Ministry of Health of the Russian Federation
Volgograd State Medical University

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GENERAL PHARMACEUTICAL CHEMISTRY

STANDARDIZATION AND VALIDATION IN PHARMACY

Lesson 5
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Discipline

GENERAL PHARMACEUTICAL CHEMISTRY

LESSON №5 Standardization and validation in pharmacy	State system for quality assurance of medicines. Standardization of medicines. Validation. Concept and principles.

QUESTIONS FOR THE LESSON

1. What is standardization?
2. What is the standard?
3. What objects of standardization do you know?
4. What are the main directions for the development of standardization in health care?
5. What are the main tasks of standardization?
6. What normative documentation for standardization exists?
7. What is validation?
8. What regulatory framework for standardization exists?
9. What types of validation exist?
10. List the main steps of validation.
11. List the main validation parameters. Give their characteristics.

STANDARDIZATION SYSTEM IN HEALTH CARE

THE MAIN DIRECTIONS OF STANDARDIZATION OF MEDICINES

Standardization in drugs circulation - establishing and applying standards that contain a set of rules, regulations, requirements for the object of standardization, including all drugs, including homeopathic, parapharmaceutical products, services and processes in drug circulation, ensuring their quality.

Standardization of medicinal products is the main guarantee of their high quality in serial production and ensures efficiency and safety of use.

A standard is a reference or sample, which is taken as a reference in order to compare other similar objects with it.

A standard as a normative document establishes a set of rules or requirements for the object of standardization. Using standards contributes to improving the quality of products.

The ***objectives*** of standardization are:

1. Protection of consumers and the state on the quality of pharmaceutical products, processes of their production, promotion, storage;
2. To increase safety of life and health of citizens, property of physical and legal persons, to improve safety, safety of life of animals and plants;
3. Provide competitiveness and quality of products (works, services);
4. Promotion of compliance with technical regulations.

Thus, standardization ensures pharmacological, environmental, technological safety and rational use of resources.

Main directions for the development of standardization in health care:

1. Standardization of health care services;
2. Standardization of pharmaceutical provision; regulation of requirements to the conditions of health care provision;
3. Standardization of professional activities;
4. The standardization of information support.

Standardization solves the following major ***tasks***:

1. Development of regulatory requirements for the quality of finished products, as well as for the quality of raw materials, semi-finished products used in their manufacture;
2. Development of requirements and regulations in the design and manufacturing of products, methods and means of testing and control;
3. Ensuring uniformity and accuracy of measurements in the country, development of new measurement standards and improvement of the existing ones;
4. Improvement of systems of terminology and designations in various branches of science and technology, participation in the work of international standardization organizations;
5. Provision of high quality of production through a unified system of quality indicators, methods of control and research of finished products, as well as raw materials and supplies necessary for their production;
6. Increasing conformity of products, processes, etc. with their functional purpose, as well as elimination of technical barriers in international exchange of goods;

7. Development of international recommendations and standards, etc. Standard for voluntary (recommendatory) multiple use establishes the characteristics of products, rules of implementation and characteristics of the processes of production, operation, storage, transportation, sale and utilization, performance of works or rendering of services. National standard shall be applied voluntarily and may serve as a proof base for implementing the relevant technical regulations.

Drug provision is a major area of standardization in its own. Medicines, their production, quality, conditions of sale are the most important objects of standardization in health care.

Requirements for the development of new medicines include regulation of creation processes, preclinical and clinical trials, technology development, registration rules, production regulations, product quality control. Marketing requirements regulate storage, transportation, certification, wholesale and retail sale rules, and dispensing of medicines to patients in health care facilities.

The goal of standardization in pharmaceutical provision is to create a regulatory framework that allows the realization of the objectives of providing the population with safe and quality medicines.

NORMATIVE DOCUMENTATION FOR STANDARDIZATION

A product standard is a technical specification document that specifies the requirements that a product must meet in order to ensure that it meets its intended use. In order to ensure that they are fit for their intended use.

There are the following main types of standards:

- State standard of Russia,
- Industry standard,
- Standard of an enterprise,
- Technical conditions.

State Standard of Russia (GOST)- adopted by the Federal Agency for Technical Regulation and Metrology - Rosstandart.

Industry standard (OST) - adopted by the state governing body within its competence.

Enterprise standard (ES) - adopted by the enterprise. It reflects the inherent features of each enterprise technological process for obtaining goods and contains a list of quality indicators, which should be below the requirements of GOST or OST for similar products.

Standards of technical specifications (TS) - establish comprehensive technical requirements, as well as set out the rules of acceptance, methods of

quality testing, requirements for packaging, labelling, transportation and storage of goods.

The International Organization for Standardization (ISO) approves **ISO International Standards**. International Standards are designed to develop universally recognized standards, regulations and similar instruments to facilitate the international exchange of goods and services.

VALIDATION

Getting reliable information about the quality of medicinal products has led to the need to select the best methods for solving standardization problems, i.e. the choice of analysis techniques.

Validation is the experimental proof of the suitability of a method for to solve a problem.

Validation - documented actions, according to good manufacturing practice, prove that a particular technique, process, equipment, raw material or system actually produce the expected results.

The word "VALID" was first used in English in 1648 and translated means "valid", meaning:

- actual, having validity,
- strong, well-founded,
- underpinned by a sound, logical foundation.

So, to validate is to make valid, to assert, to justify, giving validity. Both processes and test methodologies are validated. At the moment, validation is a mandatory part of the GMP.

REGULATORY FRAMEWORK FOR VALIDATION

Using validation in the pharmaceutical industry came about by borrowing from the aerospace industry in 1960. It was first applied to the validation of sterilisation processes and the production of solid dosage forms. Today, some 140 countries have joined the system of quality assurance (certification) of medicines in international trade, based on GMP standards.

The international documentation base for one of its sections contains regulatory documents of validation of methods: the US Pharmacopeia "Validation of Compendial Methods" and the International Harmonisation Conference (ICH) documents.

They clearly define

- the *purpose* of method validation,

- the *object* of application of the procedure: “test methods used for assessing the conformity of pharmaceutical products Techniques used to assess the conformity of pharmaceutical products with specific technical requirements”.
- *The range of techniques* to be validated is defined (new, or amended, to be submitted for validation).

The ICH documents, besides the above, contain approaches to the method validation process. A distinctive feature of validation work is the need for specialists from different disciplines to work together: pharmacists, technologists, engineers, metrologists, etc. To date, there is no unified approach to preparing validation documents - VMP, protocols, reports. Therefore, each company can develop its own form to prove that the technological process is really reliably designed and guarantees the conformity of the final product quality with the regulations and regulatory requirements.

VALIDATION PROCESS

The technological process of drug production is a set of interrelated activities. In order to prove that the process is stable and repeatable, the process must be validated at least 3 times according to an established procedure.

In Russia, validation is compulsory in pharmaceutical production is prescribed by OST 42-510-98 “Rules of manufacture and quality control of medicinal products”.

Prospective validation - validation performed prior to the start of mass production of products intended for sale.

Concurrent validation - validation that is carried out during the serial production of products intended for sale.

Retrospective validation - attestation of the serial production process of the product being sold, based on the received data on the production and control of the product series.

Revalidation - repetition of the initial process validation to ensure that changes to the process (equipment) made under the change control procedure do not impair process performance and product quality.

Revalidation is carried out:

- ✓ in a planned manner within the time frame set by the enterprise in the Validation Report.
- ✓ before the resumption of production in cases of changes in documentation and / or production conditions that may affect the quality of the semi-finished product and the finished product. Validation work is determined by the enterprise based on the changes made.

PARTICULAR CASES OF VALIDATION, THE DEFINITION OF WHICH IS GIVEN IN GMP:

Qualification - Action of proving that any premises, equipment and supporting systems work correctly and actually lead to the expected results.

Analytical Validation(AV) - documented confirmation that the approved control method is suitable for the manufacture and quality control of medicines.

Cleaning Validation (CV) - documented confirmation that an approved cleaning procedure provides the level of equipment cleanliness required for manufacturing medicines.

Process validation (PV) - the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

BASIC VALIDATION STEPS

- ✓ Clearly developed internal documentation.
- ✓ Validation master plan.

Based on the developed validation master plan, a validation protocol is prepared.

A validation protocol is an internally controlled document that describes how to proceed with process validation.

Validation of technological processes for the production of drugs represents the final stage of the entire validation process, which is carried out after the completion of the following works:

- validation of the analytical techniques to be used in the production control and the control of the finished product;
- validation of methods for controlling microbial contamination of equipment, technological clothing, production environment;
- qualification of equipment, approval of the schedule of preventive maintenance;
- validation of auxiliary processes (cleaning of equipment, sanitization of industrial premises);
- approval of industrial regulations;
- conducting an input analysis of raw materials, auxiliary and packaging materials;
- personnel training;
- implementation of the change control system.

VALIDATION PARAMETERS

In all normative documents on validation, the methodological part begins with the definition of validation parameters.

The following parameters are used to validate the techniques:

Trueness. Trueness of a technique is the closeness of the results got using the technique to the true value. The trueness of a technique can be determined by the analysis of samples of material prepared with quantitative accuracy.

Precision. The precision of a method is the degree of agreement between individual test results. It is measured by the deviation of individual results from the mean and is usually expressed as a standard deviation or as a coefficient of variation.

Convergence. This is the precision of the method when performed by the same analyst under the same conditions (same reagents, equipment, setting of any parameters and laboratory) and within a short time.

Reproducibility. It is the precision of a technique when performed under different conditions (usually in different laboratories) on separate, presumably identical samples taken from the same homogeneous series of material.

Robustness. Robustness is the ability of a technique to provide analytical results with acceptable trueness and precision when conditions change.

Linearity and range. The ***linearity*** of an analytical method is its ability to give results which are directly proportional to the concentration of the substance of analysis in the samples. The ***range*** of a technique is expressed as the highest and lowest concentration, within which the substance of analysis is demonstrated to be detected with acceptable precision, trueness, and linearity.

Specificity (Selectivity). The specificity (selectivity) of a technique is its ability to measure an analyte in such a way that it is free from the influence of other components of the analyzed sample (for example, impurities that are process impurities or degradation products).

Sensitivity. Sensitivity is the ability of a test procedure to detect small changes in concentration.

Detection Limit. The detection limit is the lowest level at which an analyte can be detected.

Quantification Limit. The quantification limit is the lowest concentration of a test substance in a sample that can be determined with suitable trueness and precision when the required method is applied.

Methods of quantitative determination, including methods of determination of impurities are subject to validation.

Identification methods are validated when it is necessary to confirm their specificity.