



Globalization and Hematology Standardization

R.M. Rowan

Health care is a major segment of the global economy, but despite its almost exponential development over the past three decades, the availability of comprehensive, high quality health care is unevenly spread throughout the world. Increasing costs have added to the problem and focused attention on cost reduction. This forces attention on the quality of health care services available to obtain best value for money. Standardization is one method of achieving improved health care services at realistic cost. In addition, regulatory and accreditation organizations have recognised the need for performance standards and are advocating the use of voluntary standards.

The primary function of laboratory testing is the production of information that assists the clinician in the processes of diagnostic decision making, formulating prognoses, and monitoring patient management. To achieve accuracy, consistency, and comparability from one time to another, from one laboratory to another, and, indeed, amongst laboratories in different nations requires standardization of process, of procedure, and of reference materials. Standardization is defined by ISO/IEC⁽¹⁾ as the "activity of establishing, with regard to actual or potential problems, provisions for common and repeated use, aimed at the achievement of the optimum degree of order in a given context." The process of standardization in a laboratory context is, therefore, the description of exemplary, uniform, and reproducible systems of measurement to ensure precision, accuracy, specificity and harmonization of test results and involves both written and material standards. A "standard" identifies specific essential requirements that must be met, in contrast to "guidelines" which may be modified within established criteria. The objective is to create harmonization, a procedure to bring results into concordance, thus ensuring safe and accurate testing, better health care, and conservation of resources.

The history of standardization demonstrates that it can be accomplished arbitrarily by decree or through consensus amongst experts, the latter method providing the framework for present day standardizing bodies. Inherent in the process is the principle of "authority" to which might be added the adjective "intellectual" rather than "political". A consensus standard has been defined by NCCLS⁽²⁾ as "a unique carefully designed process that is open to all affected

interests; actively involves these affected constituencies; is unbiased, neutral and devoid of undue influences; and gives careful consideration to all views."⁽³⁾ A consensus standard is produced from the combined input of academic and practising laboratory professionals and industry.

Global standardization in health care commenced in the 1920s instituted by the Health Committee of the League of Nations but was limited to the provision of international standards and reference materials for biological entities used in clinical therapy and preventive care. Few clinical laboratories existed at that time, and it was not until many years later that it became recognized that the results from different clinical laboratories could not be compared. Since that time, laboratory standardization has progressed steadily both at national and international levels. ICSH (the formal standardising body of ISH), IFCC, WASP and NCCLS are but a few of the well-recognised standardizing bodies. This multiplicity of standardizing bodies has, in the past, resulted in some confusion, particularly in terminology and units. However, through the coordinating activity of the International Standards Organization (ISO) some uniformity is now being achieved. In the laboratory sphere ISO/TC 212 (Clinical laboratory testing and IVD test systems) and ISO/TC 76 (transfusion, infusion and injection equipment for medical and pharmaceutical use) are good examples.

Functionality of Standardization

At first sight, the process of standardization appears complicated and is not aided by ambiguities in the English language; however, knowledge of certain definitions simplifies matters. A "standard" may be a written document or a physical device or material (measurement standard). A written standard is a "document, established by consensus and approved by a recognized body, that provides, for common and repeated use, rules, guidelines, or characteristics for activities or their results, aimed at the achievement of the optimum degree of order in a given context."⁽¹⁾ Reference methods fall into this category. A written standard is the objective of each standardization process.

A measurement standard, on the other hand, is a "measuring instrument, reference material or measuring system intended to define, realize, conserve, or reproduce a unit of measurement or one or more values of a quantity in order to

transmit them to other measuring instruments by comparison.”³ The word “etalon” is a synonym. Reference materials fall into this category.

It is important to appreciate that hierarchies for both methods and reference materials exist. A thorough knowledge and understanding of these principles is necessary for the adequate practice of laboratory testing.

The method hierarchy, as defined by ICSH⁽⁴⁾, possesses three components namely definitive, reference, and selected. ICSH describes a definitive method as one “which after exhaustive investigation is found to have no known source of inaccuracy or ambiguity as judged by defined authority. It will, however, have a degree of imprecision which should be stated”. An example of a definitive method is hemoglobin concentration measurement by atomic absorption spectrometry. A reference method is defined as “a clearly and exactly described technique for a particular determination which, in the opinion of defined authority, provides sufficiently accurate and precise laboratory data for it to be used (1) to assess the validity of other laboratory methods for this determination and (2) for characterising reference materials. The accuracy of the reference method must be established by comparison with a definitive method where one exists, and the degree of inaccuracy must be stated. The degree of imprecision must also be stated.” A selected method is one “which has been approved by ICSH as being suitable for routine use, taking account of the limits of its inaccuracy and imprecision in the context of its intended (clinical) purpose, economy of materials and labour, ease of performance and safety. Its validity must be verified by comparability with a reference method. A reference method may be used as a selected method in some instances. When a reference method is not available or is not practical, in order to ensure harmonization one selected (routine) method may be designated as an *ICSH Standardized Method*; for this, the equipment, reagents and test procedure must be clearly and exactly specified.”

A reference material is “a substance or device, one or more properties of which have been defined by a definitive or reference method. It is to be used for the verification of the accuracy of an analytical process (measurement system) used in routine practice.”⁽⁵⁾ Again there is a hierarchy with International Reference Materials (IRMs) as the highest category. IRMs serve as calibrators for supranational, national and working standards, all being linked by traceability. Traceability⁽³⁾ is defined as “property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties”.

The final concepts to be grasped in order to practise standardized hematology are those of calibration and control. ICSH defines calibration⁽⁴⁾ as “the determination of a bias conversion factor of an analytical process under specified conditions, in order to obtain accurate measurement results. The accuracy over the operating range must be established by appropriate use of reference methods, refer-

ence materials and/or calibrators.” The calibrator (with value assigned by a reference method) is then used in conjunction with a calibration procedure to perform one or a sequence of adjustments on all or part of an analytical process or instrument. Most blood cell counters are linear comparators rather than absolute measurement devices and therefore require careful calibration to ensure accuracy to match their high precision. A common mistake is to use a quality control material for calibration. This must not be done. A quality control material⁽⁴⁾ is “a substance used in routine practice for checking the concurrent performance of an analytical process (or instrument). It must be similar in properties to and be analysed along with patient specimens. It may or may not have a pre-assigned value.” The purpose of the quality control material is to detect and determine the amount of drift in an analytical process over the course of time.

The sequence of events within the individual laboratory is then as follows:

1. The analytical device is calibrated using a calibrator of established traceability to an International Reference Material, the latter having a value assigned by a reference method.
2. Once calibrated the analytical device is assessed on a several times daily basis by means of a control material to check for drift (part of IQC) and periodically by external quality assessment survey specimens to ensure accuracy and comparability with other laboratories.

Thus using standards both written and material, high quality laboratory procedures can be established and their performance monitored to ensure accuracy and harmonization of results between different laboratories.

International Committee (later Council) for Standardization in Haematology: Development and Objectives

ICSH was originally established in 1963 as a committee of the European Society of Haematology and subsequently became a committee of the International Society of Haematology. In 1968 although remaining a non-statutory professional scientific body, the Secretariat of ICSH was registered as an Independent Foundation in the Netherlands while remaining the official standardizing organization for ISH. The objectives of ICSH are:

1. to develop international reference standards of hematological importance
2. to collaborate with appropriate bodies to produce comparable national and secondary reference standards
3. to standardize analytical methods used in hematology
4. to select appropriate tests to support the different requirements of clinical medicine, research and epidemiology within available resources and facilities
5. to develop quality assurance programmes
6. to provide a forum for training and continuing education for hematologists to enable them to achieve exemplary standards of practice in their laboratories.

The productivity of ICSH over the thirty-six years of

its existence is amply illustrated by its many publications (more than 150 articles and ten books). The publication policy is to submit standards to peer review journals where possible. Other standards, particularly those for developing countries, have been published by the WHO. The ICSH has also developed a number of material standards (reference materials such as the haemoglobin cyanide standard), some of which have been adopted as International Biological Standards by the WHO.

Selection of ICSH Recommendations

- Recommendation for reference method for determination by centrifugation of packed cell volume of blood. *Journal of Clinical Pathology*, 33: 1, 1980.
- ICSH recommendations for the analysis of red cell, white cell and platelet size distribution curves: I. General principles. *Journal of Clinical Pathology*, 35: 1320, 1982.
- Recommended methods for the visual determination of white cell and platelet counts. WHO Document LAB/88.3, 1988; *Biochimica Clinica*, 12: 1385-1391, 1988.
- The assignment of values to fresh blood used for calibrating automated blood cell counters. *Clinical and Laboratory Haematology* 10: 203-212, 1988.
- Selected method for visual platelet counting. *Lab Medica* 5(4): 31, 1988.
- Recommended methods for the determination of packed cell volume by centrifugation. WHO Document LAB/89.1, 1989; *Biochimica Clinica*, 14, 4: 405-410, 1990
- ICSH recommendations for the analysis of red cell, white cell and platelet size distribution curves. Methods for fitting a single reference distribution and assessing its goodness of fit. *Clinical and Laboratory Haematology*, 12: 417-431, 1990.
- ICSH guidelines for reticulocyte counting by microscopy on supravital stained preparations, WHO/LBS/92.3
- Calibration and maintenance of semi-automated haematology equipment, WHO/LBS/92.8
- Recommendations of the International Council for Standardization in Haematology for Ethylenediamine-tetracetic acid anticoagulation of blood for blood cell counting and sizing. *American Journal of Clinical Pathology*, 100: 371-372, 1993.
- Reference method for the enumeration of erythrocytes and leucocytes. *Clinical and Laboratory Haematology*, 16: 131-138, 1994.
- Guidelines for the evaluation of blood cell analyzers including those used for differential leucocyte and reticulocyte counting and cell marker applications. *Clinical and Laboratory Haematology*, 16: 157-174, 1994.

- Recommendation of the International Council for Standardization in Haematology on reporting differential leucocyte counts. *Clinical and Laboratory Haematology*, 17: 113, 1995
- Recommendations for Reference Method for Haemoglobinometry in Human Blood (ICSH Standard 1995) and Specifications for International Haemiglobincyanide Standard (4th edition). *Journal of Clinical Pathology* 49: 271-274
- Stability of Haemiglobincyanide (HiCN) Standards, van Assendelft, O.W., Buursma, A., Zijlstra, W.G., *Journal of Clinical Pathology* 49: 275-277
- Revised recommendations for the measurement of the serum iron in human blood. *British Journal of Haematology*, 75: 615-616, 1990.
- Stable lyophilized reagents for the serum ferritin assay. *Clinical and Laboratory Haematology*, 13: 297-305, 1991.
- Recommended method for ¹¹¹In platelet survival studies. *Journal of Nuclear Medicine*, 29, 4: 564-566, 1988.
- Interpretation of Measured Red Cell Mass and Plasma Volume in Adults. *British Journal of Haematology*, 89: 748-756, 1995.
- Announcement: Nomenclature of platelet specific antigens. *British Journal of Haematology*, 74, 2: 239-240, 1990.
- Revised guidelines for compatibility testing in hospital blood banks: Important changes for quality assurance and procedures. *Clinical and Laboratory Haematology*, 12, 2: 235-236, 1990.
- Recommended screening test for pyrimidine 5'-nucleotidase deficiency. *Clinical and Laboratory Haematology*, 11: 55-56, 1989.
- Recommended procedures for the classification of acute leukaemias. *Leukaemia and Lymphoma*, 11: 37-50, 1993.
- Guidelines for measurement of blood viscosity and erythrocyte deformability: editorial. *Clinical Hemorheology*, 6: 363-364, 1986.
- ICSH recommendations for measurement of erythrocyte sedimentation rate. *Journal of Clinical Pathology*, 46: 198-203, 1993.
- Recommendations for standardization, safety and quality control of erythrocyte sedimentation rate. WHO/LAB/93.1, 1993

References

- 1 ISO/IEC Guide 2: 1986
- 2 NCCLS Strategic Plan: 1999
- 3 International vocabulary of basic and general terms in metrology (VIM:1993). 2nd ed. Geneva: ISO, 1993: 59pp.
- 4 ICSH Rules and Operating Procedures, ICSH, 1986
- 5 Van Assendelft OW, England JM (1982) Terms, quantities and units. In Van Assendelft OW & England JM (eds) *Advances in Haematological Methods: The Blood Count*, pp 2-9. Boca Raton, Florida: CRC Press