
Present: Philippe Gillery (Chair), Christa Cobbaert (Vice-Chair), Joe Passarelli (Secretary), Konstantinos Makris, Tsutomu Nobori, Mario Plebani, (Members), Gary Myers (SD Consultant/Chair JCTLM), and Heinz Schimmel (JRC Representative) were in attendance. Apologies received from Jim Pierson-Perry (Corporate Representative), 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. In fact, the EFLM WG on “Harmonisation of Total Testing Process” (WG-H) could potentially be
synergistic with IFCC standardization / harmonization activities and the ICHCLR initiative. Approaches to avoid overlap and work collaboratively are being discussed and explored.

6.1 WORLD HEALTH ORGANIZATION (WHO):
WHO meetings occur each autumn. 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. The next meeting is scheduled for October 16-19, 2017. A reference procedure and subsequent reference material for HbA2 may be discussed.

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//.
Jim Pierson-Perry has been appointed to the CLSI Board of Directors with his first term beginning January 2017. He will also serve as the IFCC liaison to CLSI and the CLSI liaison back to the IFCC Executive Board.

6.22.1 JCTLM: A new JCTLM website (www.jctlm.org) has been created. This website provides 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 WG of Graham Beastall on Traceability, Education and Promotion created the new website. As of March 2017, the JCTLM Database contains:
  • 293 available certified reference materials;
  • 184 reference measurement methods or procedures that represent about 80 different analytes in nine categories of analytes;
  • 161 reference measurement services delivered by 17 reference laboratories.
The JCTLM 2017 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, 2017. The information will now go to the various working groups to be ratified by the JCTLM Executive Committee at the December meeting and those approved will go on the website in January 2018. A review article on global traceability has been accepted for publication: Graham H. Beastall*, Nannette Brouwer, Silvia Quiroga and Gary L. Myers, prepared on behalf of the Joint Committee for Traceability in Laboratory Medicine. Traceability in laboratory medicine: a global driver for accurate results for patient care. The paper will appear in the August issue of CCLM.

6.22.2 JCGM:
Report from Working Group 1 (GUM):
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 is still in development.
Report from Working Group 2 (VIM)
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):
There continues to be few topics of relevance in the area of clinical chemistry that the SD should consider.
SD received no correspondence from CCU.

6.31 JOINT RESEARCH CENTER (JRC) – formerly the 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.
The JRC 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, its intended use and relationship to other C-peptide reference materials is the subject of a paper (Implementing a Reference Measurement System for C-peptide: Successes and Lessons Learned) now published in Clin Chem.
Insulin:
Project ongoing – NIBSC now has value-assigned their candidate standard using mass balance and are planning the next phase of the project – an assessment of its performance as a calibrator for immunoassays.
AMH:
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 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. NIBSC is preparing a report for publication highlighting the challenges of preparing a standard for AMH and suggesting some options going forward.
Prostate Specific Antigen:
Development of a replacement for NIBSC 97/670 (PSA 09:10) is progressing. Complexed and non-complexing PSA materials have been measured on multiple immunoassay platforms alongside the previous WHO International Standards in order to identify a material which closely replicates the current ratio and can therefore be introduced with minimal
impact on patient measurements. MIBSC has now filled materials to serve as candidate International Standards and these will be assessed by a collaborative study.

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:
The committee continues to focus in the following areas:

- The NPU Steering Committee continues to clarify and formalize NPU governance.
- The NPU Scientific Committee continues as the vehicle for work projects and expert review of technical queries in relation to the terminology and related metrology issues that are frequently asked of our members.
- Efforts to more closely align the NPU with the much larger SNOMED-CT medical terminology.
- Review and addition of Molecular Pathology terms with the NPU terminology.
- Creation of a more flexible (online) and up-to-date NPU User Manual.
- Wikipedia presence for the NPU: (https://en.wikipedia.org/wiki/NPU_terminology) and the NPU Website.
- Various publications related to informatics and eHealth. One of these is a manuscript that that was published in 2016 in CCA: “Understanding the ‘Silver Book’ — an important reference for standardized nomenclature in clinical laboratory sciences. The paper is more educational than scientific and quite helpful to the understanding.
- Overlapping representation in other scientific and metrology groups from committee members (e.g. VIM, VIN, and various clinical laboratory societies).

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. Expanding the number of expert laboratories is a top priority. Several laboratories have been identified and will be invited in 2017. Some current expert laboratories have a much higher activity level than other expert laboratories. Encouraging and engaging lower activity expert laboratories would benefit the centers of excellence. 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.

8.2.23 C-TLM:
The activities for the standardization of serum total protein are going quite well so far. Professor Gerhard Schumann’s reference laboratory in Hannover continues the work towards the standardization of Total Protein within the auspices of this committee. The focus is on materials from NIST which could shift reference values for TP. The range is rather large so perhaps it could only be used to provide an anchor and not that manufacturers have to re-standardize. In addition, in this approach there may not be true standardization as the NIST material is albumin based and from the 1980’s and may not be traceable. In addition, there are two methods listed on the JCTLM database which adds to the ambiguity.
In addition to these activities, the IFCC network reference laboratories coordinated by C-TLM are functioning well including the HbA1c network being coordinated by C. Weykamp. Dr. Anja Kessler is acting as RELA-consultant to support the activities of the C-TLM. There is a planned meeting of the committee in Athens.

8.2.24 C-RIDL:
The C-RIDL continues to work to establish regional reference intervals. Two committee meetings will be held during the EuroMedLab Congress in Athens 2017. During these meetings the committee will discuss and decide about the plans/suggested work items/planned publications as below:

1. A new study will be conducted to compare alternative approaches (conventional and big data) for the determination of RIs.
2. When clinical decision limit (CDL) is available in clinical guidelines and to avoid confusion, the committee plans to clarify differences in concept, of the method for determination, and the utility of each. These important points will be discussed and published as a consensus paper.
3. Validation and transference of reference intervals to be published as a checklist by C-RIDL.

Planned papers:
   a) Indirect reference intervals
   b) The checklist for determining direct reference intervals
   c) The checklist for determining indirect reference intervals
   d) The clinical decision limits versus reference intervals
   e) The checklist for validation and transference of reference intervals

Article already published directly related to the C-RIDL projects:

8.2.25 C-STFT:
Two manuscripts describing the results of the final method comparisons, the outcome of the recalibration exercises and proof-of-concept studies (= reference interval studies), one for TSH, one for free T4 have been submitted to Clin Chem. The TSH manuscript has been accepted and is already published online:
The stability study of the free T4 standardization and TSH harmonization panels is ongoing and will be followed-up. Documents describing the FT4 and TSH follow-up panels, as well as the certification protocols are in preparation to establish network laboratories. The committee intends, through collaboration with IFCC EMD, to provide educational materials for manufacturers, clinicians and patients which will support the implementation of traceable assays. C-STFT has identified key stakeholders as IVD manufacturers, laboratories (& their societies/associations), clinicians/nurses (& their societies/associations), patients (Thyroid Federation International), and international/national regulators (in the broader sense). First contacts were established, among others with representatives of the clinical laboratory profession, regulatory agencies (e.g., the US FDA, the Chinese FDA), professional societies, physicians and their patients. For most TSH assays the changes after harmonization will be within 10% and within the limits for acceptable changes currently set by the manufacturers. With regard to the dissemination of the work of the C, the AACB organized a harmonization workshop, 17-18 May 2017, Sydney, Australia. It was entitled: ‘Thyroid harmonization symposium: changes in thyroid function tests – values and reference intervals’. Dr. M. Patru, represented the C-STFT.
8.2.26 C-HAT:
A new Committee on the harmonization of autoimmune tests (C-HAT) was formed in the beginning of 2017. It will continue on the activities previously done within the WG-HAT with broader scope. The committee has the following terms of reference:

- to evaluate what are the main causes of variability for a number of diagnostically critical autoantibodies.
- to identify autoantibodies where a common calibrator could reduce the inter-assay variability
- to identify or produce commutable materials that could be used as interim calibration material for autoantibody assays.
- to produce well-characterized pure antibody preparations with known concentration and identity and use these to transfer values to a matrix preparation.
- to evaluate the impact of new reference materials on the variability of autoantibody tests and identify areas where further harmonization would improve diagnostic accuracy.

EULAR has expressed some interest to collaborate. CERM-DA483/IFCC (Immunoglobulin G proteinase 3 anti-neutrophil cytoplasmic autoantibodies (IgG PR3 ANCA)) in human serum reference material is now released.

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 is in final development. The method developed is an HPLC-ID-MS/MS measurement procedure based on peptide mapping and calibration with recombinant expressed HbA0 and HbA2 standard materials, traced back to SI units. The next step will be to validate the procedure in order to be able to assign the HbA2 values to the certified reference materials that have been developed in collaboration with the JRC. A joint meeting is planned between the WG and JRC in Athens to discuss this further. A new member has joined from Singapore which is important considering the prevalence of thalassemia syndromes is very high in that part of the world.

8.3.36 WG-CDT:
The final manuscript describing validation of the cRMP according to ISO15193 and its use was published in The Epub in ClinChimActa at the end of December 2016. The procedure is also now submitted to JCTLM. The WG is active to set up the network (three laboratories have joined so far) and actively looking for other partners. Manufacturers are keen to standardize even this year. 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 Laboratory Working Group (LWG) of the National Kidney Disease Education Program (NKDEP), USA. 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 WG-SAU is also currently developing recommendations for UA total allowable error (TEa), precision and bias goals to support standardization efforts.
manuscript describing recommended total allowable error, precision and bias goals for UA are under preparation. In addition to these studies and activities, 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 WG has struggled obtaining pregnancy serum samples to perform planned studies. This has been one of the main areas of focus in the last months. A new source is being explored. In addition, the prenatal testing market leader Perkin Elmer is not an IFCC Corporate Member any longer and therefore will not be involved in the PAPP-A WG. This adds an additional complexity and the WG is currently assessing the impact. A meeting of the WG is planned in Athens in conjunction with EuroMedLab. The WG chair (Dr. S. Wittfooth) is also scheduled to speak in Durban in October in conjunction with WorldLab 2017.

8.3.41 WG-GH:
The WG has started its activities and will focus on three main terms of reference:
1. To develop a commutable standard for the harmonization of the growth hormone methods.
2. To establish a reference method for GH.
3. Pharmacological testing in patients for growth hormone deficiency or excess to establish uniform cut-off values.

A pilot study is in progress, in which several serum pools of patients and healthy persons as potential "calibrators" are included, together with the WHO standard added to GH deficient serum. Several commercially available reagent products are being tested followed by LCMSMS. The hope is to show that a pool of patient samples are commutable and can be used as potential calibrators for the harmonization of the GH methods.

8.3.42 WG-SIA:
This is a joint project between ADA/EASD 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 has been investigating a reference material via C. Burns at NIBSC. This material is now available and has been value assigned. 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.

8.3.48 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:
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. Aβ1-42 CRM is almost complete and will become available at the end of the year. The WG is also developing a SRM mass-spec method for Aβ 1-42 in CSF, to qualify as a reference measurement procedure (RMP). The WG will continue to refine these materials and procedures as well as for Aβ40 which is gaining interest clinically. In addition, activities continue on the tau RMP.

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 comparability study of the two major clinical assays for CTX and PINP have 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. Quality assurance and study data have been submitted for analyses at one centre. A preliminary report has been presented at the annual meeting of the WG held in conjunction with the World Congress of Osteoporosis in Florence, 24 March 2017. A draft manuscript for each measurand has been distributed to participants and it is being finalized in preparation for submission to an appropriate peer-reviewed journal. An algorithm for the harmonization of the results from each assay will be derived.

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.
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 have been submitted to Clinical Chemistry as a series for inclusion in the same issue:
1. Recommendations for assessing commutability part 1: general experimental design
2. Recommendations for assessing commutability part 2: commutability assessment using the difference in bias between a reference material and clinical samples
The next meeting is planned for June in Athens in conjunction with 2017 EuroMedLab.
8.3.53 WG-ID (Immunosuppressive Drug):
A new Working Group will be formed coming from a project proposal submitted Dr. Loralie Langmann. In addition, LGC is active in this area and is releasing a pure tacrolimus reference material and also whole blood materials for tacrolimus and sirolimus. LGC remains keen to develop other materials. LGC is also in the process of listing these materials with JCTLM. Tacrolimus is already listed in whole blood. To avoid any redundancies, the next step is for communication to occur between the WG and LGC. Once this takes place, the Terms of References for the WG can be defined and elaborated and WG members selected.

8.3.54 WG-APO MS (Apolipoproteins by Mass Spectrometry):
The WG was established from the last IFCC SD EC meeting (Nov 2016) and has been quite active since then. A proposal for development of the overall accuracy basis, reference method as well as materials, was formulated and will be refined during the next WG meeting to be held during the Athens EuroMedLab meeting in June 2017. Key elements of the proposal include:
1. Develop a multiplexed primary Reference Measurement Procedure, preferentially including all clinically relevant serum apolipoproteins and especially serum apo(a).
2. Prepare separate primary reference materials for each individual apolipoprotein.
4. Metrological traceability to existing standards / systems of higher order (e.g. WHO-IFCC standards for apo A1 and B) should be aimed at, unless there are new insights.
5. Harmonize the total testing process, including consensus on the pre-analytical conditions, the type of matrix, the intended measurands, the units (molar) and the reference values and decision limits.
6. Ensure that terminology is compliant with relevant ISO documents, e.g. ISO 17511; ISO 15193; 15194; 15195 and the N-CPU Silver book.

8.3.55 WG-PE (Pancreatic Enzymes):
The WG was established from the last IFCC SD EC meeting (Nov 2016) and has started its activities. This WG comes from the closure of the previous C-RSE and has established the following Terms of Reference:
- To develop a primary reference method for pancreatic Lipase in Serum (if achievable).
- To develop a primary reference method for pancreatic Amylase in Serum.
- To support EC-JRC (Joint Research Centre, Directorate F – Health, Consumers and Reference Materials, formerly IRMM) in case of studies and certification of reference materials for enzymes.
Current projects:
- Optimization of a DODG based Lipase method to obtain a practical version to act as reference method.
A meeting is planned in conjunction with the 2017 EuroMedLab in Athens in June.

8.3.56 WG-FIT (Fecal Immunochemical Testing):
The WG was established from the last IFCC SD EC meeting (Nov 2016) and has started its activities. This WG has established the following Terms of Reference:
• To harmonize and/or standardize analysis of hemoglobin in fecal samples by immunochemistry (FIT)
• To standardize the pre-analytical phase
• To establish EQA and 3rd party IQC programs
• To determine impact of assay interference of Hb variants and other factors
• To determine the feasibility of developing reference materials and/or commutable calibrators

The first meeting of the WG will be held on Wednesday June 14th at the EuroMedLab/IFCC congress in Athens. The core members group includes invited experts in the field of FIT testing from around the world.

8.19 MEETINGS
8.19.60 60th SD Meeting – Durban, South Africa, October 20 – 21, 2017
8.19.61 61st SD Meeting – Milano, Italy, April 20 – 21, 2018
8.19.62 62nd SD Meeting – tbd.
8.19.63 63rd SD Meeting – tbd.