



## SCIENTIFIC DIVISION

### 57<sup>th</sup> MEETING

Madrid, Spain (2016 03 18 full day, portions of 20 and 21)

### MINUTES (FINAL)

Members:	Abbr.	Term and Time of Office	
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) (Chair JCTLM)	GLM	Consultant	
Chris BURNS (UK) (NIBSC Representative)	CB	Consultant	

### EXECUTIVE SUMMARY - SCIENTIFIC DIVISION 57<sup>th</sup> MEETING, Madrid, Spain, March 18, portions of 20 and 21, 2016.

**Present:** Ian Young (Chair), Philippe Gillery (Vice-Chair), Joe Passarelli (Secretary), Christa Cobbaert, Giampaolo Merlini, Jim Pierson-Perry (Corporate Representative), and Gary Myers (SD Consultant/Chair JCTLM) were in attendance. Apologies received from Tsutomu Nobori (Member), David Bunk (NIST Representative), Heinz Schimmel (IRMM Representative) and C. Burns (NIBSC Representative). Ingrid Zegers (IRMM) attended and served as proxy to Heinz Schimmel.

#### 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. Professor Eric Kilpatrick is the newly appointed EFLM SC chair. In addition, the EFLM has a newly appointed President - Professor Sverre Sandberg who replaces Mauro Panteghini whose term has come to completion.

There are topics of interest to the IFCC SD and the new EFLM SC Chair provided the following update:

##### 1. Blood Collection:

Ana-Maria Simundic has a TFG (Task Finishing Group) for the standardisation of color coding for blood collection tubes. This fortuitously coincides with a revision of the ISO standard for blood collection systems. She is also developing a set of recommendations on standardizing venous blood sampling.

2. **Biological Variation:**  
Aasne Karine Aarsand has succeeded Bill Bartlett as Chair of this WG whose main goal currently is in appraising the quality of BV papers in order to then inform the establishment of a robust BV database on the EFLM site.
3. **Patient Focused Laboratory Medicine:**  
Ian Watson and Wytze Oosterhuis are progressing with this WG and hope to be successful in a Horizon 2020 bid to progress ways of directly interacting with patients.
4. **Post Analytical Phase:**  
Eva Ajzner Chairs the WG and plans to send samples (instead of a questionnaire) to labs to ask them to interpret the results they receive.

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

WHO meetings occur each fall. PG attends and participates as the liaison from the SD. PG participated at a meeting with the Expert Committee on Biological Variation Standardization last October in Geneva. 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/](http://www.ifcc.org/ifcc-communications-publications-division-(cpd)/ifcc-publications/clsi-ifcc-joint-projects/)

#### **6.2.2.1 JCTLM:**

The JCTLM Executive Committee approved the addition of a “tag line” to the JCTLM logo. The new tag line is: “Accurate Results for Patient Care”. Several new reference measurement procedures, reference materials, and reference measurement services were approved for listing in the JCTLM database. The JCTLM Executive Committee reorganized JCTLM WG1 (materials and methods) and WG2 (reference measurement services) into one Database WG with a Chair and three Vice-Chairs. The biannual JCTLM Members and Stakeholders meeting was held on November 30 to December 1, 2015. A total of 35 presentations were given. The National Institute of Metrology, China and the BIPM are organizing a workshop on ‘Protein and Peptide Therapeutics and Diagnostics: Research and Quality Assurance’, to be held on 1-4 June 2016, in Chengdu China under the auspices of the JCTLM. The new WG-TEP submitted an abstract to the AACC Meeting: “Accurate Results for Patient Care”: The Role of Traceability in Laboratory Medicine, Graham Jones, Dave Armbruster for the JCTLM Working Group for Traceability: Education and Promotion (WG-TEP).

The February 2016 issue of the JCTLM Newsletter can be found at:

<http://www.bipm.org/utis/common/pdf/JCTLM/JCTLM-Newsletter-2016.pdf>

The previous issues can be downloaded from the following webpages:

<http://www.bipm.org/en/committees/jc/jctlm/#resources>

#### **6.2.2.2 JCGM:**

##### **Report from Working Group 1 (GUM):**

WG1 held two meetings at the BIPM since the previous meeting of the JCGM, in June and October 2015. The main topic of discussion had been the feedback received on the first Committee Draft (CD) of the revised GUM (document JCGM 100-revised: *Guide to uncertainty in measurement*, JCGM 100:201X, and its companion document JCGM 110, *Examples of uncertainty evaluations*, JCGM 110:201X). The JCGM endorsed the timetable proposed by WG1 for its progress towards revision of the GUM. It recommended delaying any decision on a “new perspective” for presentation of the GUM series of documents until after greater engagement has been carried out with stakeholders. It encouraged WG1 to proceed with the preparation of CD JCGM 103 *Supplement 3 to the GUM, Developing and using measurement models*.

## **Report from Working Group 2 (VIM)**

WG2 has focused on developing a Draft Outline of the fourth edition of the VIM (VIM4) during 2015, 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**

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 provided an update via email correspondence:

New WHO standards projects endorsed:

- a. To established the International Standard for C-peptide. Randie Little, BIPM, NIBSC, NIM, AIST in Japan have a draft manuscript describing the situation with regard to C-peptide standardization and reference materials/methods.
- b. A new reference material for PSA. The optimal approach will be to mimic as closely as possible the methods used to prepare the original "90:10" standard and to minimize numerical change in values following introduction of the replacement standard.

NIBSC has also been successful (pending finalization of contract) in obtaining research funding from EURAMET – The European Association of National Metrology Institutes. The project is to investigate and quantitate antimicrobial resistance in biofilms.

### **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](https://en.wikipedia.org/wiki/NPU_terminology)) as well as the NPU Website. The use of NPU codes is now compulsory in Norway but there is a transitional period to allow the switch from local codes.

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

The Committee plans to meet in March during the IFCC General Conference in Madrid to discuss the progress of setting up expert laboratories as well as other topics. Some progress has been achieved to date but much more still is left to do. Laboratories involved might first focus attention on sample exchange, providing guidance to new labs being set up, etc. The SD will suggest that the Committee consider and develop a new Work Item for ISO *on the subject of Criteria Required for Expert Laboratories*.

#### **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. With respect to item 1), much has already been achieved. There has been some progress on pancreatic lipase standardization but it may be unachievable and at the very least very difficult for IVD companies to maintain. Consideration has been given to refocus efforts on pancreatic amylase which may be more sustainable by reference labs and manufacturers. After some discussion between the chair and the SD it was agreed that the Committee would continue until the end of the year at which time be converted to a new WG with a specific focus on pancreatic enzymes, including lipase and amylase.

#### **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. He is a member of C-TLM and can oversee the work as it is majorly a calibration factor issue. The plan is to develop a CRM and to obtain JCTLM listing. Separate to this, a new member to the committee is needed and several excellent nominations were received and being considered.

#### **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. A new chair has been appointed and the committee will continue with these activities and with a focus to develop a program of work which would compare alternative approaches to the determination of reference intervals (conventional and "big data"). To achieve this in an efficient way, sample sets which the committee collected during the last few years, in combination with reference intervals determined in similar populations using very large anonymised datasets will be considered. In addition, CLSI C28 (now EP28AC) on reference intervals will likely be updated soon and might provide a good opportunity for collaboration and alignment.

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

The phase 4 studies are complete and the results are being reviewed and evaluated by manufacturers and the committee. Preliminary assessments look promising. 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.

### **8.3 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. The first goal will be to develop commutable reference materials through IRMM. To date, the main activities of the WG have been concerned with the development of the reference measurement procedure. In the interim, a commutability study is now being considered 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. The SD decided to allow for a two year extension of the WG with the goal to finalize the reference method. R. Paleari will remain as chair during this time.

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

A manuscript is in preparation describing the CDT reference measurement procedure. Once complete it will go out to the National Members to vote on as a Candidate Reference Procedure. The WG is actively trying to set up a network of reference laboratories which would be open to all once the reference method is published. There are currently 6 labs participating.

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

All activities of the WG-SAU are a joint effort with the NKDEP Laboratory Working Group. IVD manufacturers provided input and are actively involved 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. Studies are in progress to address these issues and will continue through 2016.

#### **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.

#### **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 AACC in August 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 WG plans for a next face-to-face meeting in August 2016 in conjunction with the AACC in Philadelphia.

#### **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. 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 provide 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:**

With respect to defining appropriate operating procedures from biological fluids, the different laboratories participating in 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 published by the end of the year. In addition, 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 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.

#### **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.

The next WG meeting is being planned in conjunction with the 2016 AACC in Philadelphia.

#### **8.3.49 WG-CSF:**

A large (5 liter) pool of CSF has been collected to be the basis for the reference material. Results showed acceptable agreement between expected (calculated) and measured values, meaning that these samples should 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 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 very good commutability of the candidate CRM, but less commutability for spiked variants. 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 have 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. 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.

#### **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 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 58th SD Meeting – Taipei, Taiwan, November 25 – 26, 2016
- 8.19.58 59th SD Meeting – Athens, Greece, June 9 – 10, 2017
- 8.19.59 60th SD Meeting – Durban, South Africa, October 20 – 21, 2017