2009 Annual Report of the IFCC Scientific Division (SD)

Mauro Panteghini
Chair IFCC Scientific Division

During 2009, the following members served on the SD Executive Committee: Mauro Panteghini (Italy) (Chair), Ian Young (UK) (Vice-Chair), Gary Myers (United States) (Secretary), Philippe Gillery (France), Lothar Siekmann (Germany), Naotaka Hamasaki (Japan) and George Brotea (United States) (corporate representative). Three representatives of International Organizations were invited to attend the SD meetings as consultants: Jean-Claude Forest (JCTLM), Heinz Schimmel (IRMM) and David Bunk (NIST). Two meetings were held during the year 2009: April 17-18 (Milan, IT) and October 2-3 (Milan, IT).

RELATIONSHIP WITH INTERNATIONAL ORGANIZATIONS

The SD continues to pursue the expansion of its activities to partner with International Organizations to promote the implementation of the concept of traceability in Laboratory Medicine and the implementation of reference measurement systems.

Joint Committee on Traceability in Laboratory Medicine (JCTLM)

The JCTLM continues its work, which is available for review on its database at www.bipm.org/jctlm. The Working Group 1 on Reference Measurement Procedures and Reference Materials continues its program of identifying and reviewing against agreed criteria (ISO standards 15193 and 15194). The Working Group 2 on Reference Measurement Services has reviewed new nominations from candidate laboratories. A procedure is in place to periodically review the lists and to remove entries when they no longer meet the established criteria. The database has become a reliable source of information particularly for the in vitro diagnostics (IVD) industry.

Institute for Reference Materials and Measurements (IRMM)

Close collaboration with IRMM continues through a number of joint ventures involving SD Committees and Working Groups. New materials for aspartate aminotransferase (AST) and C-reactive protein (CRP) have been released. Projects continue for the preparation of materials for hemoglobin A2 (HbA2), myoglobin, cystatin C, β2-microglobulin and ceruloplasmin.

Clinical and Laboratory Standards Institute (CLSI)

An updated list of joint CLSI/IFCC documents is available on the IFCC web site at: http://www.ifcc.org/index.asp?cat=Publications&scat=CLSI_(Clin_Lab_Stand_Inst)_-_IFCC_Joint_Projects&rif=6&dove=1.

National Institute of Standards and Technology (NIST)

NIST continues to undertake a large number of projects, many of which are of considerable interest to IFCC. Standard Reference Materials (SRM) released in 2009 include: vitamin D in human serum (SRM 972) and 25-hydroxyvitamin D2 and D3 calibrating solutions (SRM 2972). SRMs to be released in the near future include: steroid hormones, including thyroid hormones in human serum; drugs of abuse in human serum; metabolites in human plasma; creatinine in human urine; antiepilepsy drugs in serum; vitamins B6 and B12 in human serum; fat soluble vitamins and carotenoids in human serum.

INTERNATIONAL CONGRESS OF CLINICAL CHEMISTRY AND OTHER CONGRESSES

The SD was asked to develop proposals for symposia for the 21st International Congress of Clinical Chemistry and Laboratory Medicine (WORLDLAB 2011) held in Berlin, Germany (May 2011). Three symposia topics were suggested.

At the 18th IFCC–EFCC European Congress of Clinical Chemistry and Laboratory Medicine (Innsbruck, Austria - June 2009) two official symposia were presented by the SD on the following topics:

- How to define and determine reference intervals and decision limits in Laboratory Medicine;
- Standardization activities in endocrinology.

At the 12th Asia Pacific Congress on Clinical Biochemistry (Seoul, Korea - October 2010), the SD proposed symposium “Standardization activities in endocrinology” was accepted.

ACTIVITIES OF COMMITTEES AND WORKING GROUPS

The Committees (Cs), which are theme-oriented, carry out much of the scientific and professional activities of the SD. Their work is often in close collaboration with other International Organizations. For more specific tasks, the activities are usually accomplished through Working Groups (WGs).

Committees

C-Nomenclature, Properties and Units (C-NPU)

An updated version of the NPU terminology database has been available for download at the national Danish site, www.labterm.dk, since January 2009. Collaboration with IHTSDO (International Health Terminology Standards Development Organization), which manages SNOMED-CT, lead to a satisfactorily performed trial period April-October 2009. Securing and structural updating of information in the NPU coding system and its environment (IUPAC 2006-012-1-700): a 102 page user's guide has been edited in Danish and published on the Danish Board of health website. An English version has been drafted and is under review within the C-NPU. All of the above activities were jointly performed with International Union of Pure and Applied Chemistry (IUPAC). Copy of the 3rd edition of the International Vocabulary of Metrology (VIM3) was released on free access on the IFCC web site.

C-Molecular Diagnostics (C-MD)

The C-MD organized a "Brown Bag" session on Nucleic Acids Reference Materials at the 2009 Annual Meeting of the American Association of Clinical Chemistry (AACC). The C-MD is collaborating with the CanGeneTest research consortium on genetic laboratory services (www.cangenetest.org) for the production of a horizon-scanning newsletter in the field of Genetic Laboratory Services. The publication of a first paper on a proposed reference method for haploid DNA was accomplished. A document commenting on the UK Human Genetics Commission's public consultation on a framework on direct-to-consumer genetic testing was prepared. A consensus of available guidelines on MD testing has been compiled on the C-MD web page. A position paper on nucleic acid reference materials is in preparation. The C-MD website provides an updated census of available reference materials and EQA programs for MD. All the links of this C-MD web page have been validated and upgraded in 2009 and it now contains 324 links.

C-Plasma Proteins (C-PP)

Collaboration with IRMM was established for the production of following protein reference materials: β_2-microglobulin, CRP, ceruloplasmin and myoglobin. A study to evaluate analytical issues with assays for free light chains in serum was developed. The collaboration on the 3rd Asian study on reference intervals continued.

C-Standardization of Markers of Cardiac Damage (C-SMCD)

The C-SMCD reviewed a draft protocol for establishing a repository of samples from reference subjects for the purpose of defining 99th percentile upper limit for troponin assays. Two papers describing the experimental work for the second stage of the project to evaluate BNP, proBNP and NT-proBNP antigens from multiple commercial sources for cross-reactivity in commercial and experimental BNP, NT-proBNP and proBNP assays are in final stages of revision. The tables for cardiac troponin and natriuretic peptide assays have been reviewed, updated and posted on IFCC web site.

C-Reference Systems for Enzymes (C-RSE)

A manuscript was prepared for publication as an IFCC document entitled: "IFCC reference procedures for catalytic concentration measurement of enzymes: Corrigendum, notes and useful advice". C-RSE cooperated with C-RIDL to solve the problem of missing reference intervals for the proposed IFCC reference measurement procedure for alkaline phosphatase (ALP). Work on the development of a reference measurement procedure for lipase continues. Members of the C-RSE reference laboratory network are co-authors of the publication entitled: "Traceability of values for catalytic activity concentration of enzymes: a Certified Reference Material for aspartate transaminase" accepted for publication.

C-Point of Care Testing (C-POCT)

As a result of concern over a lack of productivity by the C-POCT, the IFCC Executive Board (EB) decided to terminate the C-POCT. See also Project Proposals.

C-Traceability in Laboratory Medicine (C-TLM)

Comments were provided on the document "Summary Technical Documentation (STED) for Demonstrating

Conformity to the Essential Principles of Safety and Performance of In Vitro Diagnostic Medical Devices" of the Global Harmonization Task Force (GHTF). The 6th ring trial for Reference Laboratories (RELA 2008) was completed in June 2009. The RELA web site was redesigned and a guideline for its use was published. ALP measurement will be added to the 2010 RELA survey.

C-Reference Intervals and Decision Limits (C-RIDL)

One review paper was published (listed below). Collection of data on reference subjects was completed for AST, ALT and GGT. The 3rd Asian study on reference intervals has been concluded. Collaboration with C-RSE to collect samples from reference subjects for ALP was done.

Working Groups

WG-Apolipoproteins (WG-A)

The IFCC-EB decided the termination of the WG. The Centre for Disease Control (CDC) is prepared to continue to act as repository for the two apolipoprotein B and A-I reference materials.

WG-Standardisation of hCG (WG-SHCG)

The paper summarizing EQA results obtained with the international reference reagents (IRR) for hCG and related molecules has been published (see publication list). The intact hCG material, which has served for IRR 99/686 prepared by WG-SHCG (recoded as 07/364), has been proposed by National Institute of Biological Standards and Controls (NISBC) as 5th WHO International Standard for hCG. As the major work of the WG has been completed, the IFCC-EB decided the termination of the WG.

WG-Standardization of HbA1c (WG-HbA1c)

Improvement to the IFCC reference measurement procedure for HbA1c by LC-ESI/MS will be investigated and assessed by the network. Currently there are 13 IFCC reference network laboratories for HbA1c (5 HPLC-MS and 8 HPLC-CE). These participate in analytical exercises demonstrating their competence with the reference measurement procedures. Their work continues to demonstrate that the master equation remains remarkably constant. Clinical and laboratory representatives of a number of countries have agreed on future reporting of HbA1c results, many of which have adopted the IFCC recommendation. These decisions will continue to be made at the national level and there are different views on this matter; the UK, Italy, Germany, Netherlands, Australia, New Zealand, Finland, Canada and Japan are likely to adopt SI (IFCC) units, whereas the US is likely to remain with National Glycohemoglobin Standardization Program (NGSP) units and may be the only country to adopt calculation of average glucose (eAG). The major work to establish an international reference system to standardize HbA1c has been completed. The priority now is the implementation of the IFCC recommendations for standardizing and reporting HbA1c results. The SD recommended closing the WG and placing the HbA1c laboratory network under the oversight of the C-TLM. As a consequence, the creation of an IFCC Integrated Project on implementation of HbA1c standardization was approved by the IFCC EB.

WG-Standardisation of Thyroid Function Tests (WG-STFT)

For free T4, a phase II proof-of-concept study consisting of a method comparison between immunoassays and the ED ID-LC/tandem mass spectrometry (MS) international conventional candidate reference measurement procedure confirmed that method comparison on using a panel of native sera is an appropriate tool to serve the purpose of standardization (through recalibration of immunoassays). A phase II proof-of-concept study for TSH was also performed which consisted of analysis of a panel of sera obtained according to the CLSI C37-A protocol (without filtration) from apparently healthy donors and comparison of each assay's results against the "all methods' trimmed mean". The consistency was within ~10%. For most assays the recalibration process by the respective manufacturers was successfully done and in agreement with mathematical recalibration; the inter-assay CV improved considerably after recalibration.

WG-Standardization of Hemoglobin A2 (WG-HbA2)

In the development of the reference method, a need for optimizing the digestion step was underlined, as well the opportunity to increase the number of MS laboratories to reduce the uncertainty. Two labeled peptides as internal standards are being prepared. The one-year stability study on the first pilot of a lyophilized secondary reference material from a human stabilized hemolysate at physiological HbA2 concentration was completed. The specimens have been tested for homogeneity and stability under various conditions, as well for the HbA2 content measured by various analytical methods. Results indicate excellent quality of this first batch. Preparation of a larger batch is being delayed until validation of the reference measurement procedure is completed.

WG-Standardisation of Carbohydrate-Deficient Transferrin (WG-CDT)

Five laboratories are performing the HPLC candidate reference method. A WG ring trial (ring trial-A) in May 2009 including both native and lyophilized serum pools at two CDT (% disialotransferrin) levels showed an inter-laboratory CV in the range 2.5-7.3% for the reference laboratories. Another ring trial (October 2009), including one native serum pool and three different lyophilized variants, showed an inter-laboratory CV for the CDT reference laboratories in the range 3.2-3.7%. Further studies are planned on the possible use of MS as a reference method for CDT. A ring trial was conducted to compare native and lyophilized serum pools at two disialotransferrin levels for all available commercial routine and research CDT methods (HPLC, capillary electrophoresis, immunoassay). The standard lyophilization process was not optimal for the N-Latex CDT immunoassay. A meeting with the IRMM representatives on a possible joint development strategy for production of CDT reference materials was held.

WG-Standardisation of Cystatin C Assays (WG-SCC)

Further characterization of both the Primary and Secondary Reference Preparations (called PRP and SRP, respectively) has been performed. New double radial immunodiffusion studies, crossed immunoelectroporesis, gel filtration and SDS-PAGE-immunoblotting studies have been used. The results indicated that both preparations contained virtually only monomeric cystatin C with MW and electrophoretic mobility characteristic of native intact cystatin C. The value assignment of cystatin C in the SRP (ERM-DA471/IFCC) has been carried out using the above-mentioned PRP. The study was conducted using the following immunochemical methods: single radial immunodiffusion, immunonephelometry and immunoturbidimetry. The total number of value assignment studies was 7, performed at four different expert laboratories, all following the same practical protocol. The mathematical analysis indicated that all assays gave comparable results and that all data therefore could be pooled for suggesting a concentration value of cystatin C in the SRP. Commutability studies by IRMM have been started. A report has been submitted to the Certification Advisory Panel at IRMM for ERM-DA471/IFCC.

WG-Standardisation of Glomerular Filtration Rate Assessment (WG-GFRA)

A collaborative study to evaluate specificity among currently available routine serum creatinine methods was completed. The study involved four major IVD systems manufacturers using 8 commercially available creatinine methods (systems) and the LC/IDMS-MS reference method. More than 20,000 serum creatinine measurements were completed for 429 native human specimens, selected for likely presence of potential interferences. Data analysis is ongoing.

WG-Standardisation of Albumin Assay in Urine (WG-SAU)

An albumin in urine reference material has been prepared by the Japanese Society of Clinical Chemistry (JSCC) and value assigned for use in Japanese internal investigations. A LC-MS/MS method developed at the Mayo Clinic, US is being validated as a reference measurement procedure to quantify intact albumin in urine. A study to evaluate adsorption of albumin onto containers used for urine collection and urine albumin measurement has been completed by CDC. Planning of a study to evaluate urine albumin physiologic variability coordinated by CDC is complete. The National Kidney Disease Education Program (NKDEP) has completed plans for a study to determine the molecular forms of urine albumin.

WG-Standardisation of Pregnacy-Associated Plasma Protein A (WG-PAPPA)

In anticipation of a project start, reagents (several PAPP-A preparations extracted from pregnancies, index antibodies) have been identified and received from Hytest Ltd, Finland.

WG-Growth Hormone (WG-GH)

A meeting with IRMM to discuss GH assay harmonization and potential ways to collaborate on commutability was held and also a meeting with representatives from clinical societies to discuss GH assay harmonization and to plan for collection of serum samples for commutability studies. A consensus workshop with the Growth Hormone Research Society, the IGF Society, assay manufacturers, representatives from laboratories and regulatory bodies (including FDA) was held to discuss assay harmonization. Development and initial validation of a MS method to quantify GH in serum/EQA samples, based on the measurement of specific fragments, in ongoing.

WG-Standardisation of Insulin Assays (WG-SIA)

Funding was provided by National Institute of Health (NIH) to support the collection and preparation of a panel of single donor samples for insulin assay harmonization.

WG–Standardisation of Troponin I (WG-TNI)

With regard the candidate reference measurement procedure, NIST has selected two monoclonal antibodies (MAbs) which showed optimized binding affinity (multibead technology).The UK National Physical Laboratory (NPL) designed 1+1 ELISA format (capture Ab 41-49 a.a. and detection Ab 83-93 a.a.) and optimised the method for reference material value assignment; the method validation is in progress. The WG has developed a pilot study protocol to investigate comparability of the candidate RMP versus current commercial cTnI assays. The WG has developed a pilot study protocol to investigate the feasibility of preparing a commutable, stable secondary reference material for cTnI by use of serum pools. The study involves NIST, NPL, hospital laboratories and industry. The collection of patient samples is underway.

Project Proposals

The IFCC EB approved the creation of 3 new WGs:
1. “Allowable Errors for Traceable Results” - WG-AETR;
2. "Harmonization of Autoantibody Tests"- WG-HAT;
3. "Quality Specifications for Glucose POCT" - WG-GPOCT.

PUBLICATIONS

SD Executive

1) Panteghini M. Traceability as a unique tool to improve standardization in laboratory medicine. Clin Biochem 2009;42:236-40.

C-MD

1) Rousseau F., Gancberg D, Schimmel H, Neumaier M, Bureau A, Mamotte C, van Schaik R, Payne D, Pazzagli M, Young I. Considerations for the development of a reference method for sequencing of haploid DNA – an opinion paper on behalf of the IFCC Committee on Molecular Diagnostics. Clin Chem Lab Med 2009;47:1343-50.

C-RIDL

1) Ceriotti F, Hinzmann R, Panteghini M. Reference intervals: the way forward. Ann Clin Biochem 2009;46:8-17.

WG-SHCG

1) Sturgeon CM, Berger P, Bidart J-M, Birken S, Bruns C, Norman RJ, Stenman UH. Differences in recognition of the 1st WHO International Reference Reagents for hCG-related isoforms by diagnostic immunoassays for human chorionic gonadotropin. Clin Chem 2009;55:1484-91.
2) Gronowski AM. Clinical assays for human chorionic gonadotropin: What should we measure and how? Clin Chem 2009;55:1900-4.

WG-SAU

1) Miller WG, Bruns DE, Hortin GL, Sandberg S, Aakre KM, McQueen MJ, Itoh Y, Lieske JC, Seccombe DW, Jones G, Bunk DM, Curhan GC, Narva AS. Current issues in measurement and reporting of urinary albumin excretion. Clin Chem 2009;55:24-38.
2) Miller WG, Bruns DE. Laboratory issues in measuring and reporting urine albumin. Nephrol Dial Transplant 2009;24:717-8.

WG-SIA

1) Miller GW, Thienpont L, Van Uytfanghe K, Clark PM, Lindstedt P, Nilsson G, Steffes MW. Toward standardization of insulin immunoassays. Clin Chem 2009;55:1011-8.

WG-GH

1) Bidlingmaier M. Freda PU. Measurement of human growth hormone by immunoassays: Current status, unsolved problems and clinical consequences. Growth Hormone & IGF Research 2009; doi:10.1016/j.ghir.2009.09.005.

APPENDIX

Synopsis of Committees and Working Groups currently active in IFCC Scientific Division. 2010 Chairs are also reported

COMMITTEE/WORKING GROUP	CHAIR
Committee on Nomenclature, Properties and Units (C-NPU)	F. Pontet (FR)
Committee on Molecular Diagnostics (C-MD)	M. Pazzagli (IT)
Committee on Plasma Proteins (C-PP)	G. Merlini (IT)
Committee on Reference Systems of Enzymes (C-RSE)	F. Ceriotti (IT)
Committee on Traceability in Laboratory Medicine (C-TLM)	A. Kessler (DE)
Committee on Reference Intervals and Decision Limits (C-RIDL)	K. Ichihara (JP)
Working Group on Standardization of Thyroid Function Tests (WG-STFT)	L. Thienpont (BE)
Working Group on Standardization of Hemoglobin A2 (WG-SHbA2)	R. Paleari (IT)
Working Group on Standardization of Carbohydrate-Deficient Transferrin (WG-CDT)	A. Helander (SE)
Working Group on Standardization of Cystatic C (WG-SCC)	A. Grubb (SE)
Working Group on Standardization of Glomerular Filtration Rate Assessment (WG-GFRA)	N. Greenberg (US)
Working Group on Standardization of Albumin Assay in Urine (WG-SMA)	G. Miller (US)
Working Group on Standardization of Pregnancy-Associated Plasma Protein A (WG-PAPPA)	K. Pettersson (FI)
Working Group on Growth Hormone (WG-GH)	M. Bidlingmaier (DE)
Working Group on Standardisation of Insulin Assays (WG-SIA)	M. Steffes (US)
Working Group on Standardisation of Troponin I (WG-TNI)	J. Tate (AU)
Working Group on Allowable Errors for Traceable Results (WG-AETR)	R. Bais (AU)
Working Group on Harmonization of Autoantibody Tests (WG-HAT)	J. Sheldon (UK)
Working Group on Quality Specifications for Glucose POCT (WG-GPOCT)	R. Tirimacco (AU)