2007 Annual Report of the IFCC Scientific Division (SD)

Mauro Panteghini
Chair IFCC Scientific Division

During 2007, 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), George Brotea (USA) (Corporate Representative), and Mathias Mueller (Austria) (EB-Liaison). 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 2007: June 7-9 (Amsterdam, in conjunction with the 17th EuroMedlab Congress) and September 28-29 (Milan).

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 has now been working for six years and its main accomplishments are 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). Some 480 reference materials have been nominated with 211 approved and listed for approximately 100 measurands. Some 180 reference methods have been nominated and 123 have been accepted as fulfilling the criteria of the appropriate ISO standard. The Working Group 2 on Reference Measurement Services has reviewed some 200 nominations from laboratories of National Institutes of Metrology, manufacturers, clinical service providers and academic centres of which 99 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 Diagnostic (IVD) industry.

Institute for Reference Material and Measurement (IRMM)

Close collaboration with IRMM continues through a number of joint ventures involving SD Committees and Working Groups. Progress continues to be made for projects including 2nd ERM-DA470 for plasma proteins, aspartate aminotransferase (AST), HbA2, and myoglobin reference materials. Reference materials for HbA0 and HbA1c have been released.

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

The good working relationship between CLSI and IFCC continues with more than 11 joint projects underway during 2007. Three were completed and 8 are currently in progress. Documents on "Mass Spectrometry in the Clinical Laboratory" (C50), "Verification of Comparability of Patient Results within one Healthcare System (C54)", and "Implementation Guide of POCT1 for Healthcare Providers (POCT2)" have been published.

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) recently released include cholesterol, sodium chloride, potassium chloride and electrolytes in frozen serum (all re-released); new reference materials include creatinine in serum and lead in caprine blood. A further group of SRMs to be released in the near future 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, and reference materials for clinical proteomics.

INTERNATIONAL CONGRESS OF CLINICAL CHEMISTRY AND OTHER CONGRESSES

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, organising two symposia entitled "Achieving Standardization in Laboratory Medicine - A Hard but Feasible Task" and "Quality Assurance in Emerging Technologies".

The SD participated in the 17th EuroMedlab held 2nd to 7th June 2007 in Amsterdam, The Netherlands, organis-

ing two symposia on "Standardization in Laboratory Medicine: the Way Forward" and "The Contribution of Laboratory Medicine in Kidney Disease". At the 11th Asia Pacific Congress of Clinical Biochemistry (14 - 19 October 2007) SD presented a symposium titled: "Traceability in Laboratory Medicine: What Does it mean in Daily Practice?".

Symposia and presentations offered by the SD have been accepted for presentation at the Congress of the Egyptian Society for Clinical Chemistry (January, 2008) and the 31st Nordic Society of Clinical Chemistry Scientific Meeting in Helsinki, FI (June, 2008).

ACTIVITIES OF COMMITTEES AND WORKING GROUPS

The Committees (Cs), which are theme-oriented, carry out many 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)

The C-NPU generic database is published on the net 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. The database is published on the IFCC homepage (SD) and IUPAC (Division of Chemistry and Human Health) homepage with a link to both servers. The database is undergoing a restructuring of its contents and a mapping to SNOMED CT system. An initial meeting with International Health Terminology Standards Development Organisation (IHTSDO) representatives, which manages SNOMED CT, was held to discuss the links between NPU terminology and SNOMED CT. All stakeholders have agreed to progress with this important project. Planning is also underway to transfer the hosting of the NPU generic database to the IFCC web site.

Projects completed during 2007 include the following: 1. The recommendation for the term and measurement unit for HbA1c was published in collaboration with the WG-HbA1c. 2. Comments on the penultimate version of VIM3 submitted and the latest version was reviewed, proof read and published on the ISO website. 3. A symposium on Nomenclature, Properties and Units in Clinical Chemistry was organized during IUPAC Worldwide Congress in Turin, August 2007. Ongoing projects include: 1. Properties and units for function examinations, 2. Properties and units for urinary calculi, 3. Internationally agreed terminology for observations in scientific communication, 4. Mapping of IFCC-IUPAC laboratory coding system to SNOMED CT, 5. Securing and structural updating of information in the NPU coding system and its environment, 6. Recent advances in Nomenclature, Properties and Units: strategy for promoting C-NPU achievements, 7. Translation of C-NPU database elements and properties into French to be accessible on the Société Française de Biologie Clinique (SFBC) website early 2008.

C-Molecular Diagnostics (C-MD)

Nominations for laboratories to be recognized as IFCC Expert Laboratories in Molecular Diagnostics have been received; however, the opportunity for further nominations remains open through the IFCC web site. It is expected that the IFCC C-MD network will initiate projects or collaborate with existing or future initiatives from other organisations interested in improving the standardization and traceability of molecular diagnostic assays. The IFCC web site hosts the Consortium on Clinical Laboratory Genetics and Genomics Standards (CLGGS, formerly IMGCLS) web site, which has been reviewed by C-MD. The C-MD is currently preparing a document on Reference Methods in Molecular Diagnostics as well as a position paper on Nucleic Acid Reference Materials.

C-Plasma Proteins (C-PP)

The preparation of the 2nd ERM-DA470 (formerly 2nd Preparation CRM470) reference material for plasma proteins in collaboration with IRMM has progressed well with certification currently underway. Stability and commutability studies have been conducted with excellent results. Material release is planned for June 2008. A simplified protocol for transferring values from ERM-DA470 reference material to commercial protein assays is being prepared for publication, although a preliminary version has been made available on the IFCC web site during 2007. Other projects for 2008 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 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 B-type natriuretic peptide assays with BNP, proBNP and NT-proBNP antigens has been completed and the results from the study accepted for publication in Clin Chem. 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. The results will be discussed at the next C-SMCD meeting. 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-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 continuing to work on the reference method for the certification of this selected material 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 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)

The document "Recommendation for Blood Glucose POCT Quality Assessment in Clinical Setting" is being revised. Members of the C-POCT serve on the CLSI Area Committee for POCT and the subcommittee for several projects. Other initiatives in 2007 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, 2. Database of potential interferents in POCT, 3. Curriculum/Training of POCT staff.

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 EQAS 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 forthcoming 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 EQAS 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 and will be released as a "proposal" (C28-P3). 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 a more detailed paragraph 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 accepted for publication in Clin Chem. Work to derive AST, alanine aminotransferase and γ-glutamyltranspeptidase reference intervals has recruited four centres. One has already completed the collection of samples from reference subjects. 400 samples were obtained from the biobank of the NORIP project (NOBIDA) and reanalyzed with standardized methods. The results were elaborated according to the exclusion criteria defined in the protocol. The resulting data are now under evaluation and will be compared with those deriving from the experimental work.

Working Groups

WG-Selective Electrodes and Biosensors (WG-SEB)

Current projects include preparation of recommendations on pH measurement in blood (an update), recommendation on 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 recommendations 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 production and characterisation of SP3-08 apolipoprotein B reference material. Particularly, these issues relate to ISO standard 15194 requirements for uncertainty infor-

mation. The WG-A Chair is currently coordinating the National Academy of Clinical Biochemistry (NACB) project for "Guidelines on emerging cardiovascular risk markers".

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

The SD and the IFCC Executive Board have approved inclusion of WHO Reference Reagent (RR) for intact hCG (IRR 99/688), originally prepared by the WG-SHCG, 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. Several recombinant hCG preparations will also be included as candidates in the Collaborative Study. These activities, together with the 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, which is already available. 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 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-SHCG is also addressing the frequency of false positive and false negative results in assays for hCG and their clinical implications.

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

Following the publication of manuscripts defining the free T4 measurand and a candidate reference measurement system for free T4, a second laboratory has been recruited to perform a sensitive equilibrium dialysis-isotope dilution (ID)-liquid chromatography/tandem mass spectrometry (MS) assay as a higher order measurement procedure for free T4. An intercomparison study is being organised between laboratories utilising an agreed standard operating protocol. A pilot study involving IVD industry members and routine MS laboratories is under consideration. Discussion continues with representatives of the American and European Thyroid Associations to identify the clinical needs of 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 A1c (WG-HbA1c)

A meeting between the IFCC, American Diabetes Association (ADA), European Association for Study on Diabetes (EASD), and International Diabetes Federation unanimously accepted the IFCC reference system as the only true anchor for standardisation of HbA1c assays. It was also agreed that HbA1c should be reported in IFCC units (mmol/mol) and derived National Glycohemoglobin Standardization Program (NGSP) units (%) and, depending on the outcome of the ongoing study, it was recommended that an estimated average glucose (eAG) be reported as an interpretation. A meeting with HbA1c manufacturers was held with good representation from the companies and there was a range of opinions expressed over implementation of the traceability to the IFCC reference system. A meeting was held between the JCTLM and HbA1c network representatives to discuss network accreditation. This was a very positive meeting with a number of proposed options to be taken to the JCTLM Executive Committee. There was general agreement of a definite advantage to form a link with the JCTLM. The results of the most recent intercomparison studies demonstrated that all overall performance of laboratory network was satisfactory. A number of important manuscripts were prepared and submitted for publication including assessment and verification of the master equations over a six year period.

WG-Standardization of Hemoglobin A2 (WG-HbA2)

The standard operating procedure for a candidate reference measurement procedure is in the final stages of preparation. A second intercomparison among the two laboratories utilizing the MS method has been performed and the data are being analyzed. Two further laboratories have been recruited to the HbA2 network. The IRMM took the formal decision to produce the secondary reference materials in the lyophilized form. The production plan commenced in September 2007 and a first pilot lyophilization batch is planned in January 2008. The raw material (human stabilized hemolysate at physiological HbA2 concentration) was sent to the IRMM in December 2007.

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

Pools of patient sera and a CDT reference material, containing authentic human serum samples spiked with isolated disialotransferrin, have been tested by different CDT methods at six laboratories. Comparison of results revealed significant variation between laboratories and/or methods; however, the concordance between the three laboratories that were using the HPLC candidate reference method was as an encouraging initial outcome. Five laboratories are expected to perform the HPLC candidate reference method in 2008. At the end of 2007, a CDT candidate reference material was distributed to each of these laboratories for another comparison study. It is expected that these laboratories will become the foundation members of an IFCC network of reference laboratories for CDT. A study of the interference of transferrin genotypes and abnormal transferrin glycoform patterns on different CDT meth-

ods has been initiated. A project has been initiated, in collaboration with a MS laboratory specializing in protein structure, to define the target epitope of disialotransferrin. At a later stage it may also be possible to develop a primary MS reference method for disialotransferrin. Possible certification of the new 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 reference materials across methods, including HPLC, capillary electrophoresis, and immunoassays, will be assessed.

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

During 2007 the secondary reference material was prepared from a stabilized serum pool from blood donors with purified recombinant human cystatin C added. It has been aliquoted and lyophilized. The ampoules are now stored at the IRMM and stability studies have been commenced. The techniques and sites for the final value assignment of the secondary reference preparation have been discussed and a protocol for the value assignment will be finalized by February 2008.

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

The WG-GFRA is preparing a study protocol to evaluate specificity among currently available serum creatinine methods. The study will examine serum creatinine 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 at least four manufacturer assays including alkaline picrate and enzymatic methods. The WG-GFRA is monitoring the performance of eGFR reporting both directly through specific studies as well as utilising the EQA survey data sets. Both sources of 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)

The National Kidney Disease Education Program (NKDEP) Laboratory Working Group in conjunction with the IFCC have agreed to address urine albumin standardization including standardization of the measurement of the albumin:creatinine ratio in urine. Two meetings were held during 2007 and projects are under consideration.

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

A new Chair has been appointed and a new project proposal was received. Key personnel have been identified who will prepare a detailed plan to address the following issues: 1) Establish well characterized reference preparations of PAPP-A representing the different forms of the analyte in blood, 2) Characterize the immunoassays and the antibodies used therein for their reactivity with these different forms of the analyte, 3) Establish a reference preparation that represents the target as it appears in biological fluids.

WG-Growth Hormone (WG-GH)

General agreement has been reached about the need for standardisation and the adoption of a common calibrant. It was agreed to initiate multicentre studies to investigate the impact of re-standardization on GH cutoff values for diagnostic assays.

WG-Standardisation of Insulin Assays (WG-SIA)

A joint WG with the ADA, EASD has been established. A candidate reference method is being developed. Data from the study comparing commercial assays to this method have been collected and are currently being analysed before preparation for publication.

Project Proposals

One new WG proposal was approved by the SD related to "Development of a Candidate Secondary Reference Immunoassay Measurement Procedure for Cardiac Troponin I" (WG-TNI).

PUBLICATIONS

SD Executive

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C-NPU, in collaboration with IUPAC

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C-PP

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C-SMCD, in collaboration with AACC

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2. NACB Writing Group Members, Apple FS, Jesse RL, Newby LK, et al. 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. Circulation 2007;115:e352-5.
3. Apple FS, Wu AHB, Jaffe AS, et al. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine practice guidelines: Analytical issues for biomarkers of heart failure. Circulation 2007;116:e95-8.

C-POCT

1. Ben Rayana MC, Burnett RW, Covington AK, et al. IFCC Guideline for sampling, measuring and reporting ionized magnesium in plasma", Clin Chem Lab Med 2008;46:21-6.

C-RIDL

1. Ceriotti F. Prerequisites for use of common reference intervals. Clin Biochem Rev 2007;28:115-21.
2. Ceriotti F, Boyd JC, Klein G, et al. Reference intervals for serum creatinine concentrations: assessment of available data for global application. Clin Chem 2008;54:doi:10.1373/clinchem.2007.099648.

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. Mosca A, Goodall I, Hoshino T, et al. Global standardization of glycated haemoglobin measurement: the position of the IFCC Working Group. Clin Chem Lab Med 2007;45:1077-80.
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WG-STFT

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WG-GH

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