IFCC Scientific Division Triennial Report 2006-2008

MEMBERS AND TIME OF OFFICE

During the 2006-2008 triennium the following members served on the Scientific Division (SD) Executive Committee:

- Mauro Panteghini (Italy) Chair;
- Ian Young (UK) Vice-Chair;
- Howard Morris (Australia) Secretary;
- Philippe Gillery (France);
- Lothar Siekmann (Germany);
- Ulf-Hakan Stenman (Finland);
- Rolf Hinzmann (Germany) Corporate Representative 2006;
- George Brotea (US) Corporate Representative 2007-2008;
- Heinz Schimmel (Belgium) Consultant from IRMM;
- David Bunk (US) Consultant from NIST;
- Jean-Claude Forest (Canada) JCTLM Chair.

MEETINGS

The following meetings were held:

2006	Damascus, Syria	April 28-29	SD 37
	Milan, Italy	September 29-30	SD 38
2007	Amsterdam, The Netherlands	June 7-9	SD 39
	Milan, Italy	September 28-29	SD 40
2008	Antalya, Turkey	April 11, 12 & 14	SD 41
	Fortaleza, Brazil	September 28-29	SD 42

RELATIONSHIP WITH INTERNATIONAL ORGANIZATIONS

The SD has pursued 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 has now been working for 7 years and its main accomplishments are available for review on its database at www.bipm.org/jctlm. The Working Group (WG) 1 on Reference Measurement Procedures and Reference Materials continues its program of identifying and reviewing against agreed criteria (ISO standards 15193 and 15194). Some 530 reference materials have been nominated with 236 approved and listed for about 100 measurands. Some 195 reference measurement procedures have been nominated and 129 have been accepted as fulfilling the criteria of the appropriate ISO standard. The WG 2 on Reference Measurement Services has reviewed some 390 nominations from laboratories of National Institutes of Metrology, manufacturers, clinical service providers and academic centres of which 197 have been approved and listed. A procedure is in place to review the lists periodically 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. A series of documents have been prepared by WG 1 describing the process for review and approval of nominated certified Reference Materials and Reference Methods, for requesting and accepting nominations for certified Reference Materials and Reference Methods, for evaluating certified Reference Materials and Reference Measurements Procedures to be listed as being of higher metrological order, processes for the demonstration of the comparability of certified values of the same measurand in multiple materials having the same nominal matrix, etc. The WG 2 has prepared a document to define the process for review of Reference Measurement Services from laboratories that are signatories to CIPM MRA or accredited as calibration laboratories (ISO17025/15195). The purpose of this endeavor was to describe the processes to be followed by review teams for reviewing nominations of Reference Measurement Services provided by reference laboratories.

Institute for Reference Materials and Measurements (IRMM)

Close collaboration with IRMM continues with practical joint ventures such as the preparation of certified

Reference Materials for the following analytes: prothrombin II wild type and mutant as genetic reference materials (released on 2006), HbA_0 and HbA_{1c} (released on 2007), 2nd ERM-DA470 plasma proteins, which has recently been released, aspartate aminotransferase (AST) and cystatin C (to be released by 2009). Other materials (e.g., myoglobin, alkaline phosphatase (ALP)) are under evaluation.

Clinical and Laboratory Standards Institute (CLSI))

The good working relationship between CLSI and IFCC continues. The documents on Analysis of Body Fluids in Clinical Chemistry (C49), Mass Spectrometry in the Clinical Laboratory: General Principles and Guidance (C50), Verification of Comparability of Patient Results Within One Healthcare System (C54), Body Fluid Analysis for Cellular Composition (H56), Immunoassay Interference by Endogenous Antibodies (I/LA30), Diagnostic Nucleic Acid Microarrays (MM12), Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods (MM13), Proficiency Testing (External Quality Assessment) for Molecular Methods (MM14), Use of External RNA Controls in Gene Expression Assays (MM16), Point-of-Care Connectivity (POCT1), Implementation Guide of POCT1 for Healthcare Providers (POCT2), Metrological Traceability and Its Implementation (X5-R) have been completed.

Current ongoing joint CLSI/IFCC projects include: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory (C28), Expression of Measurement Uncertainty in Laboratory Medicine (C51), Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine (C53), Method Comparison of Glucose Methodologies (POCT6).

National Institute of Standards and Technology (NIST)

A large number of projects are underway at NIST many of which are of considerable interest to IFCC. These include: non-peptide hormones in serum; drugs of abuse in serum; metabolites in human plasma; creatinine in human urine; vitamin D in human serum; cardiac troponin I in human serum; reference materials for clinical proteomics.

INTERNATIONAL AND REGIONAL CONGRESSES

During the 19th International Congress of Clinical Chemistry and Laboratory Medicine (ICCC) (Orlando, US, 2005), the SD was responsible for two symposia on "Achieving Standardization in Laboratory Medicine - A Hard but Feasible Task" and "Monitoring Immunosuppressive Drugs". A number of Committees and WGs participated to the scientific program. At the 20th ICCC (Fortaleza, Brazil, 2008) the SD has presented two symposia on "The Concept of Traceability in Laboratory Medicine - A Tool for Standardisation" and "Quality Assurance in Emerging Technologies".

The SD participated in the 17th IFCC - EFCC European Congress of Clinical Chemistry in Laboratory Medicine (Amsterdam, The Netherlands, 2007) organizing two symposia: "Standardization in Laboratory Medicine: the Way Forward" and "The Contribution of Laboratory Medicine in Kidney Disease".

The SD participated in the 11th Asian Pacific Congress of Clinical Chemistry (Beijing, China, 2007) on an official basis organizing the symposium: "Traceability in Laboratory Medicine: What Does It Mean in Daily Practice?". At the 11th Arab Federation of Clinical Biology Congress (Damascus, Syria, 2006) the SD presented a symposium titled "Application of ISO Standards in Laboratory Medicine".

ACTIVITIES OF COMMITTEES AND WORKING GROUPS

Committees

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

This IFCC/IUPAC Committee is responsible for the maintenance of the generic database, which is now available through the IFCC website under the URL: <http://dior.imt.liu.se/cnpu/>. An updated version is available in Danish and English at http://www.labinfo.dk/English/ifcc_iupac_uk.asp. C-NPU is currently investigating long term maintenance of the database and wider utilization at the international level. Discussions are currently underway between the IFCC and IHTSDO with regard to utilisation of the database for SNOMED-CT, the international project to develop a full electronic health record. The 3rd edition of the VIM (Vocabulary in Metrology) is now available and published on the ISO website. Other projects completed include 1. The recommendation for the term and measurement unit for HbA_{1c}, and 2. A symposium on Nomenclature, Properties and Units in Clinical Chemistry organized in IUPAC Worldwide Congress (Turin, Italy, 2007). Ongoing projects include: 1. Properties and units for function examinations, 2. Properties and units for urinary calculi, 3. Mapping of IFCC-IUPAC laboratory coding system to SNOMED-CT, 4. Securing and structural updating of information in the NPU coding system and its environment. C-NPU database elements and properties have been translated into French and are accessible on the Société Française de Biologie Clinique (SFBC) website.

C-Molecular Diagnostics (C-MD)

A document was prepared describing the concept of IFCC Molecular Diagnostic Centres (MDC) of expertise including the expertise and duties to be provided for the international laboratory community. The first three areas of specialisation are haemochromatosis, factor V Leiden and apolipoprotein E. The purpose of these centres is to enhance technology transfer of clinical testing expertise to clinical service laboratories. Following a call for expressions of interest seven laboratories were appointed as Centers of Excellence and four appointed as Member Laboratories. Applications remain open. The IFCC web site hosts the Consortium on Clinical Laboratory Genetics and Genomics Standards (CLGGS, formerly IMGCLS) web site that is reviewed by C-MD. A formal document was prepared on behalf of IFCC to provide comments to Organization for Economic Cooperation and Development (OECD) on its "Draft Guidelines on Quality Assurance in Molecular Genetic Testing".

C-Plasma Proteins (C-PP)

The preparation of the 2nd ERM-DA470k (formerly 2nd Preparation CRM470) reference material for plasma proteins in collaboration with IRMM has been completed and the certified material has now been released. Stability and commutability studies were conducted with excellent results. A simplified protocol for transferring values from ERM-DA470 reference material to calibrators of commercial protein assays is now in press on CCLM October 2008 issue. Other projects are: 1. Collaboration with carbohydrate-deficient transferrin (CDT), cystatin C, and urinary albumin WGs, and 2. Preparation of a document on the measurement of serum free light chains in the clinical contest. The C-PP also maintains its interest in proteomics.

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

A document titled "Quality specifications of BNP assays" has been published by Clinical Chemistry in 2005. The results of a preliminary study to validate the cross-reactivity of commercial BNP and NT-proBNP assays with BNP, proBNP and NT-proBNP antigens have also been published (Clin Chem 2008). A formal, multicentre natriuretic peptide cross-reactivity study has been completed and data using 9 different materials measured by 20 different platforms are currently being subjected to statistical analyses. A table of properties of commercial cardiac troponin assays has been posted on the IFCC web site (SD/C-SMCD page). The C-SMCD is working to establish a reference serum bank to be used for the establishment of reference intervals in subjects without cardiac disease for established and developing cardiac troponin assays as well as new cardiac biomarkers. A secondary reference material has been selected for myoglobin in close collaboration with IRMM. IRMM is working on the reference method for the certification of the selected material as well as its further characterization. In collaboration with the AACC Subcommittee for cardiac troponin I (cTnI) standardization and NIST, a primary reference material for cTnI (human CIT tertiary complex, NIST SRM 2921) was selected to be used for cTnI assay standardization. A manuscript titled "Future Biomarkers for Detection of Ischemia and Risk Stratification in Acute Coronary Syndrome" has been published in Clinical Chemistry 2005.

C-Reference Systems for Enzymes (C-RSE)

Work on standardisation of the amylase determination was completed with the publication of the IFCC recommended reference method. A feasibility study for a proposed reference procedure for ALP is underway including the assessment of the suitability of deep-frozen pooled human sera or processed lyophilized sera for use as control materials. Discussions with the C-RIDL are underway to develop appropriate reference intervals for ALP at the same time that the reference procedure is under development. The enzyme network has agreed on the budget of uncertainty of measurements for enzymes.

C-Point of Care Testing (C-POCT)

Members of the C-POCT have served on the CLSI Area Committee for POCT for several projects. Some of the CLSI projects for which the members participated in 2007 are: "Guidelines for comparison of glucose methodologies which use different sample types - proposed guideline"; "Implementation guide of POCT1 for healthcare providers; proposed guideline". Other initiatives were the acceptance of workshop and round table topics for presentation at the 2008 AACC annual conference. The C-POCT is continuing to work on the following projects: 1. Required trueness and precision for glucose analyses in specific clinical settings: Does POCT meet these criteria? 2. Database of potential interferents in POCT 3. Curriculum/Training of POCT staff in collaboration with AACC POCT Division.

C-Traceability in Laboratory Medicine (C-TLM)

The C-TLM continues to support reference laboratories in the context of complete reference systems (accepted reference measurement procedures of higher order, reference materials, and reference laboratories), through the External Quality Assessment Schemes (EQAS) for reference laboratories to monitor their competence as well as collaborating closely with the JCTLM. The website (available through the IFCC home page, under the DGKL logo) provides a number of services including registration for newly participating laboratories, orders for participation in forth-

coming EQAS, entering of results from laboratories, inspection of recent EQAS results, and information on forthcoming EQAS. The performance of laboratories and measurands have been analysed closely with a number of recommendations arising to continuously improve the program. Furthermore the analytical tools for assessing and comparing performance particularly concerning the estimation of uncertainty have been signicantly improved. These developments are aimed at providing more information to the laboratories participating in ring trials as well as to customers utilising the services of these laboratories. It is aimed that the results of ring trials will be supplemented by additional comments if considered helpful. The C-TLM was most saddened by the passing of Rick Miller acknowledging that it had lost a very active and competent member. His helpful contributions were always highly appreciated.

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

Collaboration with CLSI for the revision of CLSI document C28-A2 "How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline - 2nd edition" has concluded. While the document does not modify the concepts expressed in the previous IFCC documents, it introduces new aspects including concepts of multicentre reference intervals and common reference intervals, new ways to calculate reference limits and especially more details on transference and validation of existing reference intervals. A systematic review on existing creatinine reference intervals was performed with a careful analysis of the literature with particular regard to evidence of traceability of the data to accepted reference methods. Moreover previously published data on children reference intervals were recalculated with a regression based approach. The resulting manuscript has been published in Clinical Chemistry 2008. Work to derive AST, ALT and GGT reference intervals using traceable assays has recruited four centres. The resulting data are now under evaluation.

WORKING GROUPS

WG-Selective Electrodes and Biosensors (WG-SEB)

Current projects include preparation of recommendations on pH measurement in blood (an update), recommendation of the reference bovine hemoglobin control material for the evaluation of trueness of the routine measurement of total hemoglobin and the three hemoglobin derivatives (O_2Hb, COHb and MetHb) in human blood, and recommendation for measuring and reporting lactate by electrochemical biosensors in undiluted serum, plasma or blood.

WG-Apolipoproteins (WG-A)

The production and characterisation of SP3-08 reference material for Apolipoprotein B is underway. The WG-A Chair has coordinated the NACB project for "Guidelines on emerging cardiovascular risk markers".

WG-Standardization of Human Chorionic Gonadotropin (WG-SHCG)

The IFCC Executive Board has approved inclusion of WHO Reference Reagent (RR) for intact hCG (IRR 99/688), originally prepared by the WG, in a forthcoming WHO International Collaborative Study to identify the next International Standard (IS) for hCG immunoassay. Supplies of the current IS (IS 75/589) are expected to be exhausted early in the next decade. Recombinant hCG preparations will also be included as candidates in the Collaborative Study. These activities, together with a manuscript currently being finalized on the implications for between-method comparability of use of the six hCG IRRs, will provide further opportunity to publicize the IFCC hCG nomenclature. Additionally, a brief letter is being drafted to journal editors requesting that they make the use of this nomenclature mandatory. A study to determine the effect of recalibration of assays using IRR 99/688 will be commenced with the support of the IVD industry. Direct comparison of IS 75/589 and IRR 99/688 will be required with a panel of over 400 specimens to be assayed. Calibration standards will be prepared by individual companies, following their usual procedures, but a set of working standards prepared centrally will also be distributed. Results of this study are also expected to provide evidence of the appropriateness (or otherwise) of commercially available hCG methods for use in oncology, a regulatory issue of major concern as most of these methods are currently approved only for use in testing for pregnancy. The WG is also addressing the frequency of false positive and false negative results in assays for hCG and their clinical implications.

WG-Standardization of Hemoglobin A1c (WG-HbA_{1c})

The IFCC, IDF, EASD and ADA Consensus Statement has been published widely as have the minutes of a meeting with IVD manufacturers. A document providing advice on the implementation of the Consensus Statement to the profession, clinicians and the manufacturers at national level is in preparation. The procedures for the service provision to manufacturers by the reference laboratory network have been developed and are under discussion before final adoption.

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

Manuscripts defining the free T4 measurand and a candidate reference measurement procedure for free T4 have been published (Clin Chem Lab Med 2007). Two laboratories have been recruited to perform a sensitive equilibrium

dialysis-ID-LC/tandem MS assay for free T4 as a higher order measurement procedure. An intercomparison study is being organised between these laboratories utilising an agreed standard operating procedure. A pilot study comparing commercial assays for total T4, free T4 and TSH involving IVD manufacturers has been performed and the preliminary results recently presented to the companies. Support for the WG's activity has been received from the British, American, Japanese and European Thyroid Associations for the standardization work. The aim is to establish a consensus forum of clinical, laboratory and industry representatives to plan and coordinate the standardization process.

WG-Standardization of Hemoglobin A_2 (WG-HbA_2)

Batches of primary reference materials for HbA_0 and HbA_2 have been prepared with small aliquots transferred to IRMM for internal use. Samples are available from the University of Milano. Following comparison of results from the two laboratories performing the candidate reference measurement procedure, a new standard operating procedure is being prepared. One further laboratory has been enrolled. A pilot batch of the secondary reference material has been prepared at IRMM and is now under evaluation. The question of units for reporting this measurand will be derived in consultation with the C-NPU. Analysis of data obtained from the retrospective study, involving the clinical cases with borderline high HbA_2 values and normal MCV, is almost complete and preliminary results have been presented at an International meeting.

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

A manuscript defining the measurand for CDT as disialotransferrin has been published (Clin Chem Lab Med 2007). Pools of patient sera and a CDT candidate reference material, containing authentic human serum samples spiked with isolated disialotransferrin, have been tested by six different CDT methods. Comparison of results revealed significant variation between methods; however, the concordance between laboratories using the HPLC candidate reference method was as an encouraging initial outcome. Five laboratories performed the HPLC candidate reference method and they will become the foundation members of a reference network for CDT. A CDT candidate reference material was distributed to each of these laboratories for a second comparison study. A study of the interference of transferrin genotypes and abnormal transferrin glycoform patterns on different CDT methods has been initiated. A project has been initiated, in collaboration with a mass spectrometry laboratory specializing in protein structure, to define the target epitope of disialotransferrin. The aim is to develop a primary MS reference method for disialotransferrin. Possible certification of the new ERM-DA470k protein reference material (IRMM) for disialotransferrin will be coordinated with the IFCC C-PP. Collaboration with EQA organizations will be considered and also the commutability of control materials across methods, including HPLC, capillary electrophoresis, and immunoassays, will be assessed.

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

Approximately 5000 vials of the Secondary Reference Preparation (SRP) have been prepared using recombinant human cystatin C and stored at IRMM. The value assignment of the SRP is now being pursued. Value transfer from primary recombinant material will utilize the same procedure as used for ERM-DA470. The stability of the SRP is being tested and certification of this material is scheduled to be completed by the end of 2008.

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

The WG current projects are: 1. In cooperation with the US National Kidney Disease Education Program (NKDEP), develop guidelines to coordinate the global introduction of standardized creatinine measurements, together with the new (revised) MDRD GFR estimating equation, 2. Educate laboratory professionals regarding the importance of assessing chronic kidney disease and support the international circulation of relevant documents and education materials, 3. Prepare an IFCC recommendation for the use of specific assays for creatinine measurement. The WG in collaboration with IVD industry has prepared a study protocol to evaluate specificity among currently available serum creatinine methods. The study is examining serum creatinine concentrations from some 400 patient specimens representing a selection of clinically relevant pathological populations. In addition to ID-MS measurements each of the specimens will be analysed by four manufacturer assays including alkaline picrate and enzymatic methods. This study will address creatinine assay specificity because there is little recent literature addressing contemporary methods. An expected outcome is that the study results will allow the WG to develop recommendations for specificity performance requirements. The results are expected to be published before the end of 2009. The WG is monitoring the performance of eGFR reporting particularly amongst US laboratories. Data indicate that there is significant disparity between laboratories and that the transition of laboratories to ID-MS traceable creatinine assays for routine use is slower than expected possibly because of the lack of traceable creatinine assays from some manufacturers and the delay with the development of new creatinine methods, especially enzymatic methods.

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

A meeting held in March 2007 (Washington DC, US) formulated a number of key recommendations and a manuscript has been submitted for publication. As well, the proceedings and discussion held at the recent (March 2008)

Bergmeyer Conference will inform on the work of the WG-SAU. A program of recommendations has been drawn up and protocols will be prepared to address each of the raised issues. These include the following: sample collection and handling requirements for minimizing pre-analytical variability; characterization of the measurand in the urine sample and the variability of the urine matrix; clarification of thresholds related to risk of kidney damage by age, gender, ethnicity and concomitant disease; development of a reference measurement procedure at the Mayo Clinic (US) and secondary reference materials from Japanese colleagues.

WG-Standardization of Pregnancy-Associated Plasma Protein A (WG-PAPPA)

A new reference preparation for PAPP-A is required as soon as possible since the current WHO material has had to be withdrawn because of contamination. Work on this project has been commenced with particular attention to evaluation of potential material for use as a primary standard.

WG-Growth Hormone (WG-GH)

The aim is to achieve worldwide reporting of GH results in mass units of GH IS 98/574, which is a recombinant DNA-derived preparation of higher purity than previous material (IS 80/505). Reporting GH values in mass units based on 98/574 will require confirming new decision limits. Publicity for these changes will utilize EQA schemes, a letter to journals, and presentations at relevant scientific meetings. Factors affecting method comparability including secondary calibrators, matrix, GH binding proteins, and the feasibility of antibody epitope mapping will be investigated.

WG-Standardisation of Insulin Assays (WG-SIA)

A joint WG with the ADA, EASD and the IFCC has been established. Data from the study comparing commercial assays have been collected and prepared for publication. The quality of performance of insulin assays has been assessed by comparing such results with those from an ID-LC/tandem MS assay calibrated with recombinant insulin. Materials have been assessed for their ability to improve standardization and a panel of single-donation sera proved to provide excellent harmonization and assessment of quality against a criterion of a total error of 32%, which was established by the ADA. A meeting with IVD industry was held in July 2008 where these results were presented. However, no definitive recommendations can be made until a complete reference measurement system is in place, including the availability of a pool of certified single-donation sera from a National Metrology Institute and reference laboratory services, which are listed by JCTLM.

WG-Standardisation of Troponin I (WG-TnI)

Fundamental studies on the interactions between cTnI antigen-antibodies are being undertaken by NIST with several well characterized monoclonal antibodies. The aim is to identify antibodies to the stable domain of the cTnI molecule, which would provide a suitable combination for an immunoassay that may be suitable as a candidate reference method. Studies are underway at the UK National Physical Laboratory to develop a sandwich-based non-competitive immunoassay for cTnI to be used to determine the sources of and to quantify the level of uncertainty through intercomparison studies.

SPECIALIZED CONFERENCES

Bergmeyer Conference

A conference on the topic of "Biomarkers in Kidney Disease" held in March 2008 was most successful. The Proceedings including the plenary discussions has been published as a Supplement of the Scand J Clin Lab Investigation. This collection of documents will provide a foundation for an IFCC Integrated Project on Chronic Kidney Disease.

IFCC Ortho Diagnostics Conference

Agreement has been reached with Ortho Diagnostics to sponsor a series of Specialized Conferences with the inaugural event being held in May 2008 in conjunction with the ACB Focus meeting. The topic was "Biochemical Markers in Clinical Cardiology: Perspectives from Present to Future". Publications of a number of manuscripts related to the conference presentations are planned in Clin Chem Lab Med with the Chair of the SD as Guest Editor.