

WORKSHOP ON MEASUREMENT TRACEABILITY FOR CLINICAL
LABORATORY TESTING AND IN VITRO DIAGNOSTIC TEST SYSTEMS:
A Report on the Workshop

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In early November of the year 2000, the footings for a new bridge were laid in Gaithersburg, Maryland, just outside Washington, DC. Representatives of government, the IVD industry, and the medical professions from 15 nations representing four continents gathered at the National Institute of Standards and Technology to participate in the “Workshop on Measurement Traceability for Clinical Laboratory Testing and *in vitro* Diagnostic Test Systems”. Their goal: to develop recommendations regarding the needs for measurement traceability for health status markers to (1) address IVD industry needs for compliance with international standards (e.g., EU IVD Directive) and (2) improve comparability of clinical measurement data to facilitate better decision making by medical professionals.

As these 135 scientific experts and stakeholders from around the globe (25% were from outside the United States) entered the NIST “Green Auditorium” for the start of this intense two-day workshop, their eyes were drawn to the huge screen displaying the icon for the meeting - a bridge superimposed on a map of the world. This bridge symbolized three fundamental concepts related to the workshop. First, a bridge is a means to get from one place to another, often across a formidable gap. The first day of the Workshop was filled with 10 talks delivered by experts providing the background and current status, thereby anchoring one end of the bridge. The second day was spent in breakout sessions and general discussions intended to plan the size and direction of the path forward. Secondly, just as a bridge is a critical part of the infrastructure for the transportation system that facilitates free and open commerce, so too is traceability a vital piece of the measurement infrastructure for the global healthcare system that supports equitable and open trade, as well as assuring improved comparability and reliability of clinical testing. And finally, the bridge on this Workshop’s logo spans the waters of the world. Healthcare is now more than ever a global issue and a global commodity, demanding global solutions.

Before recounting the details and conclusions of the meeting, it is essential to understand the driving force behind the need for this workshop. Traceability to internationally recognized and accepted standards is an important component in assuring the accuracy and comparability of clinical laboratory measurements. In addition, the global marketplace is presenting new demands for measurement traceability. NIST has a long history of providing certified measurement standards in several fields including the clinical laboratory disciplines, and is continuing its efforts to develop new reference methods and materials for important health-status markers to meet on-going and future needs for traceability. NCCLS is a globally recognized, voluntary consensus standards-developing organization that enhances the value of medical testing within the healthcare community through the development and dissemination of standards, guidelines, and best

practices. NCCLS has the Secretariat responsibility for the ISO Technical Committee 212 (ISO/TC 212) on Clinical Laboratory Testing and In Vitro Diagnostic Test Systems, and is the home of the National Reference System for the Clinical Laboratory (NRSCL), a collection of broadly understood reference systems intended to improve the comparability of test results, consistent with the needs of medical practice. Recently, an important opportunity has emerged that applies new pressure to the quest for traceability and the demand for reference systems. Prompted by the European Union's In Vitro Diagnostics Directive (IVDD), the European Committee for Standardization's Technical Committee 140 (CEN/TC 140), *in vitro* diagnostic systems, began drafting a standard on metrological traceability. By working closely together, CEN/TC 140 and ISO/TC 212 will develop identical European and ISO standards on this topic. Full implementation of the IVD Directive is expected by December 2003 and will require that calibration of all IVD assays be traceable to available reference materials or methods of higher metrological order. (See Don Powers Article in IVD Tech, July, 2000, <http://www.devicelink.com/ivdt/archive/00/07/003.html>)

During the first day of lectures, the attendees learned directly from the leading authorities in Europe about the European IVD Directive. Dr. Kim Carniero, Danish Institute of Fundamental Metrology and representing the European Commission, presented a succinct summary of the Directive, its basis, purpose, implementation, and implications. Dr. Emil Voelkert, Roche Diagnostics GmbH and chair of CEN/TC140, described the standards activities within CEN and ISO, focusing on CEN/TC 140 and ISO/TC212, in support of the IVD Directive and with the goal of harmonized standards within Europe. Professor Lothar Siekmann, University of Bonn and representing the IFCC, discussed the concept of traceability as applied to the field of clinical chemical analysis, remarking that traceability provides probably the most important strategy to achieve standardization in laboratory medicine. He went on to illustrate the process for credentialing reference laboratories, methods and materials in Germany. Rounding out the European viewpoint was Dr. Heinz Schimmel, Institute for Reference Materials and Measurements (IRMM), who informed the audience of the EU's current and planned clinical reference material development activities.

To segue back to the United States, Dr. Hrach Semerjian, National Institute of Standards and Technology, related the important and increasing role that national metrology institutes (NMI), such as NIST, PTB and DFM, have in establishing mutual recognition of measurements and tests between nations. In October 1999, the NMI Directors of the 38 member states of the Meter Convention signed "the mutual recognition arrangement (MRA) on national measurement standards and calibration and measurement certificates issued by national metrology institutes." In addition, the US and EU have entered into an MRA to facilitate bilateral trade between the US and European Community realizing that mutual recognition of conformity assessment activities is an important means of enhancing market access. Continuing with efforts at NIST, Dr. Willie May, NIST, explained how NIST serves as the primary US reference laboratory for health-related chemical measurements through: the development of high-accuracy measurement methods; the development, certification and distribution of Standard Reference Materials; interactive measurement quality assessment activities; and international comparison

exercises with other NMIs. Highlighting a subtle but significant change in his title, Dr. Neil Greenberg, Ortho-Clinical Diagnostics, presented the perspective held by the global (originally the US) IVD industry of the Directive's requirement for calibrator traceability. He made a special note that the IVD Directive does not specifically call for the development of new or improved reference materials, but only that available reference materials and measurement procedures of higher metrological order be used for traceability purposes. Nevertheless, ISO/CD 17511 states that it is the aim of metrology in laboratory medicine to improve traceability by providing the missing reference measurement procedures and materials, based on international consensus. As a result, reference material and methods development projects will be initiated in the name of the Directive. Whereas IVD companies value standards because they help define market needs and provide a clear universal definition of goals, as well as an objective assessment of product attributes, it is unlikely that they will take a lead position in advocating for new standards at this time. However, the inclusion of manufacturing scientists and experts in IVD standards projects led by professional, government and public health groups is absolutely necessary for project success.

Adhering to the philosophy that one should know where one has been in order to better know where to go next, Dr. John Eckfeldt, Fairview-University Medical Center and representing the College of American Pathologists, presented a historical review of reference systems for clinical measurements. Evolving from the Belk and Sunderman's study in 1947 involving 59 clinical laboratories, using 24 samples, and testing for 7 analytes, the CAP PT/EQUAS Program today encompasses over 25,000 laboratories with over a quarter of a million samples and testing for over 500 analytes. He cited several examples to illustrate the role of performance testing for assessing traceability, noting that some programs were more successful than others, often due to limitations of the analyte being tested (e.g., non-commutability, poorly defined or heterogeneous analyte). He concluded that establishing and maintaining the documentation for traceability in field methods is both difficult and expensive. Dr. George Klee, Mayo Clinic, expanded on the need for commutability, noting that reference materials, even when available and used in conjunction with established reference methods, do not necessarily assure harmonization of test values on patient samples. He concluded that a combination of commutable control materials (based on panels of commutable human specimens) with traceable reference values and mathematical algorithms using adjusted patient test values could be used for calibration adjustment. This approach will complement the role of reference materials in improving patient care. And finally, Ms. Joan Walsh Cassedy, ACIL, presented models of reference systems used by other industries, emphasizing that measurement traceability forms the foundation of a quality program, and that absence of traceability leads to chaos.

Armed with this information, the participants reconvened the next morning in five separate breakout sessions led by: Neil Greenberg (Priorities for National and International Investments in New or Improved Reference Systems in Support of Clinical Laboratory Measurement); Don Powers (Reference Materials and Reference Measurement Procedures to Support Traceability Requirements of the IVD Directive); Greg Miller (Impact of Method-Material Matrix Interactions on Calibration Traceability

Protocols for Successful Harmonization of Patient Results); William F. Koch (Development of International Consensus on the Credentialing Process for Reference Systems); and Gary L. Myers (Creating and Sustaining Reference Method Laboratory Networks). Four hours of spirited discussions and consensus-building within each group resulted in five reports that were presented to the re-assembled audience in the afternoon. Although each group brought forward unique perspectives and recommendations based on the topical area, there was general agreement on some critical attributes of the traceability bridge. The need for global reference systems composed of reference methods, reference materials and a mechanism for demonstrating competence and equivalence was of paramount importance. Internationally recognized and accepted reference laboratories should implement these reference systems, using a networked approach. In order to meet the immediate requirements of the IVD Directive, a catalog of the available reference methods and reference materials must be communicated to the IVD manufacturers. There was concurrence that when properly implemented, traceability is a value-added exercise that will improve patient care, testing accuracy, reliability and availability, market access, and, in the long run, reduce costs. However, it was emphasized that efforts undertaken must be designed to minimize redundancy and barriers, encourage new technologies and facilitate global collaborations.

And now that we know where to build our bridge and have some idea of what the bridge will look like, what are the next steps? The closing session of the workshop achieved concurrence on the following actions:

- Develop a web-enabled database of currently available reference methods and internationally recognized CRMs. NIST will undertake this activity while realizing that the EU has submitted a proposal to be reviewed in several months for a similar exercise. If the EU proposal is funded, NIST will coordinate with the EU.
- Organize an internationally accepted “oversight” group that is industry-led (but composed of government experts and medical professionals as well as industry experts) whose task will be to:
 - Set priorities for new reference methods and materials based on medical importance, need, and commutability.
 - Identify sources and secure funding for developing reference methods and materials.
 - Develop the process for international consensus on reference systems
- Develop interpretive guidelines on traceability requirements.
- Develop a global process for approving reference methods and for distributing certified reference materials (CRMs).
- Identify alternative approaches for those analytes for which SI traceable reference methods and/or materials are impossible, at this time.
- Convene a follow-up meeting in Dublin, preceding the ISO/TC212 Meeting in June 2001. Progress in the above bulleted action items will be reviewed and further design and construction of the bridge will proceed.

It is clear that the Traceability Bridge is far from complete. This Workshop was only the beginning, but we should be encouraged by the broad representation, both geographic and sector, and by the level of effort, enthusiasm and commitment exhibited at this groundbreaking in Gaithersburg. The waters under the bridge need not be troubled if international consensus on measurement traceability can be achieved.