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Originally Published [IVDT](#) March 2006

COMMENTARY

An international effort to achieve comparability of test results

Craig M. Jackson, Robert I. Wielgosz, and Willie E. May

Globalization trends are spreading through the IVD industry just as in other industries. One major difference, however, is that while consumer product producers are largely unregulated, manufacturers of health-related products are subject to numerous regulatory requirements.

Professionals from laboratory medicine companies, the IVD industry, and chemical metrology organizations have come together to address these regulatory challenges as well as the effects of globalization on medical product manufacturing and the needs of laboratories for quality and uniform testing results. The Joint Committee for Traceability in Laboratory Medicine (JCTLM) has been formed to aid laboratories, patients, and physicians in this pursuit by providing services to IVD manufacturers and regulators. Descriptions of JCTLM and an example of traceability have been presented in previous issues of *IVD Technology*.¹⁻⁴

The traceability of diagnostic test results is a requirement of the European Union's Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVD Directive). Annex 1, section 3, of the Directive states the following:

The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.⁵

The term higher order is not defined in this directive, nor is a mechanism for meeting the regulation provided. Hence, the necessity for an organization to help fill this gap.

JCTLM is committed to the goal of creating comparability of laboratory diagnostic test results by advancing the adoption of common worldwide reference systems. A critical step in reaching this goal is to ensure the traceability of diagnostic test values to a universally recognized and accepted reference point such as the international system of units (SI). JCTLM is addressing this issue by providing lists of higher-order reference materials and reference measurement procedures to which traceability can be established.

Finding Common Ground

Sidebar:
[Traceability Online](#)

Metrological traceability to a common system of units provides the links among different levels of measurement results, from the highest level (which is commonly impractical and too expensive for routine use) to kit calibrators used for patient sample testing in the clinical lab. Because different measurement procedures are often differentially influenced by the chemical and physical properties of the sample matrix, traceability alone does not ensure equivalence of measurement results. However, many technical challenges to achieving measurement comparability are difficult to address until traceability has been established. For this reason alone, the efforts of the organizations participating in JCTLM are of great importance.

JCTLM does not produce reference materials, nor does it develop reference measurement procedures. Rather, the committee was charged by its founders with establishing a process for identifying and reviewing the higher-order reference materials and reference measurement procedures required by the IVD Directive against agreed-upon criteria. Working group 1 (WG1) was established to meet this obligation and maintain a published list of certified reference materials and procedures. A second team, working group 2 (WG2), has set up a reference laboratory network that provides outside calibration services to those needing to assign traceable values to calibrator and control materials.

To accomplish its tasks, JCTLM, through WG1, solicits nominations for its database from national and international organizations. These groups provide reference materials, develop reference measurement procedures, or provide calibration



L to R: Craig M. Jackson, PhD, is quality system procedures team leader of JCTLM Working Group 1 and is president and cofounder of Hemosaga Diagnostics Corp. (San Diego). Robert I. Wielgosz, PhD, is JCTLM secretariat and head of the chemistry section of the Bureau International des Poids et Mesures (Sèvres, France). Willie E. May, PhD, is cochair of JCTLM Working Group 1 and director of the Chemical Science and Technology Laboratory at the National Institute of Standards and Technology (NIST; Gaithersburg, MD). The authors can be reached at cjackso2@san.rr.com, rwielgosz@bipm.org, and willie.may@nist.gov, respectively.

services as part of their charters or as a professional service to their members. In a few cases, the producers and providers are independent commercial entities. The database currently contains approximately 200 different materials for more than 140 different measurands (analytes), and 125 reference measurement procedures for approximately 75 health-status markers.

Using expert volunteers from professional societies, accreditation organizations, IVD manufacturers, and national metrology institutes, JCTLM teams review the submitted nominations against the requirements of the relevant ISO standards. As far as is possible, each review team is represented by manufacturers and groups from the United States, Europe, and the Asia-Pacific region. Membership on expert review teams is voluntary and individuals willing to participate are encouraged to apply or be nominated to serve on the review teams. The expectations of reviewers and the application form are available at JCTLM's Web site (see sidebar).

Since its founding, JCTLM has committed itself to ensuring that its activities be transparent to all stakeholders. Thus, the review process occurs according to written procedures that together make up the JCTLM WG1 quality system. In particular, as part of the organization's philosophy of continuous improvement, the quality system undergoes continuous review and revision. This commitment is formalized in WG1 Procedure 7.

Unfortunately, materials that fulfill the criteria of ISO 15194, a standard that describes reference materials, may not behave the same as patient samples in different measurement procedures. Likewise, procedures for a substance that fulfills the criteria of the ISO 15193, which describes reference measurement procedures, may yield somewhat different results. JCTLM is addressing this discrepancy by promoting comparisons of reference materials and reference measurement procedures. Procedures 4a and 4b of the WG1 quality system have been designed to address this issue. Reassuringly concordant, albeit limited, results from example studies performed at the National Institute of Standards and Technology (Gaithersburg, MD)—the U.S. national metrology organization—are included in the cited WG1 procedure documents.

A Call to Action

A new appeal for nominations for certified reference materials and reference measurement methods has been issued. All forms and instructions for nominating are available from the JCTLM Web site. Formally, nominations are received by the JCTLM secretariat, then transferred to WG1, whose chairs distribute the nominations to the appropriate review teams. Reviews are performed by the expert review teams according to WG1 Procedures 3, 4a, or 4b.

The need for identifying new reference materials and reference measurement procedures is pressing. The rapid development of new health and disease markers provides clear evidence of this. In any given issue of the journal *Clinical Chemistry*, new and extremely useful laboratory procedures are presented; however, the results of these, depending upon method and manufacturer, often provide different values for the same substance.

When the need for reference materials for new markers cannot be met with currently available materials, IVD manufacturers should communicate with organizations that produce such materials (for example, their national metrology institutes).

JCTLM, through WG2, will soon identify and, via accreditation through other organizations, validate a list of reference measurement service providers for customers that require product traceability. These labs are academic, government, and commercial organizations that provide calibration and value-assignment services for IVD manufacturers' external quality-assessment programs. The results from the measurement services of these laboratories will be traceable to the entries on the JCTLM lists of materials and measurement procedures. The first list of reference measurement services is expected to appear in the latter half of 2006. After that, the list will be reviewed and updated annually.

To demonstrate their competence and be listed by JCTLM, reference measurement service providers must participate in interlaboratory comparison studies. Measurement results from the studies also provide the data needed to verify equivalence of results obtained using JCTLM-listed materials and measurement procedures.

Conclusion

JCTLM has been working to meet the need for obtaining comparability and equivalence of measurement results throughout the world. JCTLM's international reach, along with the active participation of experts from professional societies, the IVD industry, and international and national accreditation groups, has enabled the organization to take a leading role in meeting these comparability goals. Although the founding of JCTLM was prompted by the European IVD Directive, its benefits far exceed simply providing lists to meet regulations. The transparency of its operations and its broad and open participation can be expected to make it successful where other organizations with similar goals have faltered.

Acknowledgment

The authors wish to thank Donna Kimball at the National Institute of Standards and Technology (NIST; Gaithersburg, MD) for producing the original documents from which this commentary was developed. JCTLM WG1 review team leaders were responsible for the processes embodied in the WG1 quality system.

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