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STANDARDIZATION AND REFERENCE SYSTEMS WITH A VIEW
TO CLINICAL LABORATORY PERFORMANCE

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In clinical diagnostic laboratory practice normally the patient does not come to the laboratory, but his different excreta (urine, faeces), secreta (sputum, saliva, gastric juice, bile), tissues (blood, biopsies, smears) or other materials are collected, in order to be analysed by macroscopically and microscopically (micro)biological, (bio)chemical and physical methods.

Because of their biological nature the patient materials, to be analysed, have intrinsic uncertainties depending on:

- individual variations;
- physiological fluctuations;
- instability of specimens.

The collection and transport of the specimens influences their properties and their composition through:

- methods of procurement;
- construction and material composition of containers;
- measures of preservation and transport conditions.

The microbiological, biochemical, physical and other analytical procedures are influenced by the biological nature of the specimen and the conditions where the examinations have to be performed. These make that:

- results become method dependent;
- reference materials must have comparable biological properties;
- specific qualities of reagents influence the results.

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All these variables preclude that clinical pathologists, clinical chemists, haematologists, microbiologists and other specialists performing clinical laboratory tests can make use of absolute or quasi-absolute methods, as is the case in pure analytical chemistry and physical chemistry.

Moreover, the biological activities of biological substances and systems, such as sera, vaccines and other immunologically defined substances, toxins, antitoxins, enzymes, hormones, antibiotics cannot yet be defined otherwise than as expressed in "units", assigned by consensus to well-preserved reference substances, commonly known as "biological standards".

In order to assure optimal quality of the results of clinical laboratory tests, with a view to their practical use for the diagnosis, therapy and prevention of diseases, the following activities and procedures at the laboratory level must therefore be taken care of:

- (1) standardization
- (2) quality control
- (3) proficiency testing.

1. Standardization of methods, instruments and reagents

The variability of the outcome of laboratory methods can be reduced by meticulously adhering to well-specified methods in the hands of properly educated and well-trained personnel, using adequately calibrated instruments of well-known precision, in combination with well-defined reagents of certified quality.

In the field of biological preparations the "biological standards" of WHO have markedly influenced the consistent reliability of their properties and quality.

Several scientific and other relevant publications of internationally active standardization committees are available in microbiology, haematology, pathology, immunology and clinical chemistry. These have particularly to do with the analytical methods used by the specialists in these fields.

The standardization of instruments and reagents, marketed by industrial companies is much less developed, although the relevant specifications and performance checks of individual products certainly can be well-defined and are of a high standard.

Methods, instruments and reagents are becoming more and more sophisticated.

The standardization of combined method-instrument-reagent-systems at a national and particularly at an international level, is therefore of growing importance. Mechanization and automation of laboratory procedures tend in the same direction.

Organizations as the NCCLS in the United States of America and the ECCLS in the European sphere, have now set the stage for a tripartite collaboration of interested scientists, and other specialists from the clinical laboratory professions, with experts from the instrument and reagents industries and with experts from the government agencies for health care and health protection. Working on the voluntary basis of the "consensus mechanism" they are developing common "standards", together with relevant reference methods, reference preparations and concomittant instrument specifications, in order to reduce the variability of the laboratory performances to a consistently lower and more reproducible level.

In this respect standardization of specimen containers (ISO) and specimen collection is also of great importance. Although international studies by expert panels are underway, still a great deal of the variability in the outcomes of laboratory tests depends on fallacies already introduced at the level of the collection, the preservation and the transport of the specimens before they arrive at the laboratories.

CONCLUSION: standardization is the procedure of choice for reducing the variability of clinical laboratory-procedures

N.B. "Standards" should be arrived at by consensus and should stay open for critical evaluation and readjustment (through consensus).

2. Quality control of laboratory procedures

Each producer - and this is also true for the clinical laboratory - bears responsibility for the quality of his products. The production process of clinical laboratory test results, begins at the taking of the specimen (A) and ends at the moment, that the report is delivered to the client (Z), who ordered the examination. Such "A-Z production-line" must be considered as a more or less well-defined continuous process of one or more discrete and interlinked stages, performed by one or more persons along the "line".

The performance of such a "production system" must be regularly and systematically controlled in order to assure consistently reproducible results of acceptable quality. This is "quality control".

Per definition "quality control" is therefore the system of measures taken by the responsible producer in one laboratory for assuring the quality of the performance of his laboratory test system(s). One method of quality control consists of systematically adding samples of known value into the "production-line" and monitoring the results obtained. Such results should form then the feedback for a correcting steering mechanism, in the case that unacceptable deviations in the performance of the system occur.

CONCLUSION: "Quality control" is an intra-laboratory activity performed by the director of a laboratory to control the performance of a laboratory test procedure (irrespective of its degree of standardization).

N.B. In this context the expression "external quality control" becomes a contradictio in terminis. The responsibility for the quality of laboratory test results cannot lie in the hands of organizations or authorities outside the laboratory.

3. Proficiency-testing for the monitoring and evaluation of performances

The chances that consecutive specimens of materials of the same patient, must be tested in several different laboratories inside and outside the country where he lives, are for several diseases becoming more and more evident.

Standardization of clinical laboratory procedures not only reduces the variability of the outcomes of such test in one laboratory, but also creates the possibility for consistent comparability and interchangeability of laboratory results in different laboratories.

Several years ago methods of proficiency testing have already been developed in order to monitor and evaluate in interlaboratory trials the effects on the performance of clinical laboratory tests by the introduction of standardization of methods and by the use of reference preparations and calibrated instruments in the day-to-day practice.

It has been shown that taking part in such schemes for intercomparison of laboratory results has a distinct "educational" value and furthers the reduction of the variability of the laboratory results, especially in those laboratories, working with standardized and other well-specified and calibrated methods, instruments and reagents.

It is clear that not only the doctors and their patients and the health authorities attach great value to consistently reliable performances of clinical diagnostic laboratories, also the health care organizations, that have to pay for all the laboratory tests want to receive reliable and qualitatively valuable products for their money. In some countries therefore the taking part in a proficiency testing scheme (organized by or in cooperation with

public health authorities) has been made compulsory, and the payment for clinical laboratory analyses in such cases is made dependent of a certain degree of performance, specified by those authorities.

Proficiency testing - being a method for the monitoring and evaluation of performance - is not only related to the intercomparison of (standardization) analytical methods, it also related to intercomparison of performances of instruments (for the information of producers of such apparatus), and to intercomparison of performance of reagents (also for the information of the producers of such materials). In most cases, however, it relates to the intercomparison of the performances of the combined method-instrument-reagent-systems, as operated in daily life by the users (laymen, family-physicians, laboratory personnel, specialists).

The majority of the participants in ECCLS are of the opinion that the results of intercomparison proficiency testing schemes should not only be communicated to the participants (who must know what their individual results are) but also should be published for general information, without indicating the names of the participating laboratories and industries, so that the anonymous figures can show the general situation of the performances (and their variability) in the field under trial. Consecutive tests at regular intervals, will then indicate how far improvements of performance do occur.

CONCLUSION: Proficiency testing is a method of monitoring and evaluating the performance of a group of clinical laboratories (at a regional, national or international level)

N.B. The organization and execution of proficiency testing schemes and interlaboratory comparison trials is primarily of interest for the scientific laboratory-profession (clinical laboratory specialists) and the related industries (producers of instruments and reagents). In some countries such proficiency tests are also directed by governmental agencies.

The role of the government

Beyond any doubt, it can be stated that governments bear responsibility for the quality level of health-care and health-protection in their countries (statute of the World Health Organization):

"Governments have a responsibility for the health of their peoples, which can be fulfilled only by the provision of adequate health and social measures".

Governments have the power to regulate the health-care delivery systems of which the clinical laboratory services form a constituent. Different approaches exist in different countries, and the direct and indirect regulations for health laboratories activities vary from practically non-existent to sometimes very detailed rules and prescriptions.

Through several resolutions of the World Health Assembly (WHA25.47 and WHA27.62) governments of the Member States have been recommended to:

"continue and expand their national activities in the development of standardization of health laboratory methods and reagents"

and have been urged to:

"to take steps as rapidly as possible to control the quality of commercially distributed diagnostic materials in accordance with accepted standards, either national or international".

Whatever system may be followed, the government has at least an obligation to:

(a) institute reference systems (and the reference values) to be used for arriving at and checking the interchangeability of comparable laboratory results;

(b) assure the availability (at the national level) of officially accepted primary reference materials;

(c) certify the performance of secondary reference preparations (to be used in practice) as related to the primary reference materials.

N.B. In this context WHO's "biological standards" must be considered as reference material, to which units of biological activity have been assigned (as internationally agreed by an expert panel of scientists).

In several countries the above-mentioned tasks have been assigned by governments to governmental or parastatal institutes (a, b and c) or agencies (national institutions for health, for biological standards and control for calibration and gauging of instruments, for biological and pharmaceutical products, etc.).

Considering the narrow interrelationship and even interdependency of clinical laboratory-methods-instruments and reagents on the one hand and on the other hand the need for governments to legislate and regulate in conformity with the consensus of clinical scientists and the experts of related industries, with respect to the most proficient diagnostical procedures to be used in daily practice, it seems to be necessary that governmental experts closely work together with industrial and professional experts in a "consensus-making process" for clinical laboratory reference systems. Such cooperation must produce the solid basis for a generally acceptable level of performance of clinical laboratories.

CONCLUSION: Governments should undertake the institution and maintenance of a national reference laboratory organization for clinical laboratory-methods

N.B. Such an activity should be performed by governmental agencies and experts in close collaboration with scientists and experts from the related health laboratory professions and the relevant industries, in order to create a scientifically and practically sound basis for adequately executed proficiency testing programmes to demonstrate the performances of individual laboratories, instruments and reagents and the combinations thereof.