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STANDARDIZATION OF METHODOLOGY AND REAGENTS

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The word "standardization" as it relates to clinical and public health laboratory practice should be interpreted broadly as covering the utilization of scientifically and technically sound test methods, recommended laboratory practices, well characterized materials and/or their definition and performance specifications, and the promotion of related knowledge.

The WHO programme

The Twenty-fifth World Health Assembly requested the Director-General to explore the means for extending the work of WHO in the development of standards for chemical and biological diagnostic materials and related aspects of laboratory methods. As a consequence of this resolution, an International Conference on Standardization of Diagnostic Materials, co-sponsored by WHO and the Center for Disease Control, was held in Atlanta, Georgia in June 1973. In attendance were 68 participants and 86 observers representing 27 countries. Additionally, nine international organizations actively involved in clinical laboratory standardization were represented and a number of experts from governmental health agencies in several countries were present. There was good agreement on general principles and guidelines for establishing an international standardization programme for diagnostic materials. It was recognized that problems to be addressed initially should be agreement in terminology, investigation of various laboratory procedures, mechanisms for evaluating candidate preparations for standard materials, and requirements for the control of such materials. It was felt that WHO could provide leadership in these efforts and contribute significantly to the international acceptability of standard materials through formal approval by its Member governments.

It was realized that it would be impossible to develop an international standardization programme for all of the several thousand different diagnostic materials being used and it was decided to select priorities separately in each of five laboratory disciplines. In determining the priorities, several factors were considered including the technology available, the reagents obtainable, the intended use of the laboratory test, and the extent to which the test results were crucial for clinical or public health programmes. It was recognized that this would be a long-term effort with WHO having responsibility to (1) serve as a focal point for, and maintain close liaison with all programmes related to or benefiting from the

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standardization of diagnostic materials and to coordinate standardization efforts within WHO; (2) serve as a control agency to review proposed specifications, organize collaborative evaluations of methods and materials, and to achieve a consensus on acceptability, and (3) provide administration and support for the programme.

In May 1974, the Director-General presented the study report requested earlier and it was favourably received and discussed during the Twenty-seventh World Health Assembly. Shortly thereafter in June 1974, WHO began to prepare a basic plan for standards development as a prerequisite for implementation of a standardization programme.

The promotion of research and development of laboratory standards and reference or comparison materials, including international collaborative studies is supported by WHO through modest research grants to institutions participating in WHO programmes. WHO also provides services to Member countries through the dissemination of technical information on recommended reference methods, the provision of reference or standard materials and the organization of training activities on the best way to use these methods and materials. This effort also includes the formulation of specifications for laboratory reagents, and advice on their preparation and testing.

A next major step in the WHO standardization programme was a consultation on standardization held in Geneva in November 1974, with the participation of international experts from governmental institutions, regulatory agencies, scientific societies, and research laboratories, with observers from reagent manufacturers. The following objectives were agreed as appropriate to the WHO standardization programme:

- (1) adopt international specifications for labelling of diagnostic reagents;
- (2) provide instructions for installation, maintenance and operation of laboratory instruments and equipment;
- (3) publish and regularly review reference and accepted routine methods;
- (4) establish, maintain and distribute international reference (standard) and calibration materials;
- (5) introduce and/or improve internal and external quality control procedures;
- (6) organize training and promote education in all types of health laboratory work particularly in quality control;
- (7) encourage the establishment of appropriate reference values for quantitative laboratory tests;
- (8) support international agreement on nomenclature, quantities and units.

WHO recognized that for many years there had been a great deal of activity by many organizations, both national and international, regarding standardization of diagnostic methods and materials. WHO would therefore:

- (1) assume responsibility for coordinating and promoting uniform standards and specifications for development and adoption of reference methods and materials;
- (2) develop the WHO programme in collaboration with national institutions, international scientific and professional organizations, research workers and industry;
- (3) set up a flexible operational structure;
- (4) establish a priority listing of areas where effort is needed;
- (5) use expert advice from national and international sources;

- (6) encourage health authorities in each country to designate and support a focal point which would assume responsibility for a national standardization effort; and
- (7) encourage Member countries to adopt internationally agreed methods and materials.

Following these organizational developments of the early 1970s, WHO has made progress in implementing its programme of standardization. By 1976 WHO had received recommendations from expert groups of consultants in the specialities on microbiology, clinical chemistry, and haematology. These groups had made many recommendations that were consistent in broad terms, and each related to particular subject areas of the expert groups. One consistent recommendation was for international specifications for adequate and meaningful labelling of diagnostic materials. WHO, therefore, prepared a draft proposal for "Guiding Principles and Recommendations on Labelling of Laboratory Materials" and circulated the draft to a large number of experts in laboratory science for their views and comments. The finalized guiding principles and recommendations on labelling were published as a WHO memorandum in 1978.

Since 1975, WHO has organized a network of collaborating centres for research and reference services related to standardization. Among the collaborating centres added to the network were those for: diagnostic methods and materials, clinical chemistry, haematology, human blood products and blood derivatives, microbiology, and subdisciplines of the major clinical laboratory disciplines.

These collaborating centres are located throughout the world. They plan and organize international collaborative studies to test the quality of certain proposed reference materials and will have a direct responsibility, in cooperation with WHO, in the storage and distribution of reference materials. Additionally, the centres provide assistance to WHO in conducting training courses, particularly in the promotion of quality control in health laboratory technology. In connexion with the training activities, manuals have been developed which include principles of tests, apparatus and reagents needed, detailed descriptions of performance, quality control specimens needed to monitor performance, calculation of results, units to report with conversion factors to SI units, and reference values. Although all of these methods are not standard or reference methods, they do assist laboratories in improving their performance and do bring a certain level of standardization to the international level.

The list of WHO reference materials developed and under current development is too extensive to list totally here, but a few recent examples are:

- (1) liquid bovine reference serum in clinical chemistry, with defined values for eight chemical constituents;
- (2) a similar lyophilized human reference serum for clinical chemistry, defined for seven analytes;
- (3) reference grouping sera for Neisseria meningitidis;
- (4) reference serums for Rubella;
- (5) abnormal haemoglobin reference preparation.

Currently, work continues in all facets of the standardization programme with particular renewed interest in international and national quality control programmes in clinical chemistry and haematology; workshops in quality control in haematology and microbiology; technical support for national quality control programmes and production of quality control materials; development and evaluation of reference methods in clinical chemistry, haematology, and microbiology; development of additional manuals containing working methods; and advice on planning and organizing laboratory services, particularly at the primary health care level.

### Other international programmes

The International Society of Clinical Pathology was founded in 1948, and early in the history of the Society, a Standards Committee was formed. In 1960, the Standards Committee was renamed the Commission on World Standards (COWS) and the parent association was changed to the World Association of Societies of Pathology (WASP). Presently there are 112 members from 81 nations. The aim of COWS is to promote worldwide communication concerning standards related to all aspects of clinical pathology.

Two conferences have been held on the SI units and a third is planned for 1980. COWS has recommended several types of standards including standards for chemical substances, methods, laboratory practice, and performance.

COWS has adopted the cyanmethemoglobin standard recommended by the International Committee for Standardization in Hematology (ICSH), and the hexokinase method for glucose as proposed by WHO has reached the tentative recommended stage. Regular exchanges of proposals have been carried out with the ICSH, the International Federation of Clinical Chemists (IFCC), the National Committee for Clinical Laboratory Standards (NCCLS) and WHO. Publications on the efforts of each of these organizations have taken place frequently in the WASP News Bulletin. WHO consultations have been reported frequently and specific requests for review and comments have been fulfilled. A recently organized committee, Reference Materials Committee (REMCO), has many areas which relate to medical laboratories. A subcommittee formed to study the relationship of standardization and the medical usefulness of laboratory data has become a separate Commission on Medical Usefulness under the WASP structure.

The International Standardization in Hematology (ICSH) works to develop reference preparations and methods to recommend standardized techniques in diagnostic haematology, blood transfusion practices and related disciplines. These objectives are attained by expert panels and standing committees established by ICSH in topics proposed by national delegates, international bodies such as WHO, and by individual practising haematologists. In 1979 the ICSH had 13 standards published or in preparation.

The International Committee on Thrombosis and Haemostasis (ICTH) works to develop standards, to investigate bioassays and diagnostic reagents to develop and recommend appropriate nomenclature, and to assess the needs for clinical trials of new materials. A number of working groups/task forces are assigned to specific topics, and in 1979, there were 17 standards published or in preparation.

The International Federation of Clinical Chemists (IFCC) works on the development of clinical chemical standard reagents; assists in the education and training of clinical chemists; and emphasizes the importance of quality control in clinical chemistry. In 1979 the IFCC had three published standards and 11 proposals under review.

The International Union of Immunological Societies (IUIS) goals include writing specifications for recommended methods of testing; providing material standards; and organizing and reviewing international assays to submit to WHO for acceptance as international standards. In 1979, the IUIS had 17 standards published or in preparation, several of which have been reviewed by WHO.

The International Working Group on Mycobacterial Taxonomy (IWGMT) works to standardize and establish reproducibility of methods and to classify and identify mycobacteria. In 1979, the IWGMT had 11 standards completed or under review which related to laboratory identification of mycobacteria or drug sensitive assays.

### Regional activities

The European Committee for Clinical Laboratory Standards (ECCLS) has been established with a current membership of approximately 90, composed of founding members, regular members, and corresponding members. It is a balanced organization with members representing

professions, governmental institutions, and industry. A general meeting is scheduled for April 1980 where an advisory council would be established consisting of one representative from each of the three membership categories in each country in which there are ECCLS members. Initially, the membership was limited to a number of Western European countries, but members have now been invited from the Mediterranean and Eastern European countries, and corresponding members have joined from Africa. The ICSH has offered to establish a reciprocal relationship for the mutual benefit of both organizations. Additionally, the ECCLS has a close relationship and rapport with the National Committee for Clinical Laboratory Standards (NCCLS) in the United States of America.

Some priorities have been selected for candidate standards and internal procedures established for production of standards. A major objective of the ECCLS is to identify and develop standards for which there is reasonable expectation that European consensus can be achieved. Even in areas where consensus cannot be reached, the arguments made on each side of a disputed scientific issue may be used in educational materials published by the ECCLS.

#### National activities

##### Netherlands

The Dutch Committee on Clinical Laboratory Standards (CCKL) was formed in 1975. The present members are 26 professional societies, two manufacturers trade associations and representatives of government agencies. Two working groups have been organized to consider quality control of kits and reagents, and quality control of analytical procedures and results. The CCKL became a founding member of the ECCLS and might itself become a national CCLS in the future.

##### United Kingdom

The United Kingdom Committee for Clinical Laboratory Standards was founded shortly before the ECCLS met for the first time. It is intended that national committees like the one in the United Kingdom will have a major role in the ECCLS and formation of similar committees in other countries has been encouraged.

##### United States of America

The National Committee for Clinical Laboratory Standards (NCCLS) in the United States of America was established in 1968. Today, the professions, industry, and the Government of the United States of America look to and rely upon NCCLS to develop standards in the laboratory community and to function in a major role in relationships with the Government, other standards setting bodies, and international organizations. The original goal of the NCCLS - the development of useful standards for the practising clinical laboratory, and the strict adherence to the voluntary consensus process - has been maintained. Active membership includes: 17 sustaining members from industry, 21 professional societies, 8 state and national government organizations, 91 industries, 4 industrial trade organizations, 491 corresponding United States members, and 44 corresponding international members from 17 countries.

At the end of 1979 there were approximately 600 scientists working on 62 committees and subcommittees. The present NCCLS listing contains 43 standards which are published and available for purchase. The 491 United States and 44 international coresponding members provide a broad based user group where NCCLS standards are applied in day-to-day clinical laboratory operations and undergo the most crucial evaluation. In 1979 a survey form was enclosed with each copy of tentative and approved standards. Results from the survey indicated that a majority of users and purchasers of NCCLS documents made changes in their practices, procedures, or purchasing habits in accordance with the recommendations and specifications contained in the NCCLS standards. For 1980 the survey is being continued in an effort to broaden the data base and better evaluate the impact of NCCLS standards in the field of laboratory medicine.

The American National Standards Institute, the largest producer of material and process standard specifications in the United States of America, has accredited the NCCLS as the United States national standards body for the clinical laboratory field.

## Approaches to standardization

### Legal

The United States Medical Device Amendments of 1976 created a system of controls meant to ensure that only safe and effective medical devices reached the medical marketplace. By definition, laboratory reagents and equipment are medical devices and subject to legal regulation. The United States regulations are administered by the Food and Drug Administration (FDA). The law includes a range of controls intended to provide only the minimum regulation necessary to assure safety and effectiveness and included under general controls are: (1) uniform labelling requirements for container labels and package instructions; (2) mandatory adherence to good manufacturing practices; (3) compulsory registration of manufacturing sites and listing of products; and (4) provisions for classification of products so that products may be subject to various levels of regulation as required to assure safety and effectiveness.

The United States labelling requirements for diagnostic reagents were published in 1976. These legal requirements are similar to the WHO guiding principles and recommendations on labelling published by WHO as a memorandum in 1978.

The United States Good Manufacturing Practice (GMP) regulations for medical devices were published in 1978. Compliance with GMPs is ongoing and subject to unannounced government inspection and audit at the plant of manufacture.

Under the United States regulatory system all products are classified into one of three classes: Class I being minimal, general controls; Class II including performance standards; and Class III requiring premarket review and approval by FDA. The FDS has used expert advisory committees to classify all current products. Several hundred laboratory products have been classified in Class II, requiring performance standards.

The process for development of a regulatory performance standard is lengthy and none have been published to date. The process includes a provision for accepting an existing standard provided the standard is based upon scientific data and information and it has been subjected to scientific consideration. Standards that are consistent with the regulatory need, that are created in a voluntary and open process, and that are voluntarily implemented can be effectively substituted for regulatory standards for Class II medical devices. Some principal problems in adopting a voluntary consensus standard as a legal standard are: (1) the voluntary standard may be more restrictive than the law would require; (2) the voluntary standard may not have wide industry and user acceptance; (3) the voluntary standard as a legal requirement may place limitations on new product innovations; (4) the voluntary standard as a legal requirement may impose unnecessary standardization in an area: limiting a professional's choice of products by eliminating some safe and effective products from the market; and (5) the standards development process consumes substantial manpower resources and if a standard's scope is broad it will take longer to reach consensus. Compliance with regulatory standards may affect product costs and contribute to increasing overall health care costs.

### Voluntary

Although compliance with a voluntary standard is not mandatory, such standards are likely to have substantial public impact. When adopted by manufacturers and users, they can have a profound effect on the features and performance of products available in the marketplace. Voluntary standards can also become a source for regulatory requirements in many countries. Fundamental to development of practical voluntary standards are consistent representation, sensitivity to the concerns of all represented, well-thought-out positions and effective advocacy. Consensus on a standard is achieved when all individuals having a direct and substantial concern with the scope and provisions of the standard achieve substantial agreement according to the judgement of a duly appointed authority. To be a true voluntary standard it must not only be developed with the voluntary cooperation of all concerned, but the standard must also be used voluntarily by those it affects. The initial

standards writing or development process, unlike the consensus process, may be limited in the number of participating experts; but, as a proposed standard proceeds toward national and international acceptance it will require broader exposure.

To facilitate broad acceptance of a voluntary standard some basic concepts are applicable: (1) safety and effectiveness should be given priority over convenience concerns; (2) innovation should be restricted no more than is necessary; (3) design and constituent parameters should be avoided to concentrate on performance aspects; (4) test methods should avoid specialized equipment where possible and should give reproducible results; and (5) a rationale should be given for the important provisions of each standard.

Documentation of standards development is critical to the long-term viability of a standard. This aids the understanding, application, and subsequent revision of a standard.

The major national, regional and international standards development organizations have separately stated processes for development and application of laboratory standard methods and materials, but all embrace the concepts stated above.

### Types of standards

#### Design and constituents

Design requirements impose limiting values on the design of a product or the constituents of a material. Those who criticize standards frequently charge that design requirements inhibit innovation and lead to undesirable uniformity. This may sometimes be true but in some cases the uniformity may be necessary. A design standard should be developed only if a performance standard cannot, and if a standard is essential for safety or effectiveness.

#### Performance

Performance requirements impose limiting values on how the product or material will behave under a given set of conditions. They leave to the manufacturer's ingenuity the method of achieving the performance established by the requirements. To satisfactorily establish performance requirements, both the product and its specific application must be considered. If a product has more than one application, then more than one set of performance requirements may be necessary. The magnitude of the task of writing application-specific standards may result in all products of a generic type meeting requirements for the most stringent application. This process could lead to a reduced availability of lesser performing products for which there are useful and beneficial applications and force the user to pay higher prices for unnecessary performance. Conversely, establishment of minimum performance requirements is based on the current state-of-the-art at the time the standard is adopted, and without continued review and updating the requirements become the goals to be achieved, not minimums to be exceeded. Manufacturers may tend to invest resources in reducing the production costs of products which meet the minimum standard rather than in developing and improving product capabilities beyond those spelled out in a standard.

#### Parametric

An alternate product standards development technique is the parametric approach. This approach requires that for a given product, manufacturers must provide values for a set of parameters which describe the products' performance characteristics. This type of standard lists for each product, regardless of application, those parameters for which values must be provided and standard test methodology for measuring the required parameters. The emphasis of this type of standardization effort is placed entirely upon defining those parameters which will most completely delineate the safety and effectiveness of the product. This process allows the individual user to define the specific minimum performance requirements for each application of a product and to select those products which, according to the product labelling, meet the needs of the laboratory.

Summary

The present state of development in national and international standardization is encouraging. Planning and coordination of international standardization will be greatly enhanced if information is maintained on existing national and international standards, and early information on national and international standards efforts is obtained. International standardization bodies must recognize the fact that consumers are becoming more self-assured in voicing their interest in fields where technical specifications are involved. Requirements for methods and products will have to be graded in such a way that, within the framework of a uniform system, all countries can make adjustments according to their economic and technical conditions.

The traditional procedures of the national and international standard setting organizations are well designed to complete the standards development process in an open manner with due concern for all involved in application of the resultant standards. Standardization provides impetus for the exchange of goods and services in international trade and the means for exchange of information with a common understanding. Within each country of the world, standardization provides benefit for the following.

Industry: standardization provides a mechanism for monetary savings through mass production, and reduction of time and materials through standard designs, equipment, procedures and testings.

Purchasing agents: standardization offers increased efficiency by freeing him from the need of preparing individual sets of specifications and descriptions for each purchase.

National professional technical and trade associations: voluntary standardization allows them to bring their consumers' interests into consonance with current technology, engineering and manufacturing practices, and laboratory and medical practices.

National governments: as large business enterprises, standardization is a mechanism to regulate government purchasing of commodities and services and to fulfil value objectives and standards for society.

Physician consumers: standardization contributes to the availability of reliable laboratory results that are consistent from day to day and from one institution to another.

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