

Standardization for **medical laboratory testing**, including in vitro diagnostic test systems

by René Dybkaer, James H. Jorgensen, Donald M. Powers and Klaus E. Stinshoff

In memory of Desmond Kenny, Convenor of Working Group 1 of ISO/TC 212, who died on 18 December 2006.

ISO/TC 212 was established in 1995 to promote quality and safety in medical laboratory testing and develop International Standards for medical laboratories and in vitro diagnostic (IVD) manufacturers. The scope of TC 212 is comprised of WG 1, *Quality and competence in the medical laboratory*; WG 2, *Reference systems*; WG 3, *In vitro diagnostic products*; and WG 4, *Antimicrobial susceptibility testing*.

WG 1, Quality and competence in the medical laboratory

The most important project of WG 1 is ISO 15189:2003, *Medical laboratories – Particular requirements for quality and competence*. This standard addresses both quality management and accreditation aspects because medical laboratories work concurrently in the commercial and public domains. Therefore, agreement and cooperation from TC 176 (quality management) and CASCO (conformity assessment) were essential to give medical laboratories confidence that if they based their work on this document, they could obtain both certification and accreditation. After intense discussions, a cooperative three-party agreement was reached.

ISO 15189:2003 has become the basis for accreditation of medical laboratories in many countries. Consequently, such success has generated pressure to review and update the standard frequently. WG 1 is currently working on a major revision, forming a series of standards that will integrate additional laboratory management topics like safety and risk management, some of which are covered now in separate standards.

About the authors



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Donald M. Powers, received his PhD in Biochemistry from Cornell University in Ithaca, New York. He held senior scientific and management positions at the National Institutes of Health,

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Klaus E. Stinshoff, Dr. rer. nat. received his PhD in Chemistry from the University of Munich. He held senior positions at Boehringer Mannheim, DuPont Medical, Dade Behring, Digene Corp.

and at Swissmedic. He was a member of the WHO Expert Panel on Health Laboratory Services, convener of CEN/TC 140/WG 8 and chairman of ISO/TC 212. He serves on the board of Directors of the CLSI and runs his own firm for regulatory and quality consultancy for medical devices.



WG 2, Reference systems

The most significant contributions of WG 2 have been two landmark standards on traceability in laboratory medicine,^{1,2)} supported by corollary standards on reference measurement procedures,³⁾ reference materials,⁴⁾ and reference laboratories,⁵⁾. These standards were developed in order to ensure the accuracy of quantitative measurement procedures, so that, ideally, a patient would be able to obtain the same result in every laboratory in the world within the measurement uncertainty of the measured quantity value. The work was done in collaboration with its sister and namesake in the European Committee for Standardization (CEN), TC 140/WG 4.

“The challenge to WG 2 is to strike the right balance between theory and practice.”

To continue the pursuit of this goal, WG 2 has recently begun work on a new project, *Medical laboratories – Estimation and expression of measurement uncertainty*,⁶⁾ also in collaboration with its CEN counterpart. This project is particularly pertinent to medical laboratories that are being accredited according to ISO/IEC 17025 or ISO 15189, as many are finding it difficult to meet the challenging requirement to calculate measurement uncertainty.

Strictly speaking, meaningful comparison of a measured value with other values is impossible without taking into account their reliability, as indicated by their measurement uncertainty. Since such comparisons are used for diagnosis and monitoring, potentially harmful medical errors could result if the laboratories do not know the measurement uncertainty.

The *Guide to the expression of uncertainty in measurement (GUM)*⁷⁾ enables laboratories to identify all individual sources of random and system-

atic effects producing variability and to combine them, based on a measurement model, to give a value for measurement uncertainty. Unfortunately, the GUM is not an easy text. The detailed procedure is suitable for a metrology institute, but is beyond the resources of routine medical laboratories.

The remedy chosen by WG 2 is to assemble the effects in groups such as those from intraindividual variation, sampling, calibration, and intermediate measurement precision. They are usually assessed anyway during validation of the measurement procedure and can be expected to apply for measurements in statistical control. The project will provide procedures consistent with the GUM, but replace its detailed bottom-up approach by a simplified approach involving the grouping of individual contributions to the measurement uncertainty and submitting them to a combining algorithm. This approach will be demonstrated in examples. The challenge to WG 2 is to strike the right balance between theory and practice.

1) ISO 17511:2003, *In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values assigned to calibrators and control materials*

2) ISO 18153:2003, *In vitro diagnostic medical devices – Measurement of quantities in biological samples – Metrological traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials*

3) ISO 15193:2002, *In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Presentation of reference measurement procedures*

4) ISO 15194:2002, *In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Description of reference materials*

5) ISO 15195:2003, *Laboratory medicine – Requirements for reference measurement laboratories*

6) ISO/WD TS 25680 (2006), *Medical laboratories – Estimation and expression of measurement uncertainty*

7) ISO Guide 98:1995, *Guide to the expression of uncertainty in measurement (GUM)*

The main audiences are medical laboratories, accrediting bodies, and manufacturers of in vitro diagnostic medical devices. An advanced draft will be discussed by WG 2 and CEN/TC 140/WG 4 in February 2007.

WG 3, In vitro diagnostic products

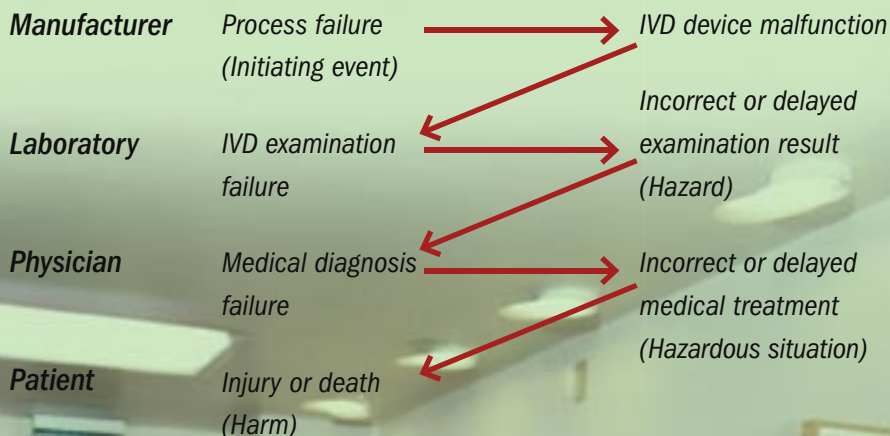
Several WG 3 projects were undertaken with an objective of reducing risk to patients. Two standards were written to ensure that monitoring

devices used in performing self-testing for blood glucose and oral anticoagulants would meet medical requirements and not present an unacceptable risk,^{8),9)} and another standard established minimum requirements for IVD manufacturers to validate the effectiveness of user quality control procedures for their devices.¹⁰⁾

WG 3 is currently developing a series of standards that will implement the essential labelling principles of the Global Harmonization Task Force (GHTF) with the ultimate goal of harmonizing IVD labelling requirements around the world.¹¹⁾ Appropriate labelling instructions and information for safety are key means of controlling risk from the improper use of IVD medical devices.

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Figure 1 - The ISO 14971 annex describes the risk scenario for a typical IVD medical device.



8) ISO 15197:2003, *In vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus*

9) ISO/FDIS 17593 (2006), *In vitro diagnostic test systems – Requirements for in vitro monitoring systems for self-testing of oral-anticoagulant therapy*

10) ISO 15198:2004, *In vitro diagnostic medical devices – Validation of user quality control procedures by the manufacturer*

11) ISO/DIS 18113 (2006), *In vitro diagnostic test systems – Information supplied by the manufacturer (labelling) -- Parts 1-5*

12) Annex H, Guidance on risk management for in vitro diagnostic medical devices, in ISO/FDIS 14971 (2006)

13) ISO 20776-1:2006, *Reference method for in vitro testing of the susceptibility of antimicrobial agents against aerobic bacteria involved in infectious diseases*

14) ISO/DIS 20776-2 (2006), *Evaluation of performance of antimicrobial susceptibility testing devices*

To help IVD manufacturers implement their risk management program, WG 3 wrote a practical IVD-specific annex to be included in the second edition of ISO 14971, *Medical devices – Application of risk management to medical devices*.¹²⁾ What made this project unusual is that ISO 14971 belongs to TC 210, which invited TC 212 to participate and provide medical laboratory and IVD medical device expertise.

Although ISO 14971 has been highly successful in promoting safer medical devices, many in vitro diagnostic manufacturers found the risk management principles difficult to apply to their products.

The main reason is that the risk to a patient from failure of an IVD medical device is indirect – that is, a product's failure would cause a laboratory error, which could then mislead a physician to a diagnosis or treatment that has the potential to harm the patient. The cascade from **Figure 1** of the ISO 14971 annex describes the risk scenario for a typical IVD medical device.

Among the challenges the IVD risk management guidance had to address were how to determine which device failures could create serious hazards to patients, e.g., by contributing to an incorrect or delayed laboratory examination value; how to estimate the probability and the severity of the patient harm that could result; and how to reduce and control the risks. Given the diversity of IVD products, the guidance provides manufacturers with detailed “points to consider” rather than a fixed approach.

WG 4, Antimicrobial susceptibility testing

WG 4 has been presented with an important opportunity to define a global reference method for antimicrobial susceptibility testing of aerobic bacteria and criteria for acceptable performance of antimicrobial susceptibility testing devices. WG 4 has worked closely with a parallel working group of CEN to develop the two standards. The international reference

method is based on the broth microdilution test described by the Clinical and Laboratory Standards Institute (CLSI) and the European Union Committee on Antimicrobial Susceptibility Testing (EUCAST).

The first of the two documents, *Reference method for in vitro testing of the susceptibility of antimicrobial agents against aerobic bacteria involved in infectious diseases*,¹³⁾ was published in November, 2006 after unanimous vote of participating members.

The second document, *Evaluation of performance of antimicrobial susceptibility testing devices*¹⁴⁾ was approved at the DIS level, and is being prepared for its final FDIS vote. It outlines specifically how an evaluation should be organized, how many bacterial strains need to be tested, and strict methods for evaluating and categorizing the study results that include direct comparison to the ISO reference method. The document is intended to provide guidance for use by device manufacturers and by regulatory bodies for registration of a device for marketing in a country or region.

Summary

ISO/TC 212 has published 15 standards, many of them considered groundbreaking by laboratories, regulators and manufacturers. A key to the success of ISO/TC 212 has been the way this committee cooperates with other committees and institutions. By actively seeking this cooperation, developing mechanisms of sharing responsibilities in drafting, reviewing and voting, and reaching pragmatic yet technically sound compromises, ISO/TC 212 has been able to improve our own standards and contribute to the quality of others. We believe that this approach represents a good model for sharing the work, the responsibilities and ultimately the success of international standards. ■

