МЕТРОЛОГІЯ, ЯКІСТЬ, СТАНДАРТИЗАЦІЯ ТА СЕРТИФІКАЦІЯ

NORMATIVE AND METROLOGICAL PROVIDING OF CLINICAL-DIAGNOSTIC LABORATORIES

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Анотація. Клініко-лабораторна діагностика (лабораторна медицина) є одним із найважливіших компонентів системи охорони здоров'я, яка надає медичну діагностичну допомогу пацієнтам щодо оцінки стану здоров'я, діагностики захворювань, моніторингу результатів лікування, подальшого прогнозування перебігу хвороби та якості життя, що має загальнодержавне значення для збереження та поліпшення здоров'я населення. Якість життя хворої людини в сучасній медицині розглядається як невід'ємна характеристика її стану, що складається із фізичних, психологічних та соціальних компонентів. У кожному з них міститься низка компонентів, наприклад, фізичні – симптоми захворювання, здатність виконувати фізичну роботу, здатність до самообслуговування; психологічний – тривога, депресія, ворожа поведінка; соціально-соціальна підтримка, робота, зв'язки з громадськістю тощо. Їх комплексне дослідження дає змогу визначити рівень якості життя та з'ясувати їхній вплив на неї.

Клінічна лабораторна діагностика – особлива галузь медичного обслуговування. Результати лабораторного обстеження хворого складаються з приблизно 80 % інформації, необхідної лікареві для підтвердження або встановлення діагнозу. Стратегія розвитку клінічної лабораторної діагностики повинна бути підпорядкована загальній концепції розвитку охорони здоров'я та її діагностичної доктрини. Йдеться про послідовне структурування високотехнологічного виробництва, яке передбачає клінічні та економічно обгрунтовані дії з відповідними організаторськими рішеннями, регулярне і матеріальне обладнання, уніфіковану документацію.

Актуальною проблемою лабораторних досліджень є забезпечення точності їхніх результатів. У європейській практиці вже давно існують вимоги до метрологічної простежуваності калібраторів та контрольних матеріалів та метрологічного забезпечення лабораторного обладнання, а також методів дослідження. Основним завданням забезпечення метрологічної простежуваності є виробники обладнання, калібратори, контрольні матеріали.

Ключові слова: клініко-діагностична лабораторія, лабораторні дослідження, контроль якості, лабораторні порівняння, нормативне забезпечення, метрологічне забезпечення.

Abstract. Clinical laboratory diagnostics (laboratory medicine) is one of the most important components of the health care system, which provides medical diagnostic assistance to patients in assessing health status, diagnosis of diseases, monitoring of the results of treatment, further prediction of the course of the disease and quality of life that has a national importance in preserving and improving the health of the population. The quality of life of a sick person in modern medicine is considered as an integral characteristic of her condition consisting of physical, psychological, and social components. Each of them in turn contains a number of components, for example, physical – the symptoms of the disease, the ability to perform physical work, the ability to self-service; psychological – anxiety, depression, hostile behavior; social – social support, work, public relations, etc. Their comprehensive study allows you to determine the level of quality of life and find out their influence on it. It is a fact that the patient is involved in the assessment of his condition and his active involvement in collaboration is important, since only the patient can provide adequate information about the degree of satisfaction with aspects of his life that are directly related to the symptoms of the disease and its psychological, social and other consequences.

Key words: Clinical Diagnostic Laboratory, Laboratory Research, Quality Control, Laboratory Comparisons, Regulatory Support, Metrological Support.

1. Introduction

The readiness of the Clinical and Diagnostic Laboratories (KDL) of Ukraine to carry out their accreditation in accordance with the international standard [1,2] is inadequate, due to the imperfection of the provision of medical services, outdated diagnostic equipment, the poor state of regulatory documents, which carry out laboratory studies, the absence of national harmonized analogues of international standards in the field of laboratory medicine.

Unfortunately, as it was recognized (including at the Ministry of Health), despite such a large number of performed analyzes, the provision of laboratory

diagnostic services does not meet current requirements and hinders the development of domestic medicine due to the imperfect organization of this work, its low efficiency and the inadequate quality of the results researches.

In the normative provision of the KDL today is a largely spontaneously formed conglomerate of practically mutually uncoordinated obsolete remnants of previously existing normative documents and some new recommendations and provisions on the organization and implementation of clinical laboratory research.

On some issues, laboratories are forced to use certain early recommendations and methods that have already been abolished in Ukraine [3] at their own risk.

There is a widespread insufficiently methodically controlled invasion in the field of modern specialized devices and laboratory research systems in the absence of an established procedure for evaluation and admission to the use of medical products for in vitro diagnosis.

The key issues of the metrological provision of clinical laboratory research in Ukraine, which impedes the implementation of the achievements of national and world evidence-based medicine, are not regulated, which may lead to non-recognition of the results of laboratory tests performed in Ukraine or abroad.

2. Results of the study

The tests in KDL cannot be considered reliable without quality control. The accreditation procedure for KDL still does not meet the requirements recommended by EU experts. These requirements prescribe the necessity of their introduction into the practice of laboratories. To date, none of the existing domestic KDLs has been accredited for compliance with the given standards. The level of requirements for the competence of such laboratories is much higher than that established in the international standard [2].

CDLs provide results of clinically useful information on the chemical and morphological composition of biological organisms in the body. Modern clinical laboratory diagnostics carries out research on human biomaterial using morphological, biochemical, immunological, molecular-biological, bacteriological, genetic, cytological, toxicological, virological and other methods.

As there is a system of "voluntary" accreditation of laboratories in Europe, including clinical ones, standards and requirements for international organizations in the field of medicine and standardization, such as the World Health Organization (WHO) and the International Organization for Standardization (ISO), which includes the Technical Committee TC 212- "Clinical Laboratory Research and In-Vitro Diagnostic Test Systems".

Standard [2] is the basic and defines the requirements for the KDL. It prescribes requirements for management, organization and management of the laboratory, which are aimed at ensuring the quality of laboratory research, technical requirements for personnel, premises, laboratory equipment, standard preanalytical and analytical procedures, environmental protection measures, and so on. An important aspect of this standard is that it is addressed to any medical laboratory, regardless of its size or ownership.

The standard [2] defines the term "medical laboratory" (clinical laboratory): a laboratory that performs biological, microbiological, immunological, chemical, hematological, biophysical, cytological, pathological or other studies of human body materials for the purpose of obtaining information for diagnosis , the prevention and treatment of diseases or the assessment of the health of a person, and who can provide advice on all aspects of laboratory research, including the interpretation of the results and the recommendation of the following affidavits.

There is still a large number of standards to be implemented in conjunction with the standard [2,3,5]. The basic standards in the field of laboratory diagnosis are shown in Fig. 1.

National practice of accreditation of medical laboratories is still far from the use of international and European requirements.

To implement standardization work in laboratory medicine, an agreement has been reached on the establishment under the Department of Technical Regulation of the Ministry of Economic Development and Trade of Ukraine with the participation of the All-Ukrainian Association of Clinical Chemistry and Laboratory Medicine of the Technical Committee 166- "Clinical Laboratory Research and Systems for Diagnosis in Vitro". And today the following standards are harmonized:

– DSTU EN ISO 15195: 2015 Laboratory medicine – Requirements for reference laboratories;

– DSTU EN ISO 15193: 2015 In vitro diagnostic medical devices – measurement of quantities in samples of biological origin-presentation of the form of methods of control measurement;

– DSTU EN ISO 20776-1: 2014 Clinical laboratory tests and in vitro diagnostic test systems for testing infectious agents for sensitivity and evaluation of device characteristics for sensitivity testing against microbial agents;

– DSTU H ISO / TR 22869: 2014 Laboratory Medicine – Manual on the use of ISO 15189: 2003 in laboratories.

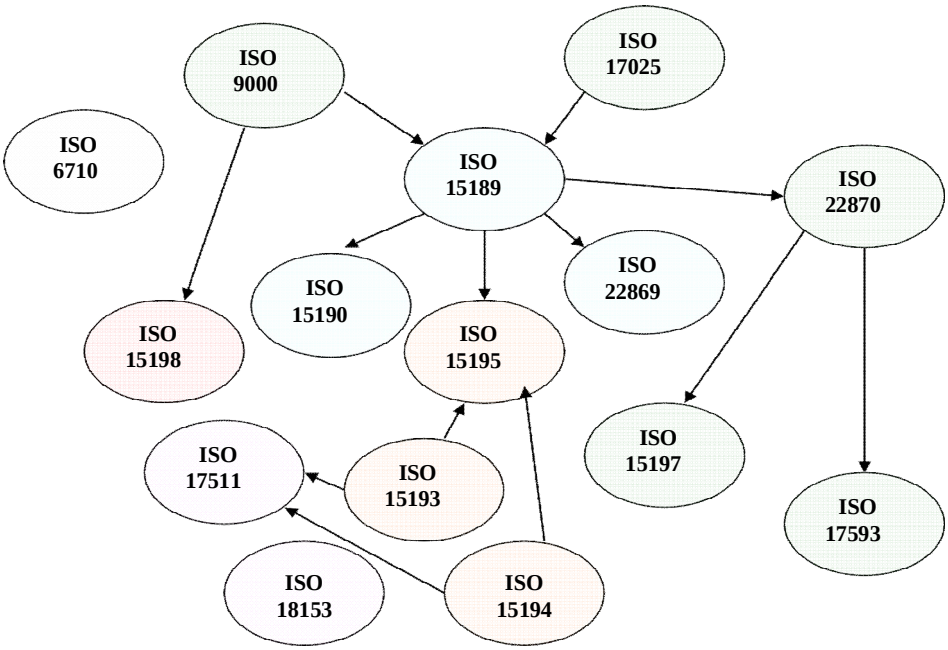

Fig. 1. Basic standards in the field of laboratory diagnostics

As we see, there is very little harmonized standards, and this is not enough to start a full-fledged program for the accreditation of medical laboratories.

The obligatory requirement of accreditation of the laboratory is the implementation of internal laboratory and interlaboratory quality control systems using referential materials. The result of the accreditation-receipt of the certificate, which confirms the competence of the clinical and diagnostic laboratory and allows to perform the range of research specified in the supplement to the certificate. The supplement has a list of diagnostic tests with the necessary equipment, means and analysis technology, the type of biological material and the code of the document that defines the relevant standard procedure, as well as the frequency of internal laboratory quality control, the type of reference sample for its implementation, and the frequency of confirmation of personnel qualification [4].

The personnel life cycle of the laboratory, obtained by the analysis of requirements [2], will have the form shown in Fig. 2. Implementation of requirements [2] for personnel in the logical sequence of the life cycle should take place as follows:

1. The laboratory should establish and approve the requirements for the qualification and competence of the personnel, based on the methods of accreditation and technical descriptions for the equipment.

2. Verification – documentary verification of personnel compliance with established requirements. Based on the results of the inspection, the laboratory forms training plans for the staff.

A separate standard is the requirements for laboratories that provide services for conducting reference analyzes [5]. The services of such laboratories are addressed when approbating new methods, registering medical products for diagnosis in vitro, as well as in cases of controversial research results.

Separately, the introduction of requirements [2] regarding the validation of test results should be considered. Applying the life cycle method, we obtain the life cycle of validation of the test result (Fig. 3).

From the last round, the probability of the result of the tests of KDL is confirmed as intra-laboratory control (using referent materials and control cards), as well as positive results of interlaboratory tests.

The approach from the standpoint of the lifecycle shows that the role of "self-diagnosis" in shaping the answer to the question of how exactly to meet the requirements set by the standard are decisive. Equally important is the unity of measurements, metrological support (traceability of results) of clinical laboratory studies in CDL.

What is metrological support and metrological traceability? Not wanting or not realizing all the importance, carrying out a full-fledged work on setting up a measurement management system and bearing certain costs, laboratories do not pay particular attention to metrology, which is very mistaken. Most laboratory experts all reduce the term "verification" without perceiving metrology. At the same time forget that verification as one of the forms of verification of equipment – only one of the components of metrological traceability. In fact, metrological support is an important aspect, the essence of which lies in ensuring the accuracy of the results of laboratory research, the basis for ensuring metrological traceability and reliability. Note that the standard ISO 15189, in addition to ISO 9001, is based on the standard DSTU ISO / IEC 17025: 2017

"General requirements for the quality and competence of test and calibration laboratories".

The first stage of metrological support is the right choice, installation and operation of measuring equipment. In accordance with the requirements of GLP [6], the management of equipment is divided into qualification stages, which are largely ignored by the laboratories. Here is a brief summary of these steps:

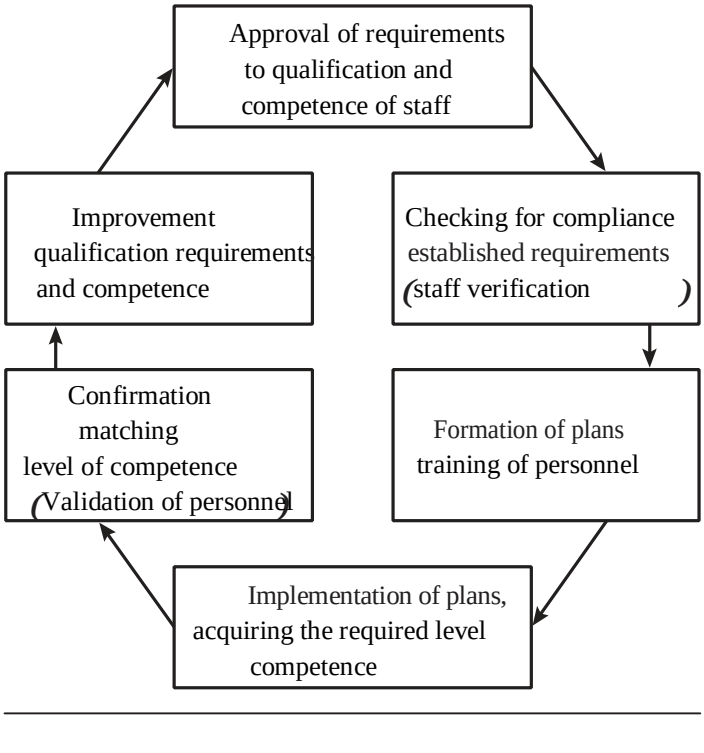

Fig. 2. Lifecycle of personnel

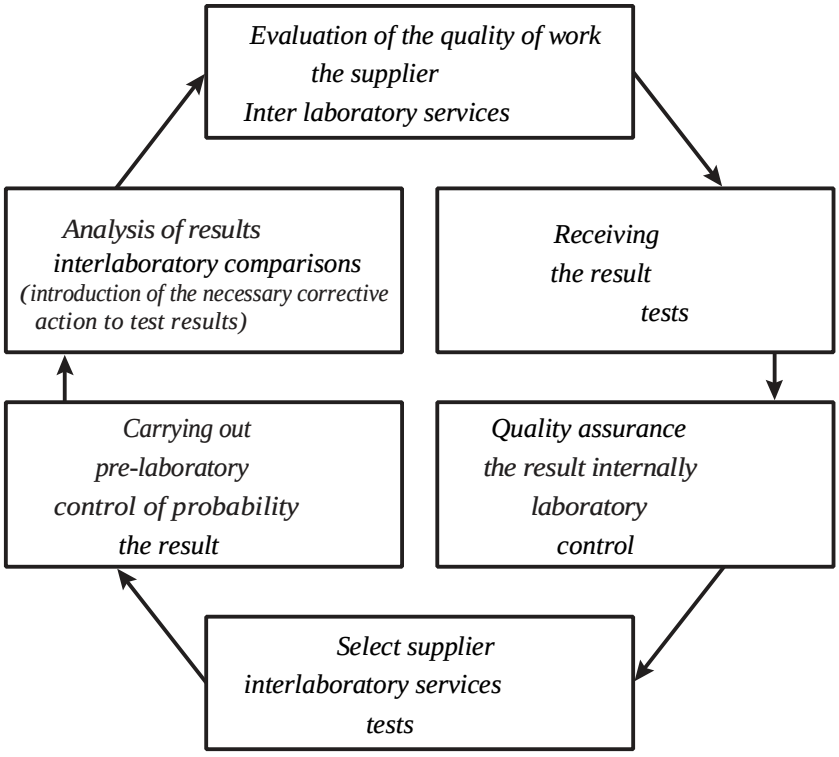

Fig. 3. Life cycle of test results

– Qualification – Assessment and Documentation of Confirmation (ODP) that project documentation, equipment, engineering systems and other conditions of operation can ensure the achievement of expected and reproducible results;

– Design qualification (DQ) qualification – RDP compliance of project documentation with requirements (GLP rules, ISO 15189);

– Installation Qualification (IQ) – RDP compliance with the quality of installation / commissioning of technological and laboratory equipment, engineering systems, "clean" premises, etc., requirements of normative and technical documentation;

– Operational Qualification (OQ) – ODP compliance of technological and laboratory equipment, engineering systems equipped with "clean" facilities, etc., requirements of normative and technical documentation;

– Performance Qualification (PQ) – RDP compliance with the reliability and efficiency of operational parameters of the technological equipment, functioning engineering systems, requirements of normative and technical documentation.

The determining condition for the suitability of the results of clinical and diagnostic research for use in medical diagnostic practice is their proper comparability (matching) in time and space, which can only be achieved if the unity and correctness of these results are ensured [7].

A key operation of any clinical laboratory study (both physical measurements and qualitative measurements) is calibration. In the generalized form, the calibration operation appears as a comparison of the analytical signal obtained from the sample (or the observed characteristics of the determined qualitative property in determining the qualitative index) with the analytical signal (or observable features of the determined qualitative property) of the calibrator (standard, standard sample) in accordance with the received calibration (calibration) function.

Due to the complexity and instability of the analytical systems used in conducting clinical laboratory studies, they are not able to hold the received calibration function for a long time; therefore, the process of such studies necessarily complements the subsystem of checking the accuracy of the results obtained: also a similar control material is also supplied to the input of the calibrated system (another standard sample) and compare the result obtained with the values of the indicators certified for this material. It is clear that in order to achieve proper comparability it is necessary that each laboratory in each measurement (definition) it conducts receives the corresponding size of the unit of measurable physical quantity (or signs of the determined qualitative property) – molar concentration, enzymatic activity, etc. (or types of nucleotide sequence of DNA , cultures of microorganisms, etc.) with indication of their uncertainty.

Therefore, for both qualitative and quantitative research, the unity and correctness of the results of the KDL provide the creation of metrological traceability. Implement this by implementing a number of calibrations, creating a documented continuous chain of sequential calibrations (each of which contributes to the overall uncertainty of the measurement result) – this chain connects the measurement result to the defined database (comparison means reference). The object of the selected metrological traceability of a calibration is to obtain a degree of compliance from a standard sample and / or a reference method of measuring up to the method of lower metrological level, that is, routine methodology. Signs of the determined qualitative properties or the size of units of measurable values at each (except the highest) of the levels of measurement (research) are obtained in the measurement carried out in the way reflected in the figure.

At the highest level, the chain of traceability begins with the very units of SI, the dimensions of which are reproduced using standards. States Members of the International Bureau of Weights and Measures have concluded an agreement on the mutual recognition of the degree of equivalence of national measurement standards supported by their national metrology institutes in order to allow the mutual recognition of calibration certificates and measurements issued by these institutions on the basis of programs of key comparisons of standards for selected national institutes of metrology. National institutes of metrology distribute their standards through gauge laboratories (which directly refer to the standards of this institute), and further to users of measuring instruments in industry and commerce, often through second-level calibration laboratories. In chemistry, medicine, and some other fields of science and technology, traceability is practiced through the use of standard samples and a hierarchy of auxiliary comparison tools used to benchmark the equipment and procedures used in test laboratories.

Each level of the continuous chain of traceability hierarchy consists of the reference method and the corresponding calibrator (standard). The highest metrological level (the upper link of the traceability chain) usually has to be reliable material realization of the sign of a certain qualitative indicator or the size of a unit of a quantitative indicator in accordance with the definition of this trait or unit of physical value – that is, the most accurate (primary or original) standard or its substitute. The lower levels of traceability hierarchy form referent techniques and corresponding calibrators (intermediate standards).

The technical basis for measuring metrological support is the system of standard samples (standards) and internationally recognized reference methods, which provides reproduction of units of quantities that characterize the composition and properties of investigated tissues, fluids and excretions of the human body. Necessary attribute of standard samples is their traceability to units of system CI (the possibility of correlation of their values with accepted records – national and international standards – with the help of an indissoluble chain of checks with established uncertainties). In addition, a system for transmitting the size of the values from the standards to all measuring instruments is required. The most acceptable scheme of metrological traceability begins with a standard unit of the SI system, internationally accepted by the primary reference method or internationally accepted certified reference material. The incompleteness of knowledge and insufficient technical capabilities lead to the fact that now the chain of metrological traceability can end at a lower level of the hierarchy. A modern scheme for the implementation of traceability systems for clinical and diagnostic research, taking into account the relevant reference materials and reference methodologies for the higher level of the Joint Tracheostomy Committee in laboratory medicine – JCTLM and the requirements of international standards. It should be noted that Directive 98/79 of the EU requires manufacturers of medical products for in vitro diagnosis of obligatory traceability of calibrators and control materials to the highest metrological level, if any. This document was adopted in Ukraine as a Technical Regulation.

Conclusions

Thus, the urgent tasks of normative and metrological support of clinical laboratory research in the KDL are:

• accelerating the process of harmonization of international standards in the field of medical services provision;

• training of qualified specialists in the operation and maintenance of modern high-performance automated equipment and information laboratory systems;

• in accordance with the state program "Creation of centralized regional clinical diagnostic laboratories on the principle of the network" – reorganization of the laboratory service of Ukraine to ensure European quality, standardization and unity of measurements in laboratories of all types of subordination;

• creation of state standard samples (SZU) of composition and properties of investigated samples;

• creation of schemes of metrological traceability from SLM to standard samples of the lower level (calibrators and control materials);

• establishing requirements for the accuracy of research;

• verification and validation of research methods;

• establishing rules for quality control of quantitative and qualitative clinical laboratory research;

• establishing rules for conducting an external evaluation of the quality of clinical laboratory research;

• generalization of comprehensive data on the actual state of clinical laboratory research and analysis of the current situation.

• creation on the basis of the systematic approach of the structural-functional model of the all-Ukrainian system of clinical laboratory research, which would correspond to the international practice of modern laboratory medicine.

Taking into account the current progressive tendencies of centralization and specialization of the implementation of clinical laboratory research, as well as the transitional conditions for health care reform in Ukraine, it seems appropriate that such a system should be based more on a functional rather than structural basis.

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