

2006 Annual Report of the IFCC Scientific Division (SD)

Mauro Panteghini

Chair IFCC SD

During 2006, the following members served on the 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), and Matthias Mueller (Austria) (EB-Liaison). Three representatives of International Organizations are invited to attend the Scientific Division meetings as consultants: Jean-Claude Forest (JCTLM), Heinz Schimmel (IRMM) and David Bunk (NIST). Two meetings were held during the year 2006: April 28-29 (Damascus, Syria, in conjunction with the 11th AFCC Congress) and September 30-October 1 (Milan, Italy).

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 5 years and is well advanced in preparing a database of metrologically-sound, higher order methods and materials together with a list of reference laboratory service providers that relate to the In Vitro Diagnostic sector. 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). During its November 2006 meeting, WG1 considered that a further 13 reference materials and 16 reference methods fulfilled the criteria for listing on the database. A periodic review of the WG1 Quality Manual will be conducted during 2007. WG2 on Reference Laboratory Services has reviewed the Cycle 1 nominations against agreed criteria and final recommendations will be submitted to the JCTLM Secretariat by February 2007.

• Institute for Reference Material and Measurement (IRMM)

Close collaboration with IRMM continues with practical joint ventures. Progress continues to be made for projects including aspartate aminotransferase (AST), myoglobin, a new preparation of CRM470, and HbA0/HbA1c reference materials.

• Clinical and Laboratory Standards Institute (CLSI) (formerly NCCLS)

The good working relationship between CLSI and IFCC continues. Joint projects with CLSI are reviewed on a regular basis. The document on "Analysis of Body Fluids in Clinical Laboratory" (C49) has been published. The document "Implementation Guide of POCT1 for Healthcare Providers" (POCT2) has been completed and reviewed by SD.

Current ongoing joint CLSI/IFCC projects include the following: How to Define and Determine Reference Intervals in the Clinical Laboratory; Mass Spectrometry in the Clinical Laboratory; Expression of Uncertainty of Measurement in Clinical Laboratory Medicine; Validate and Implement Secondary Reference Materials; Verification of Comparability of Patient Results within one Healthcare System; Immunological Assays for Human Immunoglobulin E (IgE) Antibodies of Defined Allergen Specificities; Determining Clinical Utility of Genetic Tests; Implementation Guide of POCT1 for Manufacturers; Interference with Immunoassay Results by Heterophilic Antibodies and Other Binders.

• National Institute of Standards and Technology (NIST)

A large number of projects are underway at NIST, a number of which are of considerable interest to IFCC. Standard Reference Materials (SRM) recently released include; Calcium Carbonate, Bovine Serum Albumin, Electrolytes in Frozen Human Serum, Toxic Metals in Bovine Blood, Fat-Soluble Vitamins, Carotenoids, and Cholesterol in Human Serum, Inorganic Constituents in Animal Serum, Homocysteine and Folate in Frozen Human Serum.

A further group of SRMs to be released in the near future include: Cholesterol, Creatinine in Frozen Human Serum, Non-peptide Hormones in Frozen Human Serum, Lead in Bovine Blood, Vitamin B6 in Frozen Human Serum, Vitamin B12 in Frozen Human Serum, and Arsenic Species in Frozen Human Urine.

- **International Congress of Clinical Chemistry**

The SD will participate in the XXth International Congress of Clinical Chemistry and Laboratory Medicine to be held 28 September - 2 October 2008 in Fortaleza - Brasil on an official basis organising two symposia; "Achieving Standardization in Laboratory Medicine – A Hard but Feasible Task" and "Quality Assurance in Emerging Technologies".

- **Regional and other congresses**

The SD participated in the 11th Arab Federation of Clinical Biology Congress held 29 April – 2 May 2006 in Damascus - Syria, organising a symposium: "Application of ISO Standards in Laboratory Medicine". Symposia offered by the SD have been accepted for presentation at the Congress of the Tunisian Society of Clinical Biology (May 2007), 17th FESCC-IFCC European Congress of Clinical Chemistry and Laboratory Medicine (Euromedlab 2007, 2 – 7 June 2007, topics will be: "Standardization in Laboratory Medicine: the way forward" and "The Contribution of Laboratory Medicine in Kidney Disease"), 11th Asia Pacific Congress of Clinical Biochemistry (14 – 19 October 2007, the topic will be: "Traceability in Laboratory Medicine: What Does It Mean in Daily Practice?").

ACTIVITIES OF COMMITTEES AND WORKING GROUPS

The Committees (Cs), which are theme-oriented, carry out much of the scientific and professional activities of 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)**

This IFCC/IUPAC C is responsible for the maintenance of the generic database, which is published on the IFCC (SD/C-NPU page) and IUPAC (Division of Chemistry and Human Health) homepages. The database is undergoing a restructuring of its contents and a mapping to SNOMED CT system. The cost of hosting it on the IFCC server is being assessed in order that IFCC can finalize its decision. A paper on recommendations for name and units for HbA1c was prepared and has been approved by the National Societies. Revision of ENV 1614 was published in collaboration with CEN/TC 251.

The 3rd edition of VIM is under editorial revision by all participating organizations and is anticipated to be finalized in early 2007. Current projects underway include the following: Properties and units for function examinations; Properties and units for urinary calculi; Global use of the C-NPU concept system for properties in toxicology (finalized and under review for publication); Internationally agreed terminology for observations in scientific communication; Mapping of IFCC-IUPAC laboratory coding system to SNOMED CT; Securing and structural updating of information in the NPU coding system and its environment; Recent advances in Nomenclature, Properties and Units: strategy for promoting C-NPU achievements; Translation of C-NPU database elements and properties into French.

- **C-Molecular Diagnostics (C-MD)**

A document is in preparation describing the concept of IFCC Molecular Diagnostic Centres (MDC) of expertise which will include the requested characteristics and expected duties towards the international laboratory community. It is anticipated that a call for applications will be posted shortly on the IFCC web site as well as sent to the National Society Representatives.

The C has decided that, given the numerous other organizations active in the development and validation of nucleic acid reference materials, it will not pursue this activity for the moment. It is however expected that the IFCC MDC network will actively participate in this area either by initiating projects or by collaborating with existing or future initiatives from other entities. The IFCC web site will host the Consortium on Clinical Laboratory Genetics and Genomics Standards (CLGGS, formerly IMGCLS) web site that will be reviewed by C-MD. This should be initiated in January 2007. A task force will be created to propose Reference Methods in Molecular Diagnostics as a specific project.

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 new lot of CRM470 is the main priority of the C; characterization and certification of the new material will begin in 2007.

The possibility of using world-wide, common reference intervals for plasma proteins in multiple racial and ethnic groups has been explored, but is not possible at this time because of persisting concentration/calibration differences among the protein assays from the different manufacturers. The C has developed a simplified protocol for transferring values from reference material CRM470 to commercial protein assays. A preliminary version of it was made available on the IFCC web site. C-PP is now revising this document and the new version will be available in few months. A position paper on clinical indication for transthyretin will soon be published in Clin Chem Lab Med.

Other projects for 2007 are: (1) collaboration with CDT, cystatin C and urinary albumin WGs; (2) preparation of a document on the measurement of serum free light chains in the clinical context. The C-PP will also maintain its interest in proteomics.

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

A preliminary study to validate the cross-reactivity of commercial BNP and NT-proBNP assays with BNP, proBNP and NT-proBNP antigens has been completed. The analysis of these data was considered most promising and it has been decided to conduct a formal, multi-centre study with the protocol developed from the preliminary study. Corporate members have committed their support for the study. A protocol for the standardization of cTnI assays including candidate secondary reference materials has been prepared. A table of properties of commercial cardiac troponin assays has been posted on the IFCC web site (SD/C-SMCD page). It is aimed to continue to build the database with the inclusion of package insert and literature-based information. The C 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 continuing to work on the reference method for the certification of the selected material (IRMM/IFCC 458) as well as to further characterise this material.

- **C-Reference Systems for Enzymes (C-RSE)**

Work on standardisation of the Amylase determination was completed with the publication of the reference method. A feasibility study for a proposed reference procedure for alkaline phosphatase (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 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)**

A recommendation on accuracy and precision of POCT relative to central laboratory testing performance has been submitted to the SD while work is continuing on the document "Recommendation for Blood Glucose POCT Quality Assessment in Clinical Setting". New projects initiated during 2006 included developing guidelines on the pre-analytical processes for POCT; establishment of a database on potential interferents for POCT, and preparation of a curriculum for training in POCT to be implemented in collaboration with EMD and AACC POCT Division.

- **C-Traceability in Laboratory Medicine (C-TLM)**

The main reference of C-TLM is to support reference laboratories in the context of complete reference systems (accepted reference measurement procedures of higher order, reference materials, and reference laboratories), by establishing an External Quality Assessment Schemes (EQAS) for reference laboratories in order to monitor their competence.

A procedure manual for conducting EQAS has been developed and posted on the IFCC website home page, under the DGKL logo. This website enables registration for newly participating laboratories, orders for participation in forthcoming EQAS, entering of results from laboratories, inspection of recent EQAS results and provides information on forthcoming EQAS.

A Model for the Description of Acceptance Performance Criteria in the IFCC EQAS has been proposed for discussion.

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

The activity of the C has developed in two directions: 1. theoretical, through the 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"; 2. practical, preparation of a Standard Operating Procedure (SOP) for the definition of multicenter reference intervals and organization of a pilot experiment for the definition of reference intervals of AST, ALT and γ GT. The document has been prepared and approved by SD. The SOP is based on the use of carefully calibrated, traceable routine methods to obtain results from a relatively large number of subjects allowing the production of reference intervals that take into account not only age and gender but also race and other variables. These intervals will be applicable in every laboratory that uses similar methods and serves similar populations.

- **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 (O₂Hb, 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)**

Technical issues remain to be resolved with regard to the characterisation of SP3-08 Apo B reference material. Particularly, these issues relate to ISO standard 15194 requirements for uncertainty information.

The WG Chair is currently coordinating the NACB project for Guidelines on Cardiovascular Risk Markers.

- **WG-Standardization of Human Chorionic Gonadotrophin (WG-SHCG)**

The WG is continuing to gather evidence about the appropriateness (or otherwise) of commercially available hCG assays for use in oncology. Most of these methods are approved only for use in pregnancy, a regulatory issue of major concern to clinical laboratories using the tests to monitor cancer patients. Another issue is the frequency of false positive and false negative results in assays for hCG and their clinical implication. Recommendations about appropriate action to be taken by user laboratories – to both identify and to remedy such errors - are being developed. The availability of an accepted reference method for HCG would effectively address both the above issues. A study involving a WG member has shown mass spectrometric fingerprinting to be highly useful for the characterization of glycosylation patterns of different hCG preparations, including the WHO Reference Reagents prepared by the WG. This work represents an important step towards establishing biophysical reference method for hCG. The WG is considering how best to take this forward, building on previous work both of the IFCC WG and of the hCG Antibody Workshop held under the auspices of the International Society for Oncodevelopmental Medicine (ISOBM). It will almost certainly be necessary to recruit new members of the WG with additional expertise if a reference method for hCG is to be developed. A manuscript on the implications for between-method comparability with the use of the six International Reference Reagents previously prepared by the WG will be ready for submission early in 2007.

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

Work is focussed on standardization of the total and free thyroxine (T₄) assays. A manuscript has been prepared as an IFCC position paper on the definition of the free T₄ measurand and submitted for publication. Considerable progress has been made with the development of a sensitive equilibrium dialysis-ID-LC/tandem MS assay as a higher order measurement procedure for free T₄. A second candidate reference laboratory for free T₄ measurement has been identified in Japan, in addition to the first one located in Belgium. Discussion is underway with the American Thyroid Association and the American Association of Clinical Endocrinologists on the standardization work. It is hoped that these discussions will be expanded to other countries and relevant organizations. The aim is to establish a consensus forum of clinical, laboratory and industry representatives to plan and coordinate the standardization process.

- **WG-Standardization of HbA_{1c} (WG-HbA_{1c})**

The network of HbA_{1c} reference laboratories has published a number of manuscripts on rules for value assignment to secondary reference materials used by manufacturers for standardization of routine HbA_{1c} assays. Discussions on the clinical implementation of HbA_{1c} standardization between the WG and representatives of the professional and clinical organisations including IDF, ADA and EASD have continued. Preliminary data generated by these organisations on the relationship between measured HbA_{1c} and calculated Average Blood Glucose has been presented during the IDF meeting held in Cape Town - South Africa, in December 2006. The WG is preparing a paper summarizing its position on the global glycohemoglobin standardization. The inaugural Chair of the WG (Dr Kor Miedema) has stepped down and a new Chair has been elected.

- **WG-Standardization of Hemoglobin A₂ (WG-HbA₂)**

Development of the reference method in two laboratories has progressed significantly with all technical issues being resolved. A manuscript describing the candidate reference method and the SOP is currently being prepared. A manuscript was accepted for publication describing the pre-analytical variability of HbA₂ measurement. Expressions of interest have been received from almost all the relevant manufacturers and discussions are underway with IRMM regarding the protocol for preparation of reference materials.

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

A manuscript defining the measurand for CDT as disialotransferrin has been accepted for publication. A candidate reference material (serum matrix spiked with known amounts of purified human disialotransferrin) is being evaluated. Future work will focus on development of primary reference method, using mass spectrometry. Lastly, consideration is being given to assembling a network of CDT reference laboratories.

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

A candidate secondary reference material is in preparation. Recombinant human cystatin C is available of appropriate quality suitable for spiking this material. The pilot preparation is currently being tested for stability, homogeneity between ampoules and other relevant properties. This project is carried out in collaboration with IRMM.

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

The WG current projects are: 1. In cooperation with the U.S. 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. 3. Prepare an IFCC recommendation for the use of specific assays for creatinine measurement. 4. In cooperation with C-TLM, establish an IFCC reference laboratory network for creatinine.

The final NKDEP recommendations were posted on the NKDEP web site and can also be accessed from the IFCC web site home page.

The WG is preparing a study designed to evaluate specificity among commercially available creatinine methods.

- **WG-Standardisation of Albumin Assay in Urine (WG-SMA)**

The initial aim of the WG was first to proceed with harmonization rather than standardization of the albumin measurements in urine and a joint JSCC-IFCC WG was proposed. The JSCC had been investigating the preparation of human serum albumin for over five years and this project was now incorporated into the National Standardization Scheme, sponsored by the Japanese Ministry of Industry (National Metrology Institute) and JCCLS, and supported by the Ministry of Education. This proposal for collaboration between the JSCC and the WG has not proceeded further at this stage although future collaboration will be considered. Recently the NKDEP Laboratory WG indicated an interest to address urine albumin standardization including standardization of the measurement of the albumin:creatinine ratio in urine. Representatives of the WG are participating in planning a meeting to be held in March 2007, with joint chairmanship from IFCC SD and the US NKDEP. The WG also proposes to prepare an IFCC position paper on urine albumin measurements.

- **WG-Pregnancy-Associated Plasma Protein A (WG-PAPPA)**

The current Chair has resigned and a new Chair will be appointed in 2007. There is the possibility that essential materials for standardization, such as recombinant PAPP-A, will be available.

- **WG-Growth Hormone (WG-GH)**

Membership of the WG has been assembled and a consensus statement was supported advocating an informal International Collaboration of parties interested in GH standardisation and adoption of a single calibrant with results expressed in mass units. This was published in the European Journal of Endocrinology and also published in Clinical Endocrinology. Close collaboration with national and international EQAS will also be undertaken. It is planned to explore the possibility of undertaking an antibody-mapping project for GH similar to that previously undertaken for hCG.

- **Project Proposals**

Two project proposals have been received and dealt with during 2006. One has been accepted and a joint

IFCC/ADA WG on Standardisation of Insulin Assays (WG-SIA) has been created, with the IFCC nominating two representatives.

• Publications

C-NPU

1. Fuentes-Arderiu X. Description of examinations and their results and the standard ISO 15189. *Clin Chem Lab Med* 2006;44:1164-7.
2. Fuentes-Arderiu X. Vocabulary of terms in protometry. *Accred Qual Assur* 2006;11:640-3.

C-PP

1. Johnson AM, Merlini GP, Sheldon J, Ichihara K. Clinical indications for plasma protein assays: transthyretin (prealbumin) in inflammation and malnutrition. *Clin Chem Lab Med* 2007;45:419-26.

C-SMCD

1. Apple FS, Jesse RL, Newby LK, Wu AHB, Christenson RH. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines. Analytical issues for biochemical markers of acute coronary syndromes. *Clin Chem* 2007;53:547-51.

C-RSE

1. Schumann G, Aoki R, Ferrero A, et al. IFCC primary reference procedures for the measurement of catalytic activity concentrations of enzymes at 37 °C, Part 8. Reference procedure for the measurement of catalytic concentration of α -amylase. *Clin Chem Lab Med* 2006;44:1146-55.

C-POCT

1. D'Orazio P, Burnett RW, Fogh-Andersen N, et al. Approved IFCC recommendation on reporting results for blood glucose. *Clin Chem Lab Med* 2006;44:1486-590.

C-RIDL

1. Ceriotti F, Schumann G, Panteghini M. Redefining reference limits needs more attention to the analytical aspects. *Liver Int* 2006;26:1155-6.

WG-SEB

1. Ben Rayana MC, Burnett RW, Covington AK, et al. Recommendation for measuring and reporting chloride by ISEs in undiluted serum, plasma or blood. *Clin Chem Lab Med* 2006;44:346-52.

WG-SHCG

1. Sturgeon CM, Ellis AR. Standardization of FSH, LH and hCG – Current position and future prospects. *Mol Cell Endocrinol* 2007;260-262:301-9.

WG-HbA1c

1. Konnert A, Berding C, Arends S, et al. Statistical rules for laboratory networks. *Journal of Testing and Evaluation* 2006;34:1-7.
2. Konnert A, Arends S, Schubert S, et al. Uncertainty calculation for calibrators of the IFCC HbA1c standardisation network. *Accred Qual Assur* 2006;11:316-28.

WG-STFT

1. Van Uytanghe K, Stöckl D, Ross HA, Thienpont LM. Use of frozen sera for FT4 standardization: Investigation by equilibrium dialysis combined with isotope dilution-mass spectrometry and immunoassay. *Clin Chem* 2006;52:1817-21.

WG- HbA2

1. Paleari R, Giambona A, Cannata M, et al. External Quality Assessment of hemoglobin A2 measurement: data from an Italian pilot study with fresh whole blood samples and commercial HPLC systems. *Clin Chem Lab Med* 2007;45:88-92.

WG-CDT

1. Jeppsson J-O, Arndt T, Schellenberger F, et al. Towards standardization of carbohydrate-deficient transferrin (CDT) measurements: I. Analyte definition and proposal of a candidate reference method. *Clin Chem Lab Med* 2007;45:558-62.

WG-SCC

1. Grubb A, Nordin G. Notable steps in obtaining improved estimates for glomerular filtration rate. *Clin Chem* 2006;52:169-70.

WG-GFRA

1. Myers GL, Miller WG, Coresh J, et al. Recommendations for improving serum creatinine measurement: A report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem* 2006;52:5-18.
2. Panteghini M, Myers GL, Miller GW, Greenberg N. The importance of metrological traceability on the validity of creatinine measurement as an index of renal function. *Clin Chem Lab Med* 2006;44:1187-92.

WG-GH

1. Trainer PJ, Barth J, Sturgeon C, Wieringa G. Consensus statement on the standardisation of GH assays. *Eur J Endocrinol* 2006;155: 1-2.
2. Sheppard MC. Growth hormone assay standardization: an important clinical advance. *Clin Endocrinol* 2007;65:in press.