13. *SRM Activities to Support Health-Care Measurements*

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Objective: To provide certified reference materials that support measurement accuracy and traceability for laboratories performing health-related measurements and In-vitro Diagnostic Device (IVDD) manufacturers.

Problem: Inaccuracy in health-related measurements raises overall health care costs, results in misdiagnoses, and leads to inaccurate conclusions in clinical studies. In addition, lack of certified reference materials (CRMs) hampers traceability, and with the new European Community IVDD directive which will require traceability to "standards, of the highest metrological order" there is an urgent need for new health-related SRMs.

The European Community (EC) has scheduled full implementation of a directive on in vitro diagnostic Devices (IVDD) for December 2003. The directive requires all manufacturers of IVD products sold in Europe to have an "EC Stamp," verifying that they comply with the conditions of the directive. U.S. companies are major exporters of IVDD products to European markets, and thus are directly affected by the directive. One of the major components of this directive is a requirement that products are traceable to "standards of the highest order," e.g., nationally/internationally recognized certified reference materials (CRMs). At present, neither CRMs nor reference methods are available for most of the several hundred analytes that are measured in medical laboratories. These analytes fall into two classes: "A list" analytes that are well-defined chemical species of which there are approximately 80 and "B list" analytes that are less well-defined and number in the hundreds.

One mechanism available on a limited basis for providing the necessary traceability is using clinical reference laboratories to establish traceability to higher order methods. Such laboratories are well established in Europe, but analogous laboratories in the U.S. have generally not been economically viable. With a shortage of clinical reference laboratories in the U.S., it may be difficult for U.S. manufacturers of IVDD products to get the necessary traceability. The European reference laboratory services are very expensive and may not have the reputation to properly address U.S. customer needs. From discussions with representatives of the U.S. IVDD industry, it is clear that they prefer the use of commutable, internationally recognized CRMs as their basis for establishing "traceability to standards of the highest order".

Approach: NIST works closely with the American Association for Clinical Chemistry (AACC), the Centers for Disease Control and Prevention (CDC) and other organizations interested in health-related standards to prioritize our SRM development activities. In general, most health-related SRMs are a matrix of serum or whole blood with certified concentrations of clinically important analytes that have been identified as priorities. In addition to substances normally found in blood, such as cholesterol or calcium, priorities may include toxic substances such as heavy metals, substances believed to improve health status, such as vitamins and other antioxidants, or markers that signal serious conditions, such as the heart attack marker, troponin-I. Once development has begun for a particular SRM, a variety of certification modes may be used, depending upon the measurement needs and NIST capabilities.

CDC identified a need for a whole blood SRM for toxic metals, specifically lead, cadmium, and both inorganic mercury and methyl mercury. They prepared a two-level material from bovine blood with one level representing normal human levels and the other representing elevated levels. The lead concentrations were achieved through feeding of the cows; the elevated levels of the other analytes were achieved through spiking the collected blood material. Certification measurements for cadmium involved using two independent methods at NIST, ID-ICPMS and neutron activation analysis while total mercury was assayed by CV-AAS and ID-ICPMS. Certification of lead was accomplished using the ID-ICPMS definitive method for lead in blood. Value assignment of the methyl mercury involved NIST measurements using GC-atomic emission detection.

Since first issued in 1989, SRM 968 Fat-Soluble Vitamins and Carotenoids in Human Serum has found widespread use in the clinical laboratory

community. The measurements for the third renewal of this SRM (SRM 968c Fat-Soluble Vitamins, Carotenoids and Cholesterol in Human Serum) have been completed. Fat-soluble vitamins and carotenoids were measured using two or more NIST methods involving liquid chromatography, along with liquid chromatography methods used by selected laboratories that participate in the NIST Micronutrients Quality Assurance Program. Cholesterol was measured in SRM 968c using the NIST ID/MS definitive method for serum cholesterol.

Troponin-I is a protein that is released into the blood when heart tissue is damaged. Because elevated levels of troponin-I correlate extremely well with a recent heart attack, physicians are now using troponin-I measurements as a diagnostic tool. Unfortunately, different immunoassays for troponin-I produce widely different results. In one large study, the mean from one system was more than 20 times the mean from another. This analyte was identified by the AACC Standards Committee as their highest priority for development of a reference material. NIST is using liquid chromatography/mass spectrometry and MALDI mass spectrometry to characterize purified preparations of troponin-I that are then subjected to testing in laboratories using a variety of routine assays.

Results and Future Plans: Measurements for the lead, cadmium, and total mercury in SRM 966 are complete, and measurements are underway for methyl mercury. Measurements have been completed for SRM 968c which will have certified values for cholesterol, four vitamins, and two carotenoid compounds. Reference values will be provided for nine additional vitamins and carotenoid compounds and information values will be provided for seven additional species. For troponin-I, twelve materials have been evaluated by NIST for their purity and molecular weight distributions. These materials will be sent to a group of laboratories organized by AACC for measurement by the most widely used methods for troponin-I. Those results will be correlated with NIST results and the material judged best will be chosen as a candidate SRM.

We are committed to support the U.S. IVDD industry by maintaining our existing measurement capabilities and serum-based SRMs for calcium, chloride, cholesterol, creatinine, glucose, lithium, magnesium, potassium, nodium, triglycerides, urea, and uric acid. We also plan to intensify both our in-house research program and our interactions with the medical professional and medical laboratory community to develop matrix-based SRMs for the following clinical diagnostic markers over the next 3-5 years:

- Troponin — *heart attack marker*
- Homocysteine — *risk of heart disease*
- Glycated Hemoglobin — *diabetes status*
- Cortisol — *endocrine function*
- Thyroxine — *thyroid function*
- Cadmium — *heavy metal toxicity*
- Folic Acid — *neural tube defects*
- Mercury — *heavy metal toxicity*
- Speciated Iron — *hemochromatosis, anemia*
- Human serum Albumin — *renal failure*
- Prostate Specific Antigen — *prostate cancer*
- Thyroid Stimulating Hormone — *thyroid function*