

SCIENTIFIC DIVISION

62nd MEETING Budapest, Hungary (November 8 and 9, 2018)

MINUTES (FINAL)

Members:	Abbr.	Term and Time of Office	
Philippe GILLERY (FR) (Chair)	PG	1 st	2017 01 - 2019 12
Christa COBBAERT (NL) (Vice-Chair)	CC	1 st	2017 01 - 2019 12
Joseph PASSARELLI (US) (Secretary)	JP	2 nd	2018 01 - 2020 12
Barnali Das (IN)	BD	1 st	2018 06 - 2020 12
Konstantinos MAKRIS (GR)	KM	1 st	2017 01 - 2019 12
Mario PLEBANI (IT)	MP	1 st	2017 01 - 2019 12
James PIERSON-PERRY (US) (Corporate Rep.)	JPP	2 nd	2018 01 - 2020 12
Karen PHINNEY (NIST Representative)	KP	Consultant	
Heinz SCHIMMEL (JRC Observer)	HS	Observer	
Gary MYERS (US) (Chair JCTLM)	GLM	Consultant	
Chris BURNS (UK) (NIBSC Representative)	CB	Consultant	
Greg MILLER (US) (ICHCLR Representative)	GM	Consultant	
Youchun WANG (CN) (NIFDC Representative)	YW	Observer	

EXECUTIVE SUMMARY - SCIENTIFIC DIVISION 62nd MEETING, Budapest, Hungary, November 8 – 9, 2018.

Present: Philippe Gillery (Chair), Christa Cobbaert (Vice-Chair), Joe Passarelli (Secretary), Barnali Das, Konstantinos Makris, Mario Plebani, (Members), Jim Pierson-Perry (Corporate Representative), Karen Phinney (NIST Representative), Gary Myers (SD Consultant/Chair JCTLM), Chris Burns (NIBSC Representative), and Greg Miller (ICHCLR Representative) were in attendance. Apologies received from Heinz Schimmel (JRC Observer) and Youchun Wang (NIFDC 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 is that these activities do not overlap with the IFCC SD.

PG has been in contact with the chair of the EFLM SC. Approaches to avoid overlap and work collaboratively continue to be discussed and explored.

6.1 WORLD HEALTH ORGANIZATION (WHO):

The WHO meeting occurs each autumn. PG attends and participates as the liaison from the SD. Unfortunately, he could not attend the last meeting. CB is also a full member of the WHO Expert Committee on Biological Standardization (ECBS) and did attend the last meeting just a few weeks prior to this SD meeting. Much of the focus was on public health and emerging pathogens (Zika, Ebola, polio containment). The WHO changed the rules of who can come to the ECBS meeting with some restrictions. This should not have an effect on the IFCC. CB updated the SD but much of the activities of ECBS are not relevant to the IFCC. The WHO has a different perspective with respect to metrology and as a result, commutability of some of the reference materials needs to be carefully considered.

6.2 CLINICAL AND LABORATORY STANDARDS INSTITUTE (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/).

JPP is a member of the CLSI Board of Directors and serves as the IFCC liaison to CLSI and the CLSI liaison back to the IFCC Executive Board. JPP mentioned that a project proposal was accepted by the CLSI Consensus Council for the update to EP28 (guidance document on Reference Ranges). As previously mentioned, this has direct implications to the Committee on Reference Intervals and Decision Limits (C-RIDL). As such, it is highly likely that Prof. Yeşim Özarda (chair of C-RIDL) will co-chair the CLSI Document Development Committee (DDC) for the revision to EP28. The CLSI Consensus Council is very supportive of this approach and are working through the logistics. A call for volunteers will go out soon. JPP also mentioned the release of EP34 (Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking).

6.22.1 Joint Committee on Traceability in Laboratory Medicine (JCTLM):

The SD encourages visiting the JCTLM website (www.jctlm.org) which provides useful resources to illustrate the importance of traceability in laboratory medicine. The website is targeted at non-specialists and is intended to underpin the new JCTLM tag line 'Accurate results for patient care'. Sections include: Latest News, Publications, Resources, Meetings, and Partners.

The JCTLM 2018 nomination cycle for certified reference materials, reference measurement procedures and calibration laboratories that provide reference measurement services for laboratory medicine and clinical chemistry closed May 30, 2018. As of March 2018, the JCTLM Database contains:

- 296 available certified reference materials
- 194 reference measurement methods or procedures
- 176 reference measurement services delivered by 17 reference laboratories.

The various Review Teams have completed their respective reviews of the nominations in their areas of responsibility and the results will be reviewed and approved at a meeting of the JCTLM Database WG on 5 December, 2018

JCTLM co-sponsored the 2018: Protein and Peptide Therapeutics and Diagnostics: Research and Quality Assurance International Workshop (PPTD-2018) in Chengdu, China. The theme of this workshop was "Measurement and Standards, Quality and Safety".

GLM will complete his second 2-year term as JCTLM Chair in December 2018. Therefore, a new Chair will be nominated and appointed at the Executive Committee meeting in December at BIPM.

6.22.2 Joint Committee for Guide in Metrology (JCGM): Report from Working Group 1 (GUM - Expression of Uncertainty in Measurement)

Dr. Martin Milton (JCGM Chairman) provided an update to the SD:

The circulation for review of the first Committee Draft of the document JCGM 103, Guide to the expression of uncertainty in measurement — Developing and using measurement models has been initiated. This document has been prepared by the Joint Committee for Guides in Metrology, of which the IFCC is a member, specifically by Working Group 1. This document is now being circulated for review amongst the eight member organizations (BIPM, IEC, IFCC, ILAC, ISO, IUPAC, IUPAP and OIML), and to the Directors of National Metrology Institutes.

The chair proposed to use the review process that the JCGM has used previously. Dr. Graham White has been proposed as the IFCC representative.

Report from Working Group 2 (VIM)

The chair (Dr. Charles Ehrlich) of the Joint Committee for Guides in Metrology Working Group 2 (JCGM WG2) provided the following update to the SD:

The number of members of JCGM-WG2 has expanded since the last JCGM meeting by 3, from 12 to 15, with new representatives from IUPAP (1), OIML (1), and IUPAC (2), and one representative leaving (ILAC).

The main technical activity of JCGM-WG2 in the period May 2017 – November 2018 has been to develop a ‘minimum change’ version of a first “committee draft” (CD) of the fourth edition of the VIM that more fully incorporates entries on nominal properties and, to a much lesser extent, ordinal properties. The definitions of ‘measurement’ and ‘measurement unit’ have been given careful consideration in this regard. A longer-term ‘evolutionary’ version of the VIM4 CD has also been under development. Status of these two versions of these VIM4 CDs will be presented at the 3 December 2018 JCGM meeting.

Also to be discussed are publishing options of the VIM4 (e.g., electronic, hard copy, structure, languages).

6.22.3 BUREAU INTERNATIONAL DES POIDS ET MESURES (BIPM) Consultative Committees

6.22.3.1 Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM):

PG has been added in JCGM listing (covers CCQM and CCU activities). The CCQM covers measurement standards and standardization in all branches of chemical and biological measurement science, and provides a forum where NMIs can be addressed collectively. A number of the CCQM WGs have programs in which a substantial portion of their activities are related to Laboratory Medicine, and notably for the Organic Analysis (OAWG) and Protein Analysis (PAWG) working groups. The OAWG has completed a comparison of metrology institutes with Vitamin D (D3 and D2) reference measurement procedure capabilities; this covered 7 institutes and will be published soon. The PAWG has mapped out a model system to look at the different types of pure peptide/protein types with respect to different challenges for purity assessment, with the aim of running comparisons to demonstrate NMI measurement capabilities for values assigning primary reference materials for peptides/small proteins.

6.22.3.2 CC for Units (CCU): SD received no correspondence.

6.31 JOINT RESEARCH CENTER (JRC) – formerly the INSTITUTE FOR REFERENCE MATERIALS AND MEASUREMENTS (IRMM):

The status of JRC reference materials activity is mostly covered under the respective Cs and WGs. The JRC continues to collaborate with numerous SD Cs/WGs on a variety of projects. Reference materials are still a key area of focus of the JRC.

6.33 NATIONAL INSTITUTE OF BIOLOGICAL STANDARDS AND CONTROL (NIBSC)

C. Burns provided the following update:

NIBSC successfully established 11 new WHO International Standards potentially of interest to the SD, including the first cell counting standard for CD4 enumeration:

- Anti-D immunoglobulin (human)
- Blood coagulation factor V (plasma, human)
- Adenovirus DNA for NAT-based assays
- Anti-Asian lineage Zika virus antibody (human)
- CD4 T-cells (human)
- HIV-1 p24 antigen
- HIV-2 p26 antigen
- HIV-2 RNA for NAT-based assays
- Prostate specific antigen (human) (free)
- Prostate specific antigen (human) (total: PSA-ACT + free PSA)
- von Willebrand factor (plasma) binding to recombinant glycoprotein Ib

In addition, proposed new standards projects to be endorsed by WHO (5 in total):

- Proposed 1st WHO International Genomic Reference Panel for Microsatellite Instability
- WHO 1st International standards for ctDNA
- The proposed 1st WHO international standard for anti-thyroid peroxidase antibodies
- Proposed 4th WHO IS for Ferritin
- 2nd WHO IS for Insulin-like Growth Factor-1, recombinant, human, for immunoassay

6.37 NATIONAL INSTITUTE FOR STANDARDS AND TECHNOLOGY (NIST):

The status of NIST reference materials activity is mostly covered under the respective C's and WGs.

In addition, the NIST website (www.nist.gov) can provide information on materials and services available today.

The most relevant projects to the IFCC and SD are:

- Renewal of Troponin
- Vitamin D
- Albumin in urine

8.2 MAIN ACTIVITIES OF COMMITTEES:

8.2.6 C-NOMENCLATURE, PROPERTIES AND UNITS (C-NPU):

As a reminder, in 2014 a formal agreement between IFCC and IUPAC was put in place. Wikipedia presence for the NPU was created 2015 (edited by the chair with input from many NPU members). The Wikipedia entry is a useful introduction:

(https://en.wikipedia.org/wiki/NPU_terminology) and the NPU Website is performing well.

The C has written a manuscript entitled: "Recommendation on measurement units - why and how" intended for submission in the electronic Journal of the International Federation of Clinical Chemistry and Laboratory Medicine.

In a current C-NPU activity, an online manual of NPU terminology is under development. The goal is to have a sort of encyclopedia for medical laboratory terminology that is

accessible for any medical laboratorians. The project is funded by IUPAC (https://iupac.org/projects/project-details/?project_nr=2016-044-2-700). The project is in an iterative stage of establishing, reviewing and revising homepages. The C plans to meet in Barcelona in conjunction with EuroMedLab 2019 and at the IUPAC meeting in Paris in July.

8.2.11 C-MOLECULAR DIAGNOSTICS (C-MD):

In early 2018, membership from the Task Force for Pharmacogenetics was merged into the Committee for Molecular Diagnostics. In order to transition between 2018 and 2019, a proposal was submitted and approved by the EB to designate Dr. Parviz Ahmad-Nejad to Chair for 2019, and to appoint Dr. Mark Linder, previous chair of the TF on Pharmacogenetics as a full member to the Committee.

The Terms of Reference were modified as follows:

- To foster dynamic exchanges between IFCC and molecular diagnostic laboratories and industry.
- To produce guidelines on clinical validation of tests, conduct and reporting of molecular diagnostic tests.
- Creation of a network of locus-specific IFCC Molecular Diagnostics Centres.
- Increased support for Molecular Diagnostics in Low Income Countries.

The total number of labs so far for the survey monkey is 39 which is up from the last time of 16 and now also translated into Spanish.

8.2.23 C-TRACEABILITY IN LABORATORY MEDICINE (C-TLM):

The results of RELA2017 have been evaluated and published (<http://www.dgkl-rfb.de:81>).

The number of published results increased from 343 (RELA2016) to 412 (RELA2017).

The survey RELA2018 is announced. The shipment of samples will be arranged at the beginning of November. Currently, 515 orders of 53 laboratories are registered.

RELA is an important forum and the results of the surveys are a widely used data source for laboratories which intend to be listed at JCTLM, but also for laboratories developing new reference methods. The results of RELA surveys were cited in many presentations, e.g. at Protein and Peptide Therapeutics and Diagnostics Workshop (PPTD-2018) which was held 10-12 October 2018, in Chengdu China. The event was organized jointly by the NIM (China), NIFDC (China) and BIPM, and also under the auspices of the JCTLM.

The survey program RELA has now been organized for 15 years.

The C met in Budapest and had 14 participants, including many corresponding members and representatives from the manufacturers.

8.2.24 C-REFERENCE INTERVALS AND DECISION LIMITS (C-RIDL):

Articles published on behalf of the C-RIDL:

1. Jones GRD, Haeckel R, Loh TP, Sikaris K, Streichert T, Ozarda Y,; IFCC Committee on Reference Intervals and Decision Limits. Indirect methods for reference interval determination - review and recommendations. Clin Chem Lab Med. 2018 Apr 19. pii: /j/cclm.ahead-of-print/cclm-2018-0073/cclm-2018-0073.xml. doi: 10.1515/cclm-2018-0073 [Epub ahead of print].
2. Ozarda Y, Sikaris K, Streichert T, Macri M, on behalf of IFCC-Committee on Reference intervals and Decision Limits (C-RIDL). Distinguishing Reference Intervals and Clinical Decision Limits – A review by the International Federation of Clinical Chemistry Committee on Reference Intervals and Decision Limits”. Critical Reviews in Clinical Laboratory Sciences, 2018 Sep;55(6):420-431.

Article published directly related to the C-RIDL projects;

- Ozarda Y, Higgins V, Adeli K. Verification of reference intervals in routine clinical laboratories: practical challenges and recommendations. Clin Chem Lab Med. 2018 May 5. pii: /j/cclm.ahead-of-print/cclm-2018-0059/cclm-2018-0059.xml. doi: 10.1515/cclm-2018-0059 [Epub ahead of print]

CLSI will soon start a revision project of EP28 (Reference Ranges) and the chair of C-RIDL, Dr. Ozarda has accepted the position to co-chair the CLSI committee ensuring alignment of activities and content publications.

The C plans to meet during the General Conference in Budapest in Hungary.

Plans/suggested work items:

1. Comparison of alternative approaches (conventional and big data) for the determination of reference intervals
2. Individual reference intervals
3. The update of the CLSI Guideline EP28-A3

8.2.25 C-STANDARDIZATION OF THYROID FUNCTION TESTS (C-STFT):

Establishing a system to maintain traceability of free thyroid hormone and TSH measurements has been completed and now the focus is on implementation.

- A network of laboratories operating the FT4 RMP (4 labs in network) is being established.
- There are panels of individual donor samples with reference values assigned (FT4; TSH), and network labs will be contacted for future assignment of sample panels.
- CDC intends to develop a program like their current standardization programs for Testosterone and Estradiol, which will be linked to the C-STFT through CDC's participation in the C-STFT reference laboratory network.
- In Japan, a harmonization project is currently on-going.
- C-STFT will support PT programs in order to make them traceable to the established reference measurement systems.
- The C is identifying studies and data sources suitable for defining reference intervals.
- The C is communicating with public health communities about the importance of accurate and reliable tests.
- New panels for TSH and Free T4 will be established well in time, so that they are available before the current panels are depleted.
- The C will collaborate with metrological institutes to develop reference materials that are in line with its efforts.

The committee plans to meet in conjunction with the IFCC General Conference in Budapest, Hungary and twice in 2019 at EuroMedLab and at the AACC.

8.2.26 C-HARMONIZATION OF AUTOIMMUNE TESTS (C-HAT):

The Committee is quite active. The committee continues to focus on the preparation of reference materials in collaboration with the JRC. The C continues developing plans for introducing and implementing reference materials for IgG anti MPO and IgG anti PR3. The committee is facing a similar issue as C-STFT with implementation of harmonized assays systems in that there is the need to work with manufacturers and regulatory agencies worldwide and in particular the FDA. At present IVD manufacturers have to submit a full new 510k dossier after they have re-calibrated their assay, including sometimes very expensive clinical studies. This requires considerable resources (financial, people, time) and is often a barrier to standardization/harmonization. There have been discussions with the FDA and they are supportive but their focus is primarily on comparisons to predicate devices.

Future plans:

- Other antibodies where harmonization would be beneficial

- Other areas to consider harmonization/standardization of more detailed definition:
 - concerning epitope mapping of the reference materials to try to identify sources of variation in the autoimmune assays.

The C plans to meet again next in Barcelona, Spain in conjunction with EuroMedLab 2019.

8.3 MAIN ACTIVITIES OF WORKING GROUPS:

8.3.35 WG - STANDARDISATION OF HEMOGLOBIN A2 (WG-HbA2):

A joint committee with ICSH (The International Council for Standardization in Hematology) has been formed. The method developed is an HPLC-IDMSMS measurement procedure based on peptide mapping and calibration with recombinant expressed HbA0 and HbA2 standard materials, traced back to SI units. The experimental work for the validation of the candidate reference measurement procedure assessing various target tryptic peptides is nearing completion. The method with ID-MS has been accepted for publication in Clinica Chimica Acta with the title “Determination of HbA2 by quantitative bottom-up proteomics and isotope dilution mass spectrometry” including data of new experiments proving the complete digestion of native and recombinant hemoglobins.

The preparation of a second paper (validation of the RMP) will be discussed within the meeting of the WG in Budapest, planned for Friday, November 9th.

Planning has begun for the preparation of the Certified Reference Material with the JRC. The SD also encouraged the WG to engage the ICSH as much as possible to align activities.

8.3.36 WG - STAND. OF CARBOHYDRATE-DEF. TRANSFERRIN (WG-CDT):

The following is a summary and a description of the current focus of this WG:

1. JCTLM – The document was updated and resubmitted during 2018. A final decision will be communicated in 2019.
2. There have also been continuous communication and updates requested from commercial manufacturers towards final development and release of their CDTIFCC methods.
3. Current laboratories for the HPLC RMP are: Sweden, The Netherlands, France, United States, Italy and United Kingdom.
4. Sustainability and performance of network laboratories and participating commercial manufacturers are assessed by the yearly distribution of IFCC calibrators, controls and blind samples from Dr. Weykamp’s laboratory. Laboratory performance is assessed on a pass/fail criterion and HPLC RMP performance is assessed in further detail by Dr. Schellenberg.
5. WG members have been raising awareness of CDT_{IFCC} with local authorities at regional level.
6. The notation of the term “Standardization” has now been removed from the name of the WG.

8.3.39 WG – STAND. OF ALBUMIN ASSAYS IN URINE (WG-SAU):

All activities of the WG-SAU are a joint effort with the Laboratory Working Group (LWG) of the National Kidney Disease Education Program (NKDEP), USA.

NIST and Mayo continue to develop and validate their reference measurement procedures and work to identify sources of disagreement among the methods. The Univ of Minnesota is collaborating with Mayo to actively pursue development of a LC-MS/MS candidate reference measurement procedure and both laboratories are currently working to procure a source of stable isotope-labeled human albumin for use as an internal standard in the measurement procedure. NIST is also working on securing a supply of stable isotope-labeled human albumin. Mayo and University of Minnesota are working to develop the

reference measurement procedures in accordance with ISO 15193 and other relevant standards for the purpose of JCTLM listing.

To facilitate standardization of routine methods, NIST SRM 3666 is currently being developed based on the specifications recommended by the WG-SAU and the LWG of the NKDEP. Once developed, a commutability assessment of the materials will be conducted. The acquisition of frozen pooled urine samples for preparation of NIST SRM 3666 is nearing completion is anticipated to occur by the Fall of 2018. Once completed, the individual urine samples that comprise each level of NIST SRM 3666 will be shipped to Solomon and Park for vialing and pooling. The materials will then be value assigned by NIST. The WG-SAU will continue to facilitate development of NIST SRM 3666.

A draft manuscript was sent to the SD for review and comment in October 2018:

Title: Recommendations for reporting low and high values for urine albumin and total protein. The Laboratory Working Group of the National Kidney Disease Education Program recommended several practices be adopted by all clinical laboratories.

8.3.40 WG – STAND. OF PREGNANCY-ASS. P-PROTEIN A (WG-PAPPA):

The goal of PAPP-A standardization phase 3 is to study whether pooled 3rd trimester or 2nd trimester serum can be used for harmonization of the commercial PAPP-A tests. Currently, the WG is evaluating different PAPP-A preparations in relation to the major assay constructs presently being used in routine prenatal testing. The work with evaluation of different PAPP-A preparations has continued in phase 3, in which endogenous materials of PAPP-A (PAPP-A in second trimester and third trimester sera diluted in various materials and compared to first trimester serum pools) were analyzed with assays systems of the companies involved in the WG in order to study the commutability of these materials. After some difficulties and delays all results have finally been received from companies and are being analyzed. This has improved the variation from about 50% to around 20% when various IVDs measured the material. The issue of commutability will be further assessed moving forward. The WG plans to meet during the General Conference to discuss the data generated to date. Finally, the WG is considering the removal of the term “Standardization” as activities are currently focused on “harmonization” of the various assays systems.

8.3.41 WG – GROWTH HORMONE (WG-GH)

The overall goal of the WG-GH is to achieve standardization of growth hormone through secondary reference materials and a reference measurement procedure. To achieve this goal a harmonization study was done, in which several pooled serum samples were tested for commutability. In this study different calibrators were made by pooling samples from apparently healthy persons, or patients (adults or children) to assess for commutability. In addition, IS 98/574 was diluted in GH deficient serum. All calibrators were prepared in two different concentrations: about 10 and 40 mU/L or 3.3 and 13.3 ng/mL respectively. Measurements by LCMSMS are still unavailable. However, results from all immunoassay methods were processed and have been sent to the members of the working group together with a proposal for the future direction of investigation.

Future directions: The most important change of approach will be the use of more fresh samples, in order to keep the native forms of GH preserved in the samples.

A commutability study will be repeated with 30 patient samples and two IS 98/574 and five healthy donor calibrators. All available methods that are in use for routine GH measurements will be included in the study.

8.3.42 WG – STANDARDIZATION OF INSULIN ASSAYS (WG-SIA)

This is a joint project between ADA/EASD and IFCC. The overall goal of the WG is to establish a reference system for serum/plasma insulin measurement to achieve standardization of all commercial methods to assay insulin.

Current status:

1. Ongoing development and validation of MS/MS method for intact insulin at University of Minnesota. Significant progress has been made following prioritization and financial support for development of the LC-MS/MS insulin assay at the University of Minnesota.
2. Continued collaboration with other laboratories (Quest Diagnostics, Mayo Clinic) developing insulin methods by mass spectrometry and sustained efforts to evolve reference method procedures in these laboratories.
3. In collaboration with the College of American Pathologists (CAP), established criteria for ongoing accuracy based evaluation of serum pools for testing of insulin, C-peptide, and glucose.
4. Continued collaboration with NIBSC to evaluate insulin candidate reference material and will ultimately utilize that to calibrate the mass spec method and establish it as a higher order reference method.

Future Plans and activities:

1. Implement accuracy based proficiency testing survey using serum pools for insulin (and c-peptide) via the College of American Pathologists; results will allow for assessment of comparability of results across assays, using a commutable matrix, as the WG moves towards standardization or harmonization. Implementation target date: Q1 2019.
2. Working group report or peer-reviewed publication regarding either insulin/c-peptide serum pool data across hundreds of laboratories/assays and/or lack of harmonized conversion factor across insulin assays.

The WG plans to meet next in conjunction with EuroMedLab, Barcelona, Spain May 2019 and again at the AACC Annual Meeting, Anaheim, CA 2019.

8.3.43 WG – STANDARDIZATION OF TROPONIN I (WG-TNI)

The following provides a brief summary of the status of WG-TNI:

1. The protocol for recruitment of subjects was approved by the University of Maryland, Baltimore's (UMB) Institutional Review Board for collection of samples from acute myocardial infarction to be used by the WG. Collection of samples for use in comprising RM 2922 has begun.
2. The Material Transfer Agreement (MTA) between NIST and the UMB has been completed with the final agreement allowing the WG to transfer the material that will comprise RM 2922 between organizations.
3. A casual meeting of WG-TNI available members, and others (including representatives from Siemens, Beckman Coulter, Abbott and Roche) engaged in WG-TNI Standardization activities was held at the 2018 AACC Annual Meeting in Chicago. The sense of the group was that the WG efforts should focus on the high sensitivity cTnI methods as this is clearly the future of the field. There was much discussion about lack of a reference method for assigning a true value to RM 2922 with low uncertainty. Also, issues such as how many concentrations of the material should be available were discussed. These deliberations will be continued at the WG-TNI meeting in Budapest, Friday afternoon November 9th, 2018.
4. The chair discussed with JPP and others about the CardioMet effort, which is proposed to involve a number of cardiac biomarkers with the stated aim of "Providing the measurement infrastructure to allow quantitative diagnostic methods for biomarkers of coronary heart diseases". Dr. Christenson's understanding is that

this is within the EMPiR programme and will speak with Dr. Claudia Swart and learn if there is a possible opportunity to productively collaborate and further IFCC WG-TNI charges.

8.3.48 WG – PARATHYROID HORMONE (WG-PTH):

The following provides a brief summary of WG-PTH to date:

1. An update of the systematic review on pre-analytical factors is under way.
2. Major progress is being made by Dr. Vesper's group at CDC on increasing the analytical sensitivity of the reference measurement procedure. [Published mass spec methods for PTH are approximately 10x less sensitive than current immunoassays.]
3. The protocol for a commutability study for the current International Standard is to be finalized at a meeting of the PTH Working Group in Budapest during the IFCC General Conference. The main objectives at the PTH Working Group meeting will be to discuss progress with development of the candidate reference measurement procedure and to agree the protocol for the commutability study for PTH(1-84) IS 95/646. WG-PTH will close in January 2019 and activities resumed under a new Committee on Bone Metabolism to be formed to consolidate WG-PTH, WG-SBMA, and WG-Vitamin D standardization.

8.3.49 WG – CSF PROTEINS (WG-CSF):

The WG is in contact with NIMs for the standardization of the Tau proteins. There seems to be some coordinated activities. So far the following have been accomplished:

- Two RMPs for CSF amyloid β 1-42 have been published and approved by the JCTLM (C12RMP1 and C11RMP9).
- A method for measurement of CSF amyloid β 1-40 by SRM has been published and validation of a RMP is ongoing.
- Mass spectrometric methods for measurement of CSF tau have been developed by several of the work group members.
- Three CRMs for CSF amyloid β 1-42 have been developed (ERM®-DA480/IFCC, ERM®-DA481/IFCC and ERM®-DA482/IFCC).
- Collection of CSF for development of CRMs for tau is ongoing.
- Round-Robin study of CSF-amyloid beta 1-42/1-40 ratio RMPs by mass spectrometry is in the planning stage.
- Round-Robin study of CSF tau RMPs by mass spectrometry is being planned.

8.3.50 WG – STANDARDIZATION OF BONE MARKER ASSAYS (WG-BMA):

This is a joint activity with the International Osteoporosis Foundation (IOF). 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 comparability study of the two major clinical assays for CTX has been completed at four European centres including data on the effects of serum or plasma specimen, fasting or non-fasting subjects and males and females presenting to osteoporosis clinics on the comparability of the results of assays from two manufacturers used by clinical laboratories. A draft manuscript is being finalized in preparation for submission to an appropriate peer-reviewed journal. The results of the study have been presented in a workshop during the IOF meeting in Krakow and during the ASBMR congress in Montreal.

The comparability study of the two major clinical assays for PINP has been completed at four European centres including data on the effects of serum or plasma specimen, fasting or non-fasting subjects and males and females presenting to osteoporosis clinics on the comparability of the results of assays from two manufacturers used by clinical laboratories. A draft manuscript has been prepared and sent to the members of the WG for revision. Additionally, the following publication was realized:

E. Cavalier, R. Eastell, N.R. Jørgensen, K. Makris, S. Vasikaran, H.A. Morris, on behalf of the IFCC-IOF Working Group for Standardisation of Bone Marker Assays (WG-BMA) Encyclopedia of Endocrine Diseases, 2nd Edition, published 1st October 2018.

As previously reported, the WG on standardization of bone marker assays will be merged within the IFCC Committee Bone Metabolism (C-BM) for standardization of PTH, Vitamin D and bone markers. This proposal has been approved by the members of the WG and the new Committee will also be endorsed by the IOF.

8.3.51 WG – COMMUTABILITY (WG-C):

Three papers were published in March 2018:

1. Miller WG, Schimmel H, Rej R, Greenberg N, Ceriotti F, Burns C, Budd JR, Weykamp C, Delatour V, Nilsson G, MacKenzie F, Panteghini M, Keller T, Camara JE, Zegers I, Vesper HW, for the IFCC Working Group on Commutability. IFCC Working Group Recommendations for Assessing Commutability Part 1: General Experimental Design. Clin Chem 2018;64:447-54.
2. Nilsson G, Budd JR, Greenberg N, Delatour V, Rej R, Panteghini M, Ceriotti F, Schimmel H, Weykamp C, Keller T, Camara JE, Burns C, Vesper HW, MacKenzie F, Miller WG, for the IFCC Working Group on Commutability. IFCC Working Group Recommendations for Assessing Commutability Part 2: Using the Difference in Bias Between a Reference Material and Clinical Samples. Clin Chem 2018;64:455-64.
3. Budd JR, Weykamp C, Rej R, MacKenzie F, Ceriotti F, Greenberg N, Camara JE, Schimmel H, Vesper HW, Keller T, Delatour V, Panteghini M, Burns C, Miller WG, for the IFCC Working Group on Commutability. IFCC Working Group Recommendations for Assessing Commutability Part 3: Using the Calibration Effectiveness of a Reference Material. Clin Chem 2018;64:465-74.

Manuscript currently in preparation; anticipate submission in Q1 2019:

4. IFCC working group recommendations for assessing commutability part 4: Correction of bias caused by non-commutability of a certified reference material used in the calibration hierarchy of an end-user measurement procedure.

Next topics and manuscripts to be prepared:

5. IFCC working group recommendations for assessing commutability part 5: Validation of a replacement batch of a reference material.
6. IFCC working group recommendations for assessing commutability part 6: Approaches to establish criteria for commutability assessment. This manuscript will address how to define the degree of commutability which is required for a given reference material, taking into account its intended use and the intended use of the measurand.

The overall goal is to propose standard terminology to describe the degree of commutability of a reference material, taking into account its intended use. In addition, to provide guidance to manufacturers and laboratories about what information should be provided by manufacturers in relation to the commutability of reference materials used to establish the calibration traceability of a measurement procedure.

8.3.53 WG – IMMUNOSUPPRESSIVE DRUGS (WG-ID):

The WG has been recently formed and is devoted to the establishment of candidate reference procedures and reference materials for immunosuppressive drugs (ISDs) including cyclosporine, sirolimus, tacrolimus, everolimus, and mycophenolic acid (MPA). Demonstration of the current state of the art in ISD – TDM by measurement comparison will define the need for harmonization or – if feasible – standardization of measurement services

Current projects:

- *Regulatory framework:*

- Establish and communicate the regulatory framework which allows submitting to the JCTLM reference materials, measurement methods and measurement services established within the WG-ID.
- *Measurement comparison initiative aimed to assess the state of art in ISD TDM:*
 - Baseline assessment including method comparability.
 - Influence of secondary reference materials on method comparability.
- *Production of reference materials to be listed in the JCTLM database:*
 - Characterization of primary reference materials.
 - Production of primary reference materials.
 - Characterization and production of secondary reference materials.
- *Establishment of reference methods to be listed in the JCTLM database:*
 - Design and validation of a candidate reference method by at least two to three partner institutions.
- *Establishing reference procedures:*
 - Establishment of a reference laboratory network.
 - Establishment of a reference measurement service network

Within the first year of its operation the WG will establish a regulatory framework (operational layout) for the development of reference procedures and reference materials capable to be JCTLM listed. This framework will be presented at the Budapest IFCC General Conference in November, 2018.

8.3.54 WG – APOLIPOPROTEINS BY MASS SPECTROMETRY (WG-APO MS):

The WG is progressing very well and investigating both reference materials and reference methods.

Reference measurement procedure: in 2018, the WG executed an instrument comparison study, to determine whether all three mass spectrometers (each from different vendors) perform similarly. The WG is currently performing the data evaluation and plans to finalize this work in Q4 2018. It is currently being investigated whether a common data evaluation strategy using open-source software would be necessary. Moreover, the group has evaluated the optimal digestion conditions for serum apolipoproteins to ensure maximum recovery.

Reference materials: during 2018 the WG obtained pig EDTA plasma with human apo(a) with a specified number of kringles. A first evaluation of the suitability of this material was performed. Furthermore, a stability study, assessing the stability of apo(a) at different storage conditions is ongoing and will be finalized by Q4 2018.

JRC has prioritized this topic and has appointed a full time PhD to manufacture secondary CRMs. LNE has worked on a subsidy proposal together with other NMIs and also LUMC; the aim is to obtain finances for the preparation of primary peptide - based standards. The WG continues to strive for further collaborations and finances with IVD- manufacturers.

8.3.55. WG – PANCREATIC ENZYMES (WG-PE):

The WG was established as a result of the closure of the previous C-RSE. Most of the members of WG-PE also participated in C-RSE. However, so far there has been limited participation from manufacturers. It is important to add representatives from companies like Roche, Abbott, Beckman, Siemens, etc. because the acceptance of a reference method is coupled to the commercial products these companies offer.

Project lipase:

Further investigations have been performed in Japan (Shigeru Ueda) only. However, these have now stopped.

Project pancreatic amylase (the only current focus of the WG):

Dr. Grote-Koska's (WG chair) calibration laboratory purchased two antibodies for inhibition of salivary amylase. With these, his lab investigated the inhibition rate and determined the

calibration function using inhibited and not inhibited Amylase mixture. They found good reproducibility of P-AMY. It was also shown that in the reaction mixture, P-AMY activity showed higher stability than the activity of total amylase.

Glucosidase inhibition:

Testing this inhibition is essential in the IFCC reference procedure for total amylase.

The total amylase procedure is the base for measuring P-AMY. In experiments here the inhibition of glucosidase was only slightly increased by addition of the antibodies.

A working protocol to the WG members and 3 labs willing to perform measurements was distributed mid-year. In Budapest, the WG plans to meet to define actions to further investigate the measurement procedure in additional laboratories. The WG plans to also meet again in Barcelona in May 2019 in conjunction with EuroMedLab.

8.3.56 WG – FECAL IMMUNOCHEMICAL TESTING (WG-FIT):

The WG held another successful meeting in Vienna in mid-October 2018, with approximately 20 people in attendance with an even split between manufacturer representation and group members.

The main topic of discussions;

- Preliminary results obtained from the reference material project. This work is ongoing and hopefully within the next few months WG-FIT will either have an agreed material which FIT tests are referenced or harmonized to.
- EQA material – draft report has been written and this will be amended to submit for publication.
- 3rd IQC material – none available currently so the WG plans to contact IQC companies to see if anyone is developing this and if not will work with them to do so.
- There was a proposal to put together a paper for publication to summarize pre-analytical and analytical variables of FIT

The WG plans to meet again in Barcelona in May 2019 in conjunction with EuroMedLab.

8.3.57 WG – CELL FREE DNA AND RELATED CIRCULATING BIOMARKERS (WG-cfDNA):

The activities of the WG have only recently started. The WG has reached out for corporate member sponsorships to enable face-to-face meetings.

Terms of Reference:

- To identify and provide guidance on preanalytical and analytical aspects for obtaining good and reproducible results for cfDNA and related circulating biomarkers for clinical use, and to guide the correct clinical implementation of these biomarkers.

Current projects:

- Defining pre-analytical aspects / drafting guideline
- Defining minimal analytical performance
- Setting up proficiency testing for cfDNA
- Organizing international workshops
- Defining grant proposals to address unmet needs

The chair and WG have prepared a paper about the pre-analytical aspects and the paper is currently being reviewed by the WG. The chair believes the WG members will provide expertise in lung cancer, organ rejection, and other broad areas (such as exosomes). The WG also plans to be involved early on with NMIs.

8.3.58 WG – PROCALCITONIN (WG-PCT):

The activities of the WG have recently started. The following is the status of WG-PCT to date:

Develop and validate a reference measurement procedure for PCT absolute quantification by Stable Isotope Dilution Mass Spectrometry:

- Different primary calibrators have been produced. Their purity is being characterized by high resolution mass spectrometry and PCT concentration in calibration solutions is being determined by Amino Acid Analysis (AAA)
- Different separation methods to purify PCT in biological samples are under development with the objective to validate a candidate reference measurement procedure for absolute quantification of PCT by IDMS
- Suitability of recombinant PCT and/or synthetic peptides as possible primary calibrators will be investigated based on stability and measurement uncertainties needed to meet the medical need
- The development of a candidate reference measurement procedure for absolute quantification of PCT by IDMS will be pursued to obtain sufficiently low limits of quantification
- Agreement and correlation between the different PCT assays will be evaluated through an interlaboratory comparison coupled with a commutability study involving the most popular PCT assays.
- In cooperation with IVD manufacturers, the WG will investigate what are the causes for the variability of results provided by the different commercially available PCT assays.

A Review article is expected to be prepared in 2019.

The next face-to-face meeting of the WG will most likely be held during EuroMedLab Barcelona in May 2019

8.3.59 WG – VITAMIN D STANDARDIZATION PROGRAM (WG-Vit D)

The WG has only been established since the beginning of the year. The following is a status of WG-Vit D to date:

The first meeting of WG-Vit D was on 30 July 2018 at the AACC meeting in Chicago. WG-Vit D members from universities, IVD manufacturers, clinical and commercial laboratories, and PT/EQA attended the meeting.

The meeting included a detailed presentation and discussion of the:

- (1) Overview of the Vitamin D Standardization Program (VDSP), its goals and objectives; (2) VDSP Performance Criteria – for routine laboratories, i.e. $CV \leq 10\%$ and Mean Bias $\pm 5\%$;
- (3) The problems with the current VDSP performance criteria – especially Mean Bias; and
- (4) Terms of Reference for WG-Vit D.

Following that, there was a frank and open discussion among those present. IVD manufacturers' representatives were concerned that tightening the VDSP Performance Criteria could lead to lack of participation in efforts to standardize the measurement of serum total 25-hydroxyvitamin D. It was suggested that WG-Vit D consider developing three sets of criteria for meeting or passing VDSP performance guidelines. Furthermore, it was suggested that current VDSP performance criteria be retained as the 1st Level Performance Criteria in the revised criteria. The 2nd Level and 3rd Levels would be increasingly more stringent guidelines based on attainable performance as seen in interlaboratory comparison studies.

Drs. Johanna Camara and Karen Phinney of NIST provided updates on development of RMPs for 1,25(OH)₂D₃, and Vitamin D Binding Protein and PTH, respectively.

There are plans to develop a study protocol and solicit IVD manufacturer/industry support for an international study of serum total 25(OH)D biological variation associated with immunoassays.

As previously reported, the working group on Vitamin D standardization will be merged within the new IFCC Committee on Bone Metabolism for standardization of PTH, vitamin D and bone markers in January 2019. This proposal has been approved by the members of the WG and the new Committee will also be endorsed by the IOF.

8.19 MEETINGS

- 8.19.62 62nd SD Meeting – November 8th – 9th, 2018
(in conjunction with the IFCC General Conference)
- 8.19.63 63rd SD Meeting – Barcelona, Spain, May 18th and 19th, 2019
(Saturday and Sunday), before the EuroMedLab Congress.
- 8.19.64 64th SD Meeting – Milano, Italy, October 11th and 12th, 2019 at the IFCC office.