

## SCIENTIFIC DIVISION

**56<sup>th</sup> MEETING**  
**Milan, Italy (2015 11 20-21)**

**MINUTES (FINAL Draft)**

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

### **EXECUTIVE SUMMARY - SCIENTIFIC DIVISION 56<sup>th</sup> MEETING, Milan, Italy, November 20-21, 2015.**

**Present:** Ian Young (Chair), Philippe Gillery (Vice-Chair), Joe Passarelli (Secretary), Christa Cobbaert, Heinz Schimmel (IRMM Representative), and Gary Myers (JCTLM Representative), Paola Bramati (IFCC Office), were in attendance. Apologies received from Giampaolo Merlini, Tsutomu Nobori, Jim Pierson-Perry (Corporate Representative) and David Bunk (NIST Representative).

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

The EFLM Scientific Committee and SD leadership once again agreed there should be close liaison and communication between the two groups. Elvar Theodorsson, Linköping University, Sweden, is the Chair of the EFLM Science Committee. IY indicated he has been in communication with Elvar and will continue to provide him with the minutes of SD meetings.

The current EFLM president finishes his term at the end of this year and Professor Sverre Sandberg will be the successor. The current EFLM SC chair is also finishing his term and a new chair will be appointed. Elvar Theodorsson outlined the following key areas of interest of the EFLM SC:

1. The Milan conference "Defining analytical performance goals, 15 years after the Stockholm Conference" last autumn has generated working groups within the EFLM, in particular one on biological variation.

2. A task and finish group on Total Error created after the Milan conference under the leadership of Wytze Oosterhuis is extremely active.
3. The working group on preanalytics under the leadership of Ana-Maria Simundic continues to be very active.
4. A task and finish group on the laboratory testing for dyslipidemias under the leadership of Michel Langlois and in collaboration with the European Atherosclerosis Society has been and is very active. Their consensus report was submitted for publication in November.

### **6.1 WORLD HEALTH ORGANIZATION (WHO):**

WHO meetings occur each fall. PG attends and participates as the liaison from the SD. The SD decided that there were no new projects or collaborations to propose in 2015. PG participated at a meeting with the Expert Committee on Biological Variation Standardization in October in Geneva. There were relatively few topics relevant to the SD.

### **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/](http://www.ifcc.org/ifcc-communications-publications-division-(cpd)/ifcc-publications/clsi-ifcc-joint-projects/)

#### **6.2.2.1 JCTLM:**

The JCTLM Executive is looking to increase the recognition and acknowledgement of the JCTLM and the database that it produces. To this end, a Stakeholders Meeting in early December has been organized. As part of this, the kickoff and full day meeting for a Working Group on Traceability: Education and Promotion will take place. The aim will be to produce and promote educational materials to demonstrate the value of traceability in laboratory medicine as a means to reduce between method variability in the interests of improved clinical outcomes and patient safety. Dr. Graham Beattall will serve as the new Working Group Chair. In December, JCTLM will also assess the Review Teams' recommendations regarding the reference materials, reference measurement procedures and reference measurement services submissions in 2015 for listing in the JCTLM database. Also, a stakeholders' member category has been formed to allow IVD companies to participate. In addition, there is a member category for "Signature Bodies" for professional organizations such as the AACC, etc.

#### **6.2.2.2 JCGM:**

A new version of GUM is in development that has more of a focus on users. Professor Graham White has been taking the lead on this. A key issue is to find the right balance between exactness and simplicity. The strategy selected by WG1 is to keep the GUM as simple as possible and refer to other JCGM documents for more complex cases. A first draft for the VIM4 (WG2) is in development and a review of the so-called "VIM3 Annotations" is in process. Thirty informative annotations have been developed to go beyond the formal Notes and provide more detailed description and definition of terms appearing in VIM 3. It is planned that these annotations will be published on a new BIPM website. Further annotations will be developed, all of which will be incorporated into VIM 4.

#### **6.2.2.3 BIPM Consultative Committees**

SD received no correspondence from CCQM or CCU.

### **6.31 INSTITUTE FOR REFERENCE MATERIALS AND MEASUREMENTS (IRMM):**

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 has agreed to join the SD as an Observer. Moving forward this might help strengthen and expand the collaboration with the WHO. The discussion on forming a WG to prepare new PSA reference material is still continuing. DB indicated that NIST may be interested in sending a representative to NIBSC meetings who could also attend on behalf of IFCC SD.

## **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:**

A new website for the international version of the NPU terminology – sponsored by IFCC is in development. The new website is being designed to publicize these activities and to provide a link to SNOMED – CT. Various models are being explored for the latter point. It is believed The Silver Book v.2 is now complete. Both an e-version and hard copy book will be created. Once the Silver Book goes online, the C-NPU will assume responsibility for updating when needed. IUPAC will not produce paper editions of the 'Color books' in the future.

### **8.2.11 C-MD:**

The International Network of IFCC Centres in Molecular Diagnostics has been renewed. With respect to the website, links to AIMS and Molecular Centers have been reviewed, added to, and harmonized. EQA and PT lists have also been added to the site. The committee has expanded into Latin / Central America with Mexico now included. A process has been developed for case studies illustrating key aspects in quality assurance for molecular testing and for developing checklists for technology transfer from development to clinical laboratory (draft outline available) with an emphasis on infectious diseases.

### **8.2.21 C-RSE:**

The two activities the C-RSE has in place are: 1) evaluation of the commutability of IRMM candidate CRMs for ALT, LDH, and CK and 2) refinement of the pancreatic lipase reference method. There has been some progress on pancreatic lipase standardization but it may be very difficult for IVD companies to maintain. There has been some discussion to refocus efforts on pancreatic amylase which may be more sustainable by reference labs and manufacturers. This will further be discussed and a decision will be taken by the SD at the next meeting in Madrid (March 2016).

### **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. Instead of forming a new WG however, the SD decided to organize these tasks within the C-TLM. The restandardization of Total Protein will become a focused activity within the Committee. They will report on these aspects within the reports of the Committee and it will have its own Terms of Reference. Professor Schumann will lead these activities as a member of C-TLM. The C-TLM also continues to provide an interface between IFCC and the JCTLM Working Groups.

### **8.2.24 C-RIDL:**

The C-RIDL continues to work to establish regional reference intervals. These regional reference intervals should be traceable to reference measurement procedures where possible. Considerable activity has occurred in the Middle East. Two papers have been submitted for publication. The first is focused primarily on the methodology used and the second more on the Reference Intervals themselves. Other manuscripts are likely to follow.

### **8.2.25 C-STFT:**

Major activities include the recalibration of FT4 and TSH assays after the Phase IV method comparison studies on clinically relevant samples and are intended as a technical standardization/harmonization process, by which FT4 assays will become traceable to the conventional reference measurement procedure. These studies will be performed on 120 healthy American volunteers and can be used as proof-of-concept for standardization of FT4 and harmonization of TSH by demonstrating that the traceable assays can use a

common reference interval. 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.

### **8.3 MAIN ACTIVITIES OF WORKING GROUPS:**

#### **8.3.35 WG-HbA<sub>2</sub>:**

The committee met in Paris in conjunction with 2015 EuroMedLab. The main activities of the WG have been concerned with the development of the reference measurement procedure. Preliminary experiments showed the method to be feasible and reproducible. The SD decided to allow for a 2 year extension of the WG with the goal to finalize the reference method. R. Paleari will remain as chair during this time. The International Council for Standardization in Hematology (ICSH) also has a program to standardize HbA<sub>2</sub>. A joint ICSH – IFCC group may be formed with the additional task to develop reference materials.

#### **8.3.36 WG-CDT:**

There are now 6 labs in the reference network (4 old and 2 new). The 2 new labs have demonstrated comparable results. A HPLC method has been developed and uncertainty and robustness are being assessed. Decision limits and clinical impact are also being assessed as a second step. The group plans to submit a paper on the method as well as a second paper on guidance on CDT in laboratory practice.

#### **8.3.39 WG-SAU:**

All activities of the WG-SAU are a joint effort with the NKDEP Laboratory Working Group. A meeting of the WG-SAU was held on 29 July, in conjunction with the 2015 AACC Annual Meeting. IVD manufacturers provided input on efforts to resolve concentration and dilution-dependent biases. Many of the comments reflected issues at the low end of the respective assay measuring intervals with potential mitigations from changes in assay calibration and traceability. Concerns were expressed about the potential regulatory impact of implementing such mitigations. Attendees discussed a proposed joint experiment to assess the effects of sample freeze-thaw. A protocol outline was agreed to by several IVD manufacturers. Dr. Miller proposed adoption of 2-400 mg/L as the desirable measuring interval for a urine albumin (UA) assay. This would cover two significant intervals for medical decisions (5-10 mg/L and 100-300 mg/L) in a single measurement procedure. Dr. John Lieske described the study in progress comparing UA reference methods developed by the Mayo Clinic (LC-IDMS) and by NIST (LC-MS/MS). Dr. Beasley-Green then gave an update on two standards: the primary reference material SRM 2925 (recombinant human albumin in an aqueous solution) and the secondary reference material SRM 3666 (albumin in pooled human urine).

#### **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 assays. 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.

#### **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. Progress has been slow to date and will be further discussed at the next SD meeting in March 2016.

#### **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 and focused 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 AACC also coordinated the collection of a very large number of samples at the annual meeting. These will be available in the very near future.

#### **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. A large group of well characterised clinical samples (Prof Xavier Bossuyt) will be analyzed with respect to ERM-DA476/IFCC. 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. Discussions with the FDA are currently ongoing and have been informative and supportive of these activities.

The WG has also drafted a Memorandum of Understanding for discussion with EULAR (European League Against Rheumatism). There is a proposal to form a collaboration.

#### **8.3.46 WG-cMSP:**

With respect to defining appropriate operating procedures from biological fluids, the different laboratories participating to the WG have different operating procedures to perform quantitative mass spectrometry analyses for peptides and proteins. This expertise is the basis for an article entitled "Mass spectrometry proteomics for the medical laboratory" that will be completed by the end of the year. In addition, the WG has an ongoing QA/QC program on hepcidin and plans to exchange standards to be able to compare and adjust values obtained in the different laboratories. The WG is working with the LNE to evaluate the possibility to generate a CRM for hepcidin. The WG has achieved a first Quality Assurance / Quality Control (QA/QC) Program to determine in the different participating laboratories the: Precision, Trueness, Uncertainty, LOD, LOQ, Linearity, Parallelism, Robustness and Contamination of the MS quantitative detection of hepcidin in human samples. The WG plans to use and expand these data to write next year an article entitled: "A practical guide to clinical mass spectrometry proteomics method validation".

#### **8.3.48 WG-PTH:**

The WG-PTH continues to work on developing a reference system for PTH.

#### **8.3.49 WG-CSFP:**

University of Gothenburg, Sweden collected a large (5 litre) pool of CSF to be the basis for the reference material. Results showed acceptable agreement between expected (calculated) and measured values, meaning that these samples will be suitable for the CRM. A first commutability study has been done, comparing the candidate CRM as well as spiked variants and pools containing detergents. The analyses show high correlations between the SRM method and the immunoassays, and also a very good commutability of the candidate CRM, but not for different variants of artificial CSF, or for samples containing

detergents. Based on these results, a second commutability study has been performed, in which a common calibrator (A $\beta$ 1-42 peptide) was used, and the candidate CRM included (neat and spiked at 3 levels). The analyses showed high correlations between the SRM method and the immunoassays, and also a very good commutability of the candidate CRM, but less good commutability for spiked variants. Both these commutability studies have been reported in a paper (Bjerke M, et al. Assessing the commutability of reference material formats for the harmonization of amyloid beta measurements. Clin Chem Lab Med 2015, in press.). Studies are ongoing to test the stability and homogeneity of the candidate CRM.

#### **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. The American Society of Bone and Mineral Research (ASBMR) also has a WG, but it is not certain if ASBMR will join with other groups.

Major progress has been made towards obtaining financial and reagent support for the comparability study from the IVD industry. Four European sites will participate in the study of some 800 specimens to be collected from postmenopausal women presenting to osteoporosis clinics.

**8.3.51** The study is to collect data on pre-analytical factors including serum or plasma, fasting, 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. **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 results and 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 goal is to submit a series of manuscripts during 2016 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.

### **8.19 MEETINGS**

8.19.57 57<sup>th</sup> SD Meeting – Madrid, Spain, March 18 (full day), and 20 & 21 (a few hours each day if necessary), 2016

8.19.58 58<sup>th</sup> SD Meeting – Taipei, Taiwan, November 25 – 26, 2016