SCIENTIFIC DIVISION

58th MEETING
Taipei, Taiwan (November 25 and 26, 2016)

MINUTES *(FINAL)*

Members:	Abbr.	Term and Time of Office
Ian YOUNG (UK) (Chair)	IY	2nd 2014 01 - 2016 12
Philippe GILLERY (FR) (Vice-Chair)	PG	2nd 2014 01 - 2016 12
Joseph PASSARELLI (US) (Secretary)	JP	1st 2015 01 - 2017 12
Christa COBBAERT (NL)	CC	2nd 2015 01 - 2017 12
Giampaolo MERLINI (IT)	GMl	2nd 2014 01 - 2016 12
Tsutomu NOBORI (JP)	TN	1st 2015 01 - 2017 12
James PIERSON-PERRY (US) (Corporate Rep.)	JPP	1st 2015 01 - 2017 12
David BUNK (NIST Representative)	DB	Consultant
Heinz SCHIMMEL (IRMM Representative)	HS	Consultant
Gary MYERS (US) (Chair JCTLM)	GLM	Consultant
Chris BURNS (UK) (NIBSC Representative)	CB	Consultant

EXECUTIVE SUMMARY - SCIENTIFIC DIVISION 58th MEETING, Taipei, Taiwan, November 25 – 26, 2016.

Present: Ian Young (Chair), Philippe Gillery (Vice-Chair), Joe Passarelli (Secretary), Christa Cobbaert, , Tsutomu Nobori, Jim Pierson-Perry (Corporate Representative), and Heinz Schimmel (IRMM Representative) were in attendance. Apologies received from Giampaolo Merlini, Gary Myers (SD Consultant/ChairJCTLM) , David Bunk (NIST Representative), and Chris Burns (NIBSC Representative).

5.4 EUROPEAN FEDERATION of CLINICAL CHEMISTRY and LABORATORY MEDICINE (EFLM):

The EFLM Science Committee and SD leadership once again agreed there should be close liaison and communication between the two groups. Professor Eric Kilpatrick is the EFLM SC chair. The Science Committee is responsible for scientific matters within EFLM and projects which further the scientific development of EFLM. Activities of the Committee particularly focus on promotion of research that translates the scientific results of clinical chemistry and laboratory medicine to clinical applications and improves patient outcomes through the appropriate use and interpretation of laboratory data in clinical practice. Within the EFLM SC there are working groups on cardiac biomarkers, biological variation, test evaluation, personalized laboratory medicine and a number of others but the general consensus of the SD are that these activities do not overlap with the IFCC SD. The EFLM SC has more of a focus to promote and improve science and education within the field of clinical chemistry and laboratory medicine and to improve patient outcomes and the quality and safety of patient care through the highest standards of laboratory medicine. Results of

the Committee's work are actively disseminated at conferences and workshops, published in scientific journals (e.g. CCLM) and available on the EFLM web site.

6.1 WORLD HEALTH ORGANIZATION (WHO):

WHO meetings occur each Fall. PG attends and participates as the liaison from the SD. PG participated in the World Health Organization (WHO) Expert Committee on Biological Standardization (ECBS) meeting as IFCC-SD representative in Geneva (CH) from October 16th to 18th, 2016. There were relatively few topics relevant to the SD. The SD decided that there were no new projects or collaborations to consider.

6.2 CLSI:

The complete list of cooperative IFCC/CLSI joint projects is available on the IFCC website. The link to these projects is under CPD: http://www.ifcc.org/ifcc-communications-publications-division-(cpd)/ifcc-publications/clsi-ifcc-joint-projects//

6.22.1 JCTLM: The National Institute of Metrology, China and the BIPM organized and convened a workshop on 'Protein and Peptide Therapeutics and Diagnostics: Research and Quality Assurance', that was held on 1-4 June 2016, in Chengdu China under the auspices of the JCTLM. More than 700 scientists attended the workshop. A meeting of the JCTLM Executive Committee was held 4 June 2016 in Chengdu following the Protein and Peptide Therapeutics and Diagnostics: Research and Quality Assurance Workshop. The revised text of the Declaration of Cooperation (DoC) between the BIPM, IFCC and ILAC was signed in April 2016 by the three Sponsoring Organizations, and is published on the JCTLM website. The JCTLM Executive Committee is investigating establishing liaison with other international organizations in different laboratory medicine disciplines as potential future members of the JCTLM Executive Committee. As a first step JCTLM has reached out to the International Council for Standardization in Hematology (ICSH). The current status of the database as of June 2016 was as follows: - 298 certified reference materials (CRMs) amongst which 33 are in List II (i.e. Reference Materials value assigned using an internationally agreed protocol), and 3 are in List III (i.e. Reference Materials for nominal properties), - 180 reference measurement methods covering 80 analytes, and - 146 reference measurement services covering 39 analytes. These services were delivered by 15 reference laboratories accredited for compliance against ISO 15195 and IEC/ISO 17025 as Calibration laboratories, and by two National Metrology Institutes (NMIs). Dr. Graham Jones and Mr. Craig Jackson published the following review on JCTLM. Jones GRD and Jackson C. The Joint Committee for Traceability in Laboratory Medicine (JCTLM) – its history and operation. Clinica Chimica Acta 2016;453:86-94.

6.22.2 JCGM:

Report from Working Group 1 (GUM):

WG1 held a meeting at the Bureau of International Weights and Measures (BIPM), Sèvres, Monday 30th May–3rd June 2016. Since the previous meeting, the BIPM Director wrote to the NMIs and MOs that responded to the request for feedback on the draft revision of the GUM (JCGM 100) advising that each of the thousand plus comments they had submitted will receive a response from the working group. Until this task has been completed, further development of options for overhauling the style and technical content of the revised GUM will be deferred.

JCGM 103: Modelling measurement data:

Much of the meeting was devoted to discussion and acceptance or modification of the proposed changes. What is expected to be the final committee draft will be circulated to the working group prior to the next meeting, followed by stakeholder circulation and feedback by end of 2016. Next meeting is planned for 29th Nov-2nd Dec 2016.

Report from Working Group 2 (VIM)

WG2 has focused on developing a Draft Outline of the fourth edition of the VIM (VIM4) with completion of the Draft Outline expected by the end of 2016. The scope of the VIM4 is being expanded from the VIM3 to encompass nominal properties in a significantly more comprehensive manner. At the moment, 58 new entries for inclusion into the VIM4, which are related to nominal properties, are being evaluated by WG2. A key principle for the VIM4 is to try to incorporate simplified language, similar to that used in the 'VIM Definitions with Informative Annotations'. WG2 is considering changing the name of the VIM4, to the 'International Vocabulary of Metrology 4th Edition (VIM)', from the VIM3 'International vocabulary of metrology – Basic and general concepts and associated terms (VIM) 3rd edition'. The motivation was to remove 'concepts' from the title, which was a cause of some confusion. A draft document will be available by the end of 2018 to circulate to the member organizations for comment.

6.22.3 BIPM Consultative Committees

Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM):
The report of the 22nd meeting (21-22 April 2016) to the International Committee for Weights and Measures was received and briefly discussed by the SD. There were few topics of relevance in the area of clinical chemistry.
SD received no correspondence from CCU.

6.31 INSTITUTE FOR REFERENCE MATERIALS AND MEASUREMENTS (IRMM):

The actual name "IRMM" no longer exists and is now referred to as the Joint Research Center (JRC). Within the JRC there are five Directorates. Directorate F is focused on Reference Materials.
IRMM continues to collaborate with numerous SD Cs/WGs on a variety of projects.

6.33 NATIONAL INSTITUTE OF BIOLOGICAL STANDARDS AND CONTROL (NIBSC)

C. Burns provided an update via email correspondence:

C-peptide:
The C-peptide International Standard has been established and is now available from NIBSC. The report of the study should be on the WHO website.

Insulin:
The project is ongoing and in conjunction with the IFCC WG on insulin. Currently waiting for the value assignment results from two labs and will then analyze the new data. NIBSC will then proceed with the characterization of 10,000 ampoules of a candidate reference material.

AMH (Anti-Mullerian Hormone):
The WHO endorsed a project to develop an International Standard for MIS/AMH in 2014 and a quantity of recombinant, human MIS/AMH was donated for this purpose by Professor Patricia Donahoe (Director) and Dr David Pépin of the Pediatric Surgical Research Laboratories, Massachusetts General Hospital. In collaboration with immunoassay manufacturers and using commercially available manual assays in house, a small batch of trial ampoules containing a stable formulation of MIS/AMH was evaluated by seven immunoassay methods. The MIS/AMH in the trial ampoules was recognized by all immunoassays and in each case the response was parallel to method standards. In addition, work is underway at NIBSC to develop physical chemical methods which could support the value assignment in mass units of a future, recombinant MIS/AMH International Standard.

Prolactin:
A pituitary preparation, NISBC code 83/573, was evaluated by collaborative study and established as the 4th WHO IS for Prolactin, human at the 67th meeting of the WHO ECBS in October 2016. The product replaces the 3rd WHO IS for Prolactin, 84/500.

Future replacement of this standard is likely to require the use of recombinant prolactin due to the difficulty in obtaining a donation of pituitary-derived material.

Prostate Specific Antigen:

Development of a replacement for NIBSC 97/670 (PSA 09:10) is underway. Through collaboration with UK NEQAS, trial preparations of complexed and non-complexing PSA have been measured on multiple immunoassay platforms alongside the WHO International Standards, 96/670, in order to identify a formulation which closely replicates the current ratio and can therefore be introduced with minimal impact on patient measurements.

6.37 NATIONAL INSTITUTE FOR STANDARDS AND TECHNOLOGY (NIST):

NIST continues to collaborate with numerous SD Cs/WGs on a variety of projects.

8.2 MAIN ACTIVITIES OF COMMITTEES:

8.2.6 C-NPU:

Results of a survey on the use of the NPU terminology among IFCC Members:

- Indicated that there is limited expertise in laboratory terminology but acceptance that it is an important topic
- Showed support for promotional material to explain the importance of laboratory terminology in quality healthcare. Support was suggested as distance learning/webinars; articles in journals; symposia at national scientific meetings

To this end, the Wikipedia entry is a useful introduction: (https://en.wikipedia.org/wiki/NPU_terminology) as well as the NPU Website. The use of NPU terminology is actively being used or implemented throughout Scandinavia:

a) Norway
   - Good progress has been made with NPU but much remains to do in describing the value of terminology in laboratory medicine. Six staff members are working on the project. Support is being obtained from experts in Norway and from the Danish NRC.
   - A new financial system for reimbursement will be introduced in January 2017, which will be informed by NPU codes.

b) Sweden
   - All 25 Regions in Sweden have agreed formally to use NPU. Progress is being made on implementation. A subset of the NPU database had been translated into Swedish.

c) Denmark
   - The new e-Health records (1 patient = 1 record) will be going live for ~50% of the population of Denmark in the near future. NPU coding is integral to this program.

A new project proposal has been submitted: *Online Dynamic NPU Manual.*

8.2.11 C-MD:

The committee has been active in establishing a network in this area. Eleven laboratories were selected as IFCC Network laboratories. The C-MD included in the acceptance letter that the network laboratories needed to document their participation in EQA programs in order to maintain their status as a Network laboratory. Several candidate laboratories have been identified as expert laboratories. The strategy of C-MD is to develop a survey that will be submitted to all members (full and corresponding) and the network laboratories. Once data is collected, an overview of the survey results will be published. The C-MD expects that surveys will be a powerful tool to generate discussions on standardization and quality assurance in molecular diagnostics. A goal of the C-MD committee is to capture topics of interest for network and expert laboratories. The C-MD envisions that the use of the survey tool will help identify quality needs and other needs of the molecular diagnostic community.

8.2.21 C-RSE:
The Committee will officially close at the end of 2016. The SD sincerely thanks the chair and all members for their efforts. Activities will continue with the formation of a new Working Group with more limited scope. The name of this group will be: WG-PE (Pancreatic Enzymes), with a specific focus on the standardization of pancreatic amylase within the terms of reference. A potential chair has been identified and clearly defined terms of reference will be elaborated in the beginning of 2017.

8.2.23 C-TLM:
The C-TLM requested that the SD establish a new working group to address several issues and design a generally accepted reference measurement procedure for the measurement of total protein. This was accepted by both the EB and SD. However, instead of forming a new WG or to perform the activities under the umbrella of C-TLM, it was decided that it would be more effective to work on total protein standardization in Professor Gerhard Schumann's reference lab in Hannover. Since his term as a Member of C-TLM is over at the end of 2016, he will remain on as a Consultant to ensure continuity. The plan is to develop a CRM and to obtain JCTLM listing. Given his departure, a new member to the committee is needed and a call for nominees will go out from the IFCC office through the normal process.

8.2.24 C-RIDL:
The C-RIDL continues to work to establish regional reference intervals. The committee is intending to examine alternative approaches for the determination of RIs (conventional and "big data"). For this purpose, the datasets collected during the last few years will be used in combination with RIs determined in similar populations using very large anonymized datasets. A new study will be conducted to compare alternative approaches (conventional and big data) for the determination of reference intervals, especially in the pediatric age group. A website is planned for 2017 which will provide the reference intervals obtained from the global study for practice of Evidence Based Laboratory Medicine. It will allow interactive viewing of RIs for EBLM by specifying sources of variation (gender, age, country, BMI, ABO blood groups, level of alcohol drinking, smoking, and exercise) or by specifying any two laboratory tests for analysis of correlation.

8.2.25 C-STFT:
The phase 4 studies are complete and the results have been reviewed and evaluated by manufacturers and the committee. A publication will present the data of Phase IV for TSH in Q1/2017. Another publication will be filed for FT4 in Q1/2017. All data will be published without disclaimer. Currently a proof of concept is being conducted by IVD manufacturers to recalibrate their respective assays. This will also be used as a basis for further elaboration of the reference intervals by the IVD manufacturers. In addition, the committee is in contact with all involved stakeholders for benefit-risk analysis in preparation of the implementation of the standardized/harmonized assays.

8.2.26 C-HAT:
A new Committee on the harmonization of autoimmune tests (C-HAT) will be formed in the beginning of 2017. It will continue on the activities previously done within the WG-HAT with broader scope. Additional details with respect to terms of reference, etc. will be provided in the next update.

8.3 MAIN ACTIVITIES OF WORKING GROUPS:
8.3.35 WG-HbA2:
A joint committee with ICHS (The International Council for Standardization in Hematology) has been formed. A candidate reference measurement procedure has been implemented in two different reference laboratories of the WG, i.e. INSTAND e.V., Düsseldorf, DE and

Physikalisch-Technische Bundesanstalt (PTB), Braunschweig, DE. During 2016 the measurement conditions have been optimized and the experimental work for the validation of the candidate reference measurement procedure has been completed.
In addition, the WG is trying to develop commutable reference materials through IRMM. In the interim until these materials are available, a commutability study is now being perfomed by three laboratories to test materials already available through the NIBSC and WHO as well as other materials (i.e. BioRad Lyphochek, etc.) until the materials are available through the IRMM. A. Mosca will replace R. Paleari as chair.

8.3.36 WG-CDT:
The final manuscript describing validation of the cRMP according to ISO15193 and its use was approved by the IFCC-SD, board and national societies and now accepted and declared to be a RMP. The procedure was published in The Epub in ClinChimActa at the end of December 2016. A CDT-network of five laboratories is in place and annually, an intercomparison study will be organized in which both the network laboratories and the manufacturers will participate. The focus of the WG moving forward will be global implementation and to promote the knowledge of the IFCC RMP for CDT towards diagnostic firms and national societies involved in diagnosing and monitoring of alcoholism.

8.3.39 WG-SAU:
All activities of the WG-SAU are a joint effort with the NKDEP Laboratory Working Group. Several projects are ongoing for the standardization / harmonization among commercial immunoassays for UA. To facilitate standardization of routine methods, NIST SRM 3666 is currently being prepared based on the specifications developed by the WG-SAU and the LWG of the NKDEP. The next step is to perform a freeze-thaw study to assess the ability to use frozen patient samples for the commutability study for NIST SRM 3666. In addition to these studies, NIST and the Mayo Clinic continued to perform comparison studies for their respective IDMS candidate reference measurement procedures. A joint meeting of the WG-SAU and LWG of NKDEP will be held during the 2017 AACC annual meeting.

8.3.40 WG-PAPPA:
The group is essentially restarting activities again with a new chair - Saara Wittfooth (FI). The chair submitted a revised project plan including schedule and cost estimates. The WG-PAPPA previously used purified material to assess ability to standardize assays, but this did not work for all methods. The group will assess the potential of harmonization and the goal of making assay results more comparable. Therefore, the group name will be changed to Harmonization. Activities will restart in the Spring and a meeting planned for Athens in June 2017 in conjunction with EuroMedLab.

8.3.42 WG-SIA:
This is a joint project between ADA and IFCC. Establishment of a reference measurement procedure for serum insulin is on-going. Several labs are currently testing samples with the candidate reference method. At the same time the WHO is vetting a reference material via C. Burns at NIBSC. This material will be used as calibrator for the mass spec procedure to assign values. The plan is to use the mass spec method, reference material, samples or pools or some combination of these to bring the immunoassays closer together.
The next meeting is planned for in October in conjunction with the 2017 WorldLab in Durban.

8.3.43 WG-TNI:
Currently the WG is developing a CRM for Troponin I in serum (NIST SRM 2922).
The plan is to mix pools from a normal population and one from cardiac patients. The normal pool will be evaluated in an interference study prior to being used in the production

of SRM 2922. If okay, a limit of blank study will be performed with a few different methods being considered. Once complete, value assignment will be performed. Plans for this work were outlined and discussed with a focus on how best to ensure and validate measurement quality during the value-assignment process. It was suggested that participating manufacturers be queried about their measurement batch times for the anticipated sample analyses for both the value-assignment and commutability studies. Assay manufacturers present at the WG-TNI meetings expressed concerns that performing a re-calibration of their cTnI platforms in the middle of their lifespans would be a significant financial and bureaucratic burden.
The WG plans for a next face-to-face meeting in August 2017 in conjunction with the AACC in San Diego.

8.3.45 WG-HAT:
One of the main activities of the group is to produce well-characterised pure antibody preparations with known concentration and identity and use these to transfer values to a matrix preparation. To this end, ERM DA 476 for IgG anti MPO was released in April 2015 and this material is now available from the IRMM as a Certified Reference Material. Information is in preparation to guide companies on how to transfer values from ERM-DA476/IFCC to their local or kit calibrators and to demonstrate the value of a certified reference preparation. Education is a key activity of the WG, and to offer a consistent and aligned message about ERM-DA476/IFCC and to inform users of how it is best implemented. To this end, this WG will be converted to a Committee in collaboration with EULAR (European League Against Rheumatism). EULAR has access to clinicians and will provid valuable information for implementation.
Discussions with the FDA are also currently ongoing and have been informative and supportive of these activities.

8.3.46 WG-cMSP:
Different laboratories participating in the WG have different operating procedures to perform quantitative mass spectrometry analyses for peptides and proteins. The WG has an ongoing QA/QC program on hepcidin to exchange standards to be able to compare and adjust values obtained in the different laboratories. The WG is also collaborating with the LNE to evaluate the possibility to generate a CRM for hepcidin. Samples and purified materials have been sent to 5 labs (2 within the WG and 3 in France). A few of their procedures might be able to develop into reference method. However, realization in developing a reference method for hepcidin has proven difficult and remains uncertain. The SD decided that this WG will close at the end of 2016 and thank the chair and members for their service.

8.3.48 WG-PTH:
The WG-PTH continues to work on developing a reference system for PTH. Currently, activities are focused in three areas:

1. Assessment of commutability
2. Development of a reference measurement procedure: Several groups are involved including Mayo, CDC, and NIST.
3. To gain a better understanding of what is the actual measurand being measured as many manufacturers have gone to third generation assays. Manufacturers are highly supportive and engaged.

8.3.49 WG-CSF:
A large (5 liter) pool of CSF has been collected to be the basis for the reference material. Two commutability studies have been performed. The analysis showed high correlations between the SRM method and the immunoassays, and also very good commutability of the candidate CRM, but less commutability for spiked variants. For these reasons, it was

decided that the high-volume samples for the CRM will be pooled based on the original Aβ1-42 levels, so that three different CRMs will be produced with high, medium and low levels. Three reference materials have now been produced for Aβ42, with high, middle and low Aβ42 concentration. Homogeneity and stability have been verified, long-term stability (1 year) is good. Value assignment is on-going, with four LC-MS datasets received and being analyzed. The WG is also developing a SRM mass-spec method for Aβ 1-42 in CSF, to qualify as a reference measurement procedure (RMP). There are five laboratories that are working on this in a collaborative effort. Both the Roche/Gothenburg and the UPenn methods are now accepted and listed as a RMP by the Joint Committee for Traceability in Laboratory Medicine (JCTLM). There is also a growing use of Aβ40 which the WG is now considering.

8.3.50 WG–SBMA:
This is a joint activity with the International Osteoporosis Foundation. The National Bone Health Alliance (NBHA) also has a WG focused on bone marker standardization. All three organizations will be working collaboratively on this project.
A study is in progress to collect data on pre-analytical factors including serum or plasma, fasting or non-fasting and to investigate the relationship between the values obtained from Roche and IDS CTX assays as well as the relationship between the values obtained from the Roche, IDS and Orion Diagnostica PINP assays. This comparability study should be complete by December 2016. It is planned to discuss the results in March 2017 at the Osteoporosis Conference in Florence. It is hoped that the equations describing the relationships between the various CTX and PINP assays can be used to harmonize values in order to combine data from the various assays which have been generated from clinical trials. The relationships described by the new data from this comparability study will be assessed against the relationships obtained from these historic data.

8.3.51 WG-C:
The WG determined the intended audience for their work output was the following groups as beneficiaries of advancing understanding and assessment of commutability of reference materials: patients, clinical laboratory, IVD industry, reference material providers, and EQA organizations.
A draft recommendations document is approaching completion. The recommendations address qualification of measurement procedures, qualification of clinical samples, criteria for commutability based on medical requirements for using a laboratory test result, fraction of uncertainty that can be assigned based on the intended use of a reference material, two new statistical approaches for assessing commutability, and use of a correction for non-commutability to make non-commutable reference materials more useful for achieving agreement of results among different measurement procedures.
The plan is to submit a series of manuscripts to further describe how to define the criteria for commutability that is required for a given reference material, taking into account its intended use and the intended use of the measurand. Three manuscripts are nearing completion that will be submitted to Clinical Chemistry as a series for inclusion in the same issue.
The next meeting is planned for June in Athens in conjunction with 2017 EuroMedLab.

8.19 MEETINGS

8.19.59 59th SD Meeting – Athens, Greece, June 9 – 10, 2017
8.19.60 60th SD Meeting – Durban, South Africa, October 20 – 21, 2017
8.19.61 61st SD Meeting – tbd.
8.19.62 62nd SD Meeting – tbd.