customers;
- management system requirements;
- need for supplier evaluation;
- risks to the auditee and auditee's level of performance;
- results of previous audits.

1.2 Determining and evaluating audit programme risks and opportunities

The person managing the audit programme should identify and describe to the audit client the risks, as well as the requirements for resources, so that they can be properly taken into account.

1.3 Establishing audit programme

The person managing the audit programme should determine the scope of the audit programme and the resources of the audit programme (financial and time resources, availability of auditors and technical experts whose competence corresponds to the specific objectives of the audit programme, etc.).

1.4 Implementing audit programme

The person managing the audit programme should implement the audit programme by means of the following:

- communicating the pertinent parts of the audit programme to relevant parties and informing them periodically of its progress;
- coordinating and scheduling audits and other activities relevant to the audit programme;
- ensuring the selection of audit teams with the necessary competence;
- providing necessary resources to the audit teams;
- ensuring that audit activities are recorded and records are properly managed and maintained.

Audit methods

Based on location of the auditor:

On-site audit activities are performed at the location of the auditee, involving:

- Conducting interviews.
- Completing checklists and questionnaires with auditee participation.
- Conducting document review with auditee participation.
- Sampling.

Remote audit activities are performed at any place other than the location of the auditee, regardless of the distance via interactive communication means.

Based on the level of involvement of the auditor and the auditee:

Interactive audit activities involve interaction between the auditee's personnel and the audit team.

Non-interactive audit activities involve no human interaction with persons representing the auditee but do involve interaction with documentation.

1.5 Monitoring audit programme

The person managing the audit programme should monitor its implementation considering the need to:

- evaluate conformity with audit schedules;
- evaluate the ability of the audit teams to implement the audit plan;
- evaluate feedback from auditees and auditors.

1.6 Reviewing and improving audit programme

The person managing the audit programme should review the audit programme to assess whether its objectives have been achieved.

2. Process flow for the performing an audit

2.1 Initiating audit

When an audit is initiated, the responsibility for conducting the audit remains with the assigned audit team leader until the audit is completed.

The initial contact with the auditee for the performance of the audit should be made by the audit team leader. The purposes of the initial contact are the following:

- establish communications with the auditee's representatives;
- confirm the authority to conduct the audit;
- provide information on the audit objectives, scope, methods and audit team composition, including technical experts;
- confirm the agreement with the auditee regarding the extent of the disclosure and the treatment of confidential information;
- make arrangements for the audit including scheduling the dates.

2.2 Preparing audit activities

2.2.1 Performing document review in preparation for the audit

The relevant management system documentation of the auditee should be reviewed in order to gather information to prepare audit activities.

2.2.2 Preparing the audit plan

The audit team leader should prepare an audit plan based on the information contained in the audit programme and in the documentation provided by the auditee.

The audit plan should cover or reference the following:

- the audit objectives;
- the audit scope, including identification of the organizational and functional units, as well as processes to be audited;
- the audit criteria and any reference documents;
- the locations, dates, expected time and duration of audit activities to be conducted, including meetings with the auditee's management;
- the audit methods to be used;
- the roles and responsibilities of the audit team members, as well as guides and observers.

2.2.3 Assigning work to audit team

The audit team leader, in consultation with the audit team, should assign to each team member responsibility for auditing specific processes, activities, functions or locations.

2.2.4 Preparing work documents

The audit team members should collect and review the information relevant to their audit assignments and prepare work documents.

2.3 Conducting the audit activities

2.3.1 Assigning roles and responsibilities of guides and observers

Guides and observers may accompany the audit team with approvals from the audit team leader, audit client and/or auditee. Their responsibilities should include the following:

a) assisting the auditors in identifying individuals to participate in interviews and confirming timings and locations;

b) arranging access to specific locations of the auditee.

2.3.2 Conducting the opening meeting

The purpose of the opening meeting is to:

- confirm the agreement of all parties to the audit plan;
- introduce the audit team;
- ensure that all planned audit activities can be performed.

2.3.3 Communicating during audit

During the audit, the audit team leader should periodically communicate the progress of the audit and any concerns to the auditee. Evidence collected during the audit that suggests an immediate and significant risk to the auditee should be reported without delay to the auditee.

2.3.4 Audit information availability and access

Where, when and how to access audit information is crucial to the audit. The location is where the information needed for the specific audit activity is available to the audit team. This may include physical and virtual locations.

2.3.5 Reviewing documented information while conducting audit

The auditee's relevant documented information should be reviewed to determine the conformity of the system, as far as documented, with audit criteria.

2.3.6 Collecting and verifying information

During the audit, information relevant to the audit objectives, scope and criteria should be collected by means of appropriate sampling and should be verified, as far as practicable.

2.3.7 Generating audit findings

Audit evidence should be evaluated against the audit criteria in order to determine audit findings. Audit findings can indicate conformity or nonconformity with audit criteria. Nonconformities and their supporting audit evidence should be recorded.

2.3.8 Determining audit conclusions

Audit conclusions should address issues such as the extent of conformity with the audit criteria and robustness of the management system.

Any diverging opinions regarding the audit findings or conclusions between the audit team and the auditee should be discussed and, if possible, resolved. If not resolved, this should be recorded.

2.4 Preparing and distributing audit report

The audit team leader should report the audit conclusions in accordance with the audit programme. The audit report should then be distributed to the recipients as defined in the audit programme.

2.5 Completing audit

The audit is completed when all planned audit activities have been carried out.

3. Conducting audit follow-up

The outcome of the audit can, depending on the audit objectives, indicate the need for corrections, or for corrective actions, or opportunities for improvement. Such actions are usually decided and undertaken by the auditee within an agreed timeframe. The completion and effectiveness of these actions should be verified. This verification may be part of a subsequent audit.

General material and educational support for the lecture: presentation materials for the lecture.

Self-assessment questions:

1. An audit of a pharmaceutical enterprise conducted by a government body to assess compliance with GxP requirements belongs to following type of audit:

A) Combined audit

B) Third party audit

C) Second party audit

D) Internal audit

E) Joint audit

2. When conducting an audit of a pharmaceutical enterprise to assess compliance with good manufacturing practice requirements, what documentation is used as the audit criteria?

A) GMP

B) All documents of the pharmaceutical enterprise

C) Documents of the pharmaceutical enterprise that regulate activities affecting product quality

D) Documents whose circulation is regulated by internal requirements of the pharmaceutical enterprise

E) Documented procedures of the pharmaceutical enterprise

3. When conducting an audit of a pharmaceutical enterprise, what documentation is used as the audit evidence?

A) GMP

B) Licensing conditions for the production of medicinal products, wholesale, and retail trade in medicinal products

C) Documents of the pharmaceutical enterprise

D) All options are correct

4. Who determines the scope and resources of the audit programme?

A) Person representing the auditee

B) Audit team

C) Audit client

D) Person managing the audit programme

E) Technical expert

Список використаних джерел:

1. ISO 9001:2015 Quality management systems — Requirements.
2. ISO 19011:2018 Guidelines for auditing management systems.
3. Nalezhni praktiki u farmatsiyi: navch. posib. dlya studentiv visch. navch. zakl. / V. O. Lebedinets, O. V. Tkachenko, Yu. I. Gubin ta in. Harkiv: NFaU: Zoloti storinki, 2017. 296 s. [in Ukrainian]