Metrological assistance of medical measurement devices using certified reference materials of physicochemical properties

S A Sakharova, V N Kustova, M S Vonsky

D.I. Mendeleyev Institute for Metrology, Moskovsky ave., 19, St.-Petersburg 190005, Russia
s.a.poleno@vniim.ru

Abstract. This article reviews some issues of metrological support of medical measurement devices using certified reference materials of physicochemical properties. The extensive application of modern automatic analyzers of new generation helps clinicians in diagnostics and therapy. Comparability of analyzer readings is possible only if metrological approaches to measurements are used.

The modern development of the medical industry and the shift in the focus of healthcare from medical care to disease prevention raises the higher level of the problem of medical diagnostics results reliability.

A wide range of new-generation automatic bioanalyzers helps medical doctors, optimizing the testing process and minimizing time and efforts to perform analyses. There are various types of laboratory analyzers depending on the specialization of the laboratory and the purpose of the research, such as: hematological, acid-base status analyzers, biochemical, blood gas analyzers, immunoassay, chemiluminescence, coagulometers, urine analyzers, PCR analyzers, etc. Unfortunately, metrological support of this type of equipment does not keep pace with technological progress. At present more than 400 analyzers of the approved type, widely used in bioanalytical and medical measurements, are entered in the Federal Information Fund on Ensuring Uniformity of Measurements.

Dozens of analytical technologies are currently available in laboratory analyzers to measure a wide variety of human biomaterial components (Table 1), whose deviations from reference ranges provide important information for clinical decision-making. Relevant information on laboratory tests can be found in the "Federal Laboratory Test Handbook. Handbook of Laboratory Tests" [1], developed by the Regulatory and Reference Information Service (RRIS) of the Russian Ministry of Public Health, developed at the Central Research Institute for Health Organization and Informatization.

Table 1 Components of human biomaterials that can be measured by new-generation laboratory analyzers

| Components to be measured | Value | Units |
|---------------------------|-------|-------|
| Biochemical analytes (cholesterol, creatinine, glucose, etc.) | Concentration | mmol/l, μg/ml, mg/dl, mIU/l |
| Non-organic components (calcium, magnesium, phosphorus, etc.) | Concentration | mmol/l, μg/ml, mg/dL |
| Vitamins (A, B, C, etc.) | Concentration | g/l, mg/l, μg/ml, mg/ml, μmol/l |
| Enzymes (amylase, lipase, etc.) | Concentration | kU/l, IU/l, U/l |
Comparability of analyzer indications is possible only with the use of metrological approaches and can be ensured by close interaction of analyzer developers (manufacturers) and clinicians with metrologists. At the international level, the activity of JCTML (Joint Committee for Traceability in Laboratory Medicine) is an example of such interaction. There is no such committee in the Russian Federation yet, but collaboration in certain areas is underway. The solution of the problem of assuring the uniformity of measurements performed in laboratory medicine can be found in the context of complex interdisciplinary concept of assuring the uniformity of measurements in laboratory diagnostics, proposed by V.L. Emanuel [2]. The Russian Federation legislation provides as the highest level of traceability either to the State Primary Measurement Standards (GET) of units or, in their absence, to the National Primary Measurement Standards of the corresponding units of foreign countries. At the same time, ISO 17511:2020 [3] proposes six possible calibration hierarchies in laboratory medicine, supported with available reference measurement procedures (RMPs) and primary reference materials (RMs) with full metrological traceability to SI, RMP in the absence of RM for the quantity, RMP calibrated with a particular primary calibrator traceable to SI, an international conventional calibrator or a certified reference material with a consensus-based protocol for value assignment, international protocols for harmonization of in vitro diagnostic test systems, and also manufacturer arbitrary selected RMs.

All analytical systems used in clinical diagnostic laboratories reproduce physical and chemical methods of determining these or those analyte quantities, but the specificity of biological material implies matrix-dependent methods of determining the quantitative composition of the sample under study [4]. Hence, there is also a need to ensure traceability using certified reference materials and the elaboration of reference methods.

Most modern biochemical, hematological and immunological analyzers are closed analytical systems with following metrologically important parts: photometric system, potentiometric system, conductometric system, sample and reagent dosing system, dilution system, incubation system, reaction time reference system, rotational and vibratory mixing system, washing system and others. The reagents, most importantly the calibrators used in the operation and setup of the analyzers, have a significant influence on the measurement results in the biological sample of the analyte. Calibrators included in test systems are a key element of metrological reliability of measurement results in laboratory medicine, allowing the calibration of analytical systems and metrological traceability [5]. Hence, all the above mentioned influences the reliability of analytical results obtained with the help of modern analytical systems universally used in medical clinical-diagnostic laboratories. It is to be noted that the accuracy of reproduction and reliability of obtaining a unit concentration of a particular component (analyte) of biological material directly affects the decision-making process when making a diagnosis of the patient.

More than 15 years ago the D.I. Mendeleev Institute for Metrology (VNIIM) identified the need for certified reference materials (CRMs) for metrological supporting of human biomaterials components (analytes) measurements. The work on the development and production of CRMs in this area was started. As of today, ten approved types of reference materials (GSO) of different components (analytes) developed in VNIIM have been registered in the Federal Information Fund on Ensuring Uniformity of Measurements:
- GSO 10669-2015 (GSO 9624-2010) certified reference material of blood form element composition - hematological control (set GC - VNIIM);
- GSO 9866-2011 certified reference material of the validated type of soybean DNA composition (GM-Soya-VNIIM kit);
- GSO 9913-2011 certified reference material of the validated type of molar concentration of cholesterol in blood;
- GSO 10023-2011 certified reference material of the validated type of artificial urine composition;
- GSO 10238-2013 certified reference material of the validated type of composition of hemoglobin cyanide solution;
- GSO 10390-2013 certified reference material of the validated type of molar concentration of testosterone in blood serum (testosterone-VNIIM kit);
- GSO 11192-2018 certified reference material of the validated type of the composition of low molecular weight nitrogenous substances in blood;
- GSO 11291-2019 certified reference material of the validated type of molar concentration of non-organic substances in blood;
- GSO 11291-2019 certified reference material of the validated type of molar concentration of inorganic substances in blood;
- GSO 11312-2019 certified reference material of the validated type of biochemical blood composition - biochemical control (BK-VNIIM).

At present, a new RM of DNA sequence copy concentration in human genomic DNA matrix (HeLa-VNIIM kit), designed for calibration, graduation of DNA analyzers, and control of metrological characteristics during their testing, including for type validation of real-time PCR and digital PCR analyzers, is undergoing the type approval procedure.

The traceability of unit value transmission from standard to working measuring instruments is solved by the state verification scheme for measuring instruments, which regulates the procedure of unit value transmission, methods and means of transmission, as well as their measurement errors.

At present, the following State Primary Measurement Standards are maintained in the D.I. Mendeleyev Institute for Metrology (VNIIM) and used for unit value transmission to measuring instruments operated in the field of bioanalytical and medical measurements:

- GET 164-2016 State Primary Measurement Special Standard of units of mass concentration of particles in aerodisperse media;
- GET 208-2019 State Primary Measurement Standard of units of mass (molar) fraction and mass (molar) concentration of organic components in liquid and solid substances and materials based on liquid and gas chromatography-mass spectrometry with isotope dilution and gravimetry.

In 2021 a decision to create the State Primary Measurement Standard of the unit of DNA sequence copy number was made. The goal of the creation of the State Primary Measurement Standard is to ensure the uniform measurements of DNA sequence copy number and derived quantities – sequence copy number concentration and sequences copy number ratio. Development of this State Primary Measurement Standard will allow to continue the development and certification of GSO that are in demand in laboratory medicine.

At the 54th meeting of the IGU (November 2018) five types of standard samples (GSO 9866-2011, GSO 9913-2011, GSO 10023-2011, GSO 10238-2013, GSO 10669-2015) were recognized as Interstate standard samples of composition and properties of substances and materials and registered in the Registry of ISO of the Agreement member states.

The international agreement "Agreement on cooperation in the creation and application of standard samples of composition and properties of substances and materials" was adopted in October 2019 and came into force in August 2020. The main target of signing this Agreement is to meet the needs of the states-participants of this agreement in standard samples of substances and materials and especially in the field of medicine and microbiology.
Therefore, the development and production of certified reference materials of physicochemical properties on the basis of VNIIM along with other Russian NMI's – VNIIOFI, VNIIIFTRI and VNIIMS solves the problem of metrological support of measuring instruments in laboratory medicine. These CRMs enable provision of metrological traceability for measurements in the field of laboratory medicine at the new level, which meets internationally agreed criteria.

References
[1] "Federal reference book of laboratory tests. Handbook of laboratory tests"// Regulatory service of normative-reference information (NSI) of the Ministry of Health of the Russian Federation, https://nsi.rosminzdrav.ru/#!/refbook/1.2.643.5.13.11.1080/version/3.22
[2] V.L. Emanuel, A.N. Pronin, M.S. Vonsky at al. 2021 On the way to the concept of ensuring the unity of measurements in laboratory medicine WORLD OF MEASUREMENTS 2 p. 22-26
[3] ISO 17511:2020 In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples.
[4] Vonsky M.S., Krylov A.I. 2020 National metrological institutes and ensuring the traceability of measurements in laboratory medicine Laboratory Service vol 9(3) p 41-48, https://doi.org/10.17116/labs2020903141
[5] A.A. Chubanov, V.N. Kustova, A.G. Chunovkina, M.S. Vonsky "Features of the implementation of metrological traceability in laboratory medicine" // (In Print)