Ministry of Health of the Russian Federation
Volgograd State Medical University

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GENERAL PHARMACEUTICAL CHEMISTRY

METROLOGY. BASIC CONCEPTS OF METROLOGY.

Lesson 6
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Discipline

GENERAL PHARMACEUTICAL CHEMISTRY

LESSON №6 Metrology. Basic concepts of metrology.	Metrology. Basic concepts of metrology. Metrological characteristics of the analysis results. Statistical processing of results.

QUESTIONS FOR THE LESSON

1. History of metrology. Unity of metrological standards in different countries.
2. Metrology. Main sections. Goals and objectives. Terms and definitions of metrology.
3. Medical metrology. Measurement normalization methods.
4. Metrology in pharmacy.
5. Metrological characteristics of the results of the analysis.
6. Statistical processing of results.

HISTORY OF METROLOGY

Metrology dates back to ancient times. Ancient forms of metrology comprised local authorities setting simple, arbitrary standards, often based on simple practical measurements, such as arm length. The earliest standards were introduced for quantities such as length, weight and time. This simplified commercial transactions and the recording of human activity.

Metrology gained a new significance during the industrial revolution, it became absolutely necessary to ensure mass production.

Historically important stages in the development of metrology:

- 18th century - establishment of the meter standard (the standard is kept in France, at the Museum of Weights and Measures; nowadays it is more of a historical exhibit than a scientific instrument.);
- 1832 - Karl Gauss's creation of absolute systems of units;
- 1875 - signing of the International Metric Convention;
- 1960 - development and establishment of the International System of Units (SI);
- 20th century - International Metrology Organisations coordinate metrological studies of individual countries.

International Bureau of Weights and Measures (BIPM) is a permanent organisation headquartered in Sèvres, near Paris, France. Its principal task is to ensure that a uniform system of measurements exists in all the countries that are party to the metric convention. It does this by comparing national measurement standards and by carrying out research in metrology with a view of improving accuracy. The member countries of the Metrology Convention finance the Bureau.

International Committee of Weights and Measures comprises 18 members, each representing one member country. It meets annually at the headquarters of the International Bureau of Weights and Measures. The Committee oversees the work of the International Bureau of Weights and Measures, co-ordinates metrological research in the Member countries and drafts. It advises the General Conferences on Weights and Measures.

General Conferences on Weights and Measures are convened every four years. Representatives of all countries taking part in the metric convention and observers from associate members take part in them. The Conference hears the report of the International Committee of Weights and Measures, decides aimed at improving and spreading the International System of Units (SI), approves the budget of the International Bureau of Weights and Measures for the next four years.

METROLOGY

Metrology is the science of measurements, methods and means of ensuring their unity and ways to achieve the required accuracy.

Metrology is the science of measurement and its application.

The subject of metrology is the extraction of quantitative information about the properties of objects with an accuracy and reliability; the regulatory framework for this is metrological standards.

Goals and objectives of metrology

- ✓ creation of a general theory of measurements;
- ✓ establishment of units of physical quantities and systems of units;
- ✓ development and standardization of methods and measuring instruments, methods for determining the accuracy of measurements, the foundations for ensuring the uniformity of measurements and the uniformity of measuring instruments (the so-called "legal metrology");
- ✓ creation of standards and exemplary measuring instruments, verification of measures and measuring instruments. The priority subtask of this direction is the development of a system of standards based on physical constants.

- ✓ development of the system of measures, monetary units and accounts in the historical perspective.

Sections of metrology:

- ***Theoretical or fundamental*** metrology - considers general theoretical problems (development of the theory and problems of measuring physical quantities, their units, measurement methods).
- ***Applied metrology*** – studies the issues of practical application of developments in theoretical metrology. She is in charge of all issues of metrological support.
- ***Legal metrology*** - establishes mandatory technical and legal requirements for the use of units of physical quantity, methods and measuring instruments.

Axioms of metrology:

- ✓ Any measurement is a comparison.
- ✓ Any measurement without a priori information is impossible.
- ✓ The result of any measurement without rounding off the value is a random value.

Terms and definitions of metrology

A metrologist is a specialist in metrology.

Unity of measurement is the condition of measurement in which the results are expressed in legal units whose dimensions within prescribed limits are equal to those of the units reproduced by the primary standards, and in which the errors of measurement are known and, with a given probability, are within prescribed limits.

International System of Units SI - system of units, based on the International System of Quantities (ISQ), their names and symbols, including a series of prefixes and their names and symbols, together with rules for their use, adopted by the General Conference on Weights and Measures (CGPM).

A physical quantity is one property of a physical object, which is qualitatively common for many physical objects, but quantitatively individual for each of them.

Measurement - a set of operations for the use of a technical means that stores a unit of a physical quantity, providing a ratio of the measured quantity with its unit and getting the value of this quantity.

Measuring instrument is device used for making measurements, alone or in conjunction with one supplementary devices.

Indication is quantity value provided by a measuring instrument or a measuring system.

Verification of a measuring instrument is conformity assessment procedure (other than type evaluation) which results in the affixing of a verification mark and/or issuing of a verification certificate.

Measurement error - deviation of the measurement result from the true value of the measured value.

Error of the measuring instrument is the difference between the indication of the measuring instrument and the actual value of the measured physical quantity.

Accuracy of the measuring instrument is a characteristic of the quality of the measuring instrument, reflecting the proximity of its error to zero.

License is a permit issued by the bodies of the state metrological service in the territory assigned to it by an individual or legal entity to carry out activities for the production and repair of measuring instruments.

Unit of measurement standard is a technical tool designed to transfer, store and reproduce a unit of magnitude.

MEDICAL METROLOGY

Human life and health are the most precious thing in the world. In medical institutions, doctors restore and save people's health every day. To cope with this task, accurate and reliable data about the patient's condition, got with the help of measuring equipment used in medicine, help. Therefore, ensuring the uniformity of measurements in medical practice is always relevant.

Medical metrology is a field of metrology, the principal task of which is to ensure the unity and reliability of measurements in medicine. Medical metrology data are used in medical information systems.

Medical measuring instruments, mainly measuring instruments, can be divided into three groups according to the method of normalizing their measurement ranges and accuracy characteristics

The first group is devices calibrated directly in units of those physical quantities, the values of which are the final measurement information that allows making a medical conclusion (thermometer, dynamometer).

The second group are devices in intermediate values, the measured values of which still need to be converted into final information using another device or by calculation (photoelectric colorimeters).

The third group is devices that are characterized by the representation of their metrological properties using auxiliary quantities and parameters (electrocardiograph).

One of the most important tasks of medical metrology is the development of methods and tools that will allow for all medical measuring instruments to achieve such an expression of accuracy parameters that, if the metrological requirements are met, will be sufficiently informative for the doctor. The correctness of the diagnosis and the effectiveness of the treatment prescribed by the doctor depend on the accuracy of their testimony.

All medical equipment products can only be approved for use by order of the Ministry of Health. For the use of medical measuring instruments, besides the order of the Ministry of Health, a positive decision of the State Committee of Standards is required.

- ✓ Medical devices (electrophoresis, UHF, magnetic and laser therapy, laser cameras, defibrillators, etc.), which are used for physiotherapy procedures, must pass the control of output parameters and have a valid certificate of suitability for use.
- ✓ Test equipment (drying cabinets, sieves, thermostats, ovens, etc.), which is used to reproduce normalized external influencing factors (loads), must be certified and have a valid certificate.
- ✓ Measuring equipment (diagnostic equipment, scales, blood pressure monitors, etc.), which are used to obtain data about the patient's condition, must be verified (state metrological certification) and have a valid certificate of verification (state metrological certification).

Currently, medical measurements in most cases are carried out by medical personnel who are not technically trained. Therefore, it is advisable to create medical devices graduated in units of physical quantities, the values of which are the final medical measurement information (direct measurements).

METROLOGY IN PHARMACY

Technical progress, improvement of technological processes, production of effective and safe medicines are impossible without measuring their quality parameters.

Measurements are carried out both in order to establish the actual parameters of medicines and medical equipment and their compliance with the requirements of regulatory documentation, and to check the accuracy of the technological process and improve it to prevent the occurrence of defects.

When controlling finished dosage forms, they check the compliance of the actual values of chemical, mechanical, physical and other parameters with the permissible values of these parameters established in the pharmacopoeia.

<u>Measuring</u>

Measuring instruments are used to determine the quality of preparations.

Measuring instruments - technical means, devices and equipment having normalized metrological properties.

Measuring instruments are divided into 2 classes:

1. ***Exemplary measuring instruments*** are measures, measuring instruments or transducers approved as exemplary. Exemplary measuring instruments exist and are maintained in perfect condition at the institutes of Rosstandart, regional centers of metrology. They control the correct operation of working measuring instruments - devices on the desktop in a pharmacy laboratory. Reference measuring instruments periodically are verified according to the standards that are in the national institutes of metrological support.

2. ***Working measuring instruments*** are measures, devices, or devices used for measurements during working hours.

Depending on the physical measurement principles used, there are:

- electrical;
- pneumatic;
- optical;
- photoelectric and other measuring instruments.

Measurement methods

A measurement method is a set of rules and techniques for using measuring instruments that allows solving a measurement problem.

There are direct and indirect measurement methods.

In direct measurements, the value of the measured quantity is found directly from experimental data. Most measuring instruments are based on direct measurements, such as temperature measurement with a thermometer, tablet diameter with a caliper, etc.

In indirect measurements, the desired value of the value is found by calculating the known relationship between this value and the values subjected to direct measurements, for example, measuring the concentration of the active substance - according to the consumption of the reagent used for titration.

A variation of the indirect method is the comparison method.

Comparison method - a measurement method based on the use of a working standard and a measuring device for comparison. In this case, the obtained measurement result is compared with a test under the same conditions as a working standard sample. For example, the measurement of the optical density of the test solution and the RSO solution in a quantitative analysis by spectrophotometry.

Metrology in pharmacy practice

The main operations that are used in preparing medicines are dosing, associated with measuring the mass of a substance, and measuring it in certain portions (doses). In pharmacy practice, the most used dosing methods are *weighing and measuring by volume and drops*.

The pharmacological effect of the prepared drugs, and hence their therapeutic effect on the body, depends on the accuracy of the execution of these operations. Dosing is carried out with the help of special devices, which are subject to requirements, and they use the metrological system of measures, which is accepted and mandatory in our country.

METROLOGICAL CHARACTERISTICS OF THE METHODS OF ANALYSIS

The goal of chemical analysis is to get reliable and reliable results that correctly reflect the qualitative and quantitative composition of the analyzed sample. When choosing a method, it is necessary to know the purpose of the analysis, to evaluate the advantages and limitations of the available methods of analysis. The choice of the method and technique of analysis is determined not only by the purpose of the analysis but also by the properties and characteristics of the sample. The physical properties of the analyzed object should be taken into account:

- state of aggregation
- volatility
- hygroscopicity,
- mechanical strength, etc.

When choosing an analysis method, the chemical properties of the sample, as well as the properties of the component to be determined and accompanying impurities, are decisive.

Knowing the chemical properties of the components of the analyzed object and evaluating possible interference, the **most selective method** is chosen, a method that, under given conditions, can detect or quantify the target components without interference from other components present. If a method or technique allows you to detect or determine only one component, then they are called ***specific***.

The selectivity of a method, technique, or individual reaction largely determines the success of solving an analytical problem. Thus, such methods as ionometry, atomic absorption or enzymatic method are characterized by high selectivity.

Many of the reactions on which the techniques are based are also highly selective, such as the formation of certain complex compounds with organic reagents, enzymatic and electrochemical reactions. Reactions of the interaction of iodine with starch or ammonium-containing substances with alkalis used to detect ammonium ion, specific.

The chemical analysis technique can be made more selective by changing the conditions of analysis (pH of the medium, concentration of reagents, solvent, etc.); eliminating the influence of interfering components by converting them into a non-reactive form (masking) or by separating (precipitation, extraction, chromatography) from the major component.

One of the most important characteristics of the analysis method is ***sensitivity***. The method is sensitive if minor changes in the analyte's concentration (c) cause relatively large changes in the analytical signal (y). Sensitivity is quantitatively characterized by the sensitivity coefficient:

$$H = \Delta y / \Delta c = \frac{y_2 - y_1}{c_2 - c_1}$$

The sensitivity of the method is characterized by the ***limiting (minimum) concentration*** (c_{min}, g/ml) of a substance — this is the minimum concentration at which the substance to be determined can be detected by this method.

Another characteristic of sensitivity is the ***limit of detection*** (t, μg) - this is the smallest mass of the analyte that can be unambiguously detected by this method. The limit of detection can be expressed as a percentage (mass fraction) - in this case, the detection limit shows the minimum mass fraction of the determined component in the analyzed sample, which can be established by this method.

The determination of impurities in a medicinal substance requires the use of highly sensitive methods of analysis.

The amount of a substance that can be taken for analysis depends on the sensitivity of the method. In this case, it is necessary to consider the expected content of the detected (in a qualitative analysis) or determined (in a quantitative analysis) component.

The mass or volume of the sample taken for analysis can vary widely, as specified in specific methods.

The universality of methods and techniques is the ability to detect or determine many components. Of particular importance is the detection or determination of many components simultaneously in one sample, i.e., the analysis of multi-component systems.

Analysis Accuracy

It is a collective characteristic of a method or technique, including its correctness and reproducibility. High accuracy implies the correctness of the results, a slight scatter of the analysis data. Accuracy is often characterized by the relative error of determination in percent.

Accuracy requirements are usually determined by the purpose and objectives of the analysis, the nature of the object.

Gravimetric and titrimetric methods are quite accurate, the error of which is usually 0.05-0.2 and 0.1-0.5%, respectively.

Of the modern methods, the most accurate is the coulometric method, which allows determination of components with an error of 0.001-0.01%.

Expressiveness of the method

The requirement for rapidity (speed) of analysis is often put forward as one of the main ones when choosing a method and technique.

The need to choose an express method is sometimes dictated by the task of analysis. For example, during surgical operations, sometimes there is a need to determine the concentration of a biologically active compound (urea, glucose, drug, etc.) in the blood or tissues of a patient within a few minutes.

Methods are known that allow the analysis to be carried out very quickly. For example, atomic emission spectroscopy using quantometers can determine 15-20 elements in a few seconds; in ionometry method uses ion-selective, including enzyme, electrodes. The response time of which to the content of the component is 0.5-1 min.

Analysis cost

When choosing a method (method) of analysis, it is often important, especially when conducting serial and mass analyzes, the cost of analysis, including the cost of the equipment used, reagents, the analyst's working time, and sometimes the analyzed sample itself.

The most economical are titrimetric, gravimetric, and potentiometric methods. Expensive equipment is used in voltammetric, spectrophotometric, luminescent, atomic absorption methods. The highest cost of equipment in the neutron activation method, mass spectrometry, radio spectroscopy, atomic emission spectroscopy with inductively coupled plasma.

Analysis automation

When conducting mass analyzes, one should choose a method that allows the automation of analysis: this facilitates the work of the analyst, replaces many manual, time-consuming operations with automatic ones; reduces the errors of individual operations; increases the speed of analysis; reduces its cost; in addition, analysis at a distance (outside the laboratory) becomes possible.

In modern methods of analysis, the trend towards automation is increasing.

Although analysis automation is often costly, its use is driven by automated manufacturing processes and increasing demands for product quality control.

STATISTICAL PROCESSING OF THE RESULTS OF QUANTITATIVE ANALYSIS

When carrying out a quantitative analysis, various physical quantities are measured or determined by calculation based on the measurements: the mass of the substance, the concentration of the solution, the volume of the liquid, the color intensity of the substance, the optical density of the medium, redox potentials, refractive indices of light and other analytical signals.

Without exception, all physical quantities are measured with some error. It is impossible to measure any physical quantity exactly (and the term “exactly” itself is unclear and must be specifically defined).

Therefore, when carrying out a quantitative analysis and corresponding calculations, it is necessary to take into account the determination errors in a quantitative form (numerically).

Accuracy and reproducibility of quantitation results

Accuracy (correctness) of analysis results is the closeness of the results of the analysis to the actual value of the measured value.

Accuracy depends on the magnitude of the systematic error inherent in this method of analysis.

The systematic error **Δ** is the statistically significant difference between the average value of the measurement results and the actual value of the component being determined. The content of the determinable component in the reference sample can be taken as the actual value

A systematic error can also be established by comparing the results of an analysis of the same sample got under different conditions and using different methods of analysis.

To identify errors and evaluate them numerically (especially in the development of new analytical methods), the quantitative analysis is repeated several times, i.e. carry out parallel determinations. Parallel determinations are understood as obtaining several results of single determinations for one sample under practically the same conditions.

A single determination is understood as a single carrying out of the entire sequence of operations provided for by the analysis method.

Reproducibility of the analysis is the degree of closeness to each other of the results of parallel measurements performed using the same technique and on the same device. Reproducibility is determined by the magnitude of random errors and can be characterized by the reciprocal of the relative standard deviation. Methods for estimating random errors are very diverse, although most of them are based on methods of mathematical statistics.