1. Executive summary

The CCQM is responsible for metrology in chemistry and biology, and its activities between 2011 and 2014 are reported here. It developed and published a strategy document in 2013 that addresses the key challenges it faces in the broad and complex field in which it operates. With a portfolio of over 130 key comparisons and over 100 pilot studies to date, it manages these by operating with eight Standing Working Groups and an additional three ad hoc groups. The president of the Consultative Committee changed in 2013, and the name of the committee has been extended in 2014 to include reference to metrology in biology, to better reflect the scope of its activities. It is planning the sub-division of its single Working Group on Bioanalysis to increase efficiency in the planning and execution of comparisons in this area.

In this three year period the CCQM has approved and published the results of 35 comparisons (29 key comparisons and six stand-alone pilot studies), with a further 20 comparisons currently in progress. These numbers compare well with the predicted 19 new comparisons which the CCQM foresees that it will start each year, attesting to the efficiency of the CCQM in the completion and publication of its comparisons. The number of new CCQM comparisons initiated each year is expected to stay stable, despite the broadening scope of the activities of the committee. This has been made possible by the CCQM developing new models of how different comparison results can be combined to underpin a broad range of measurement service capabilities. First time demonstrations and improvements of international equivalence of standards have characterized CCQM comparisons over this period and, when considered together with the fourteen technical workshops organized by the CCQM, attests to the vitality and interest in measurement science in this field. The CCQM has started its own review of the generation, formatting and presentation of CMCs, with 32 NMIs providing comprehensive comments on the subject in 2014. Proposals for modifying the structure for Chem/Bio CMCs are currently in development. The CCQM has continued its consultation process on proposals to redefine the mole with workshops organized on the subject in both 2012 and 2014, and further interaction with the International Union of Pure and Applied Chemistry (IUPAC) foreseen. The large number of scientists from NMIs wishing to participate in meetings of the CCQM has caused some logistical problems, however these issues are being addressed.

2. Scope of the CC

The CCQM is responsible for developing, improving and documenting the equivalence of national standards (certified reference materials and reference methods) for chemical and biological measurements. It advises the CIPM on matters related to chemical and biological measurements including advice on the BIPM scientific programme activities. The responsibilities of the CCQM are:

a. to establish global comparability of measurement results through promoting traceability to the SI, and where traceability to the SI is not yet feasible, to other internationally agreed references;
b. to contribute to the establishment of a globally recognized system of national measurement standards, methods and facilities for chemical and biological measurements;

c. to contribute to the implementation and maintenance of the CIPM MRA with respect to chemical and biological measurements;

d. to review and advise the CIPM on the uncertainties of the BIPM’s calibration and measurement services as published on the BIPM website;

e. to act as a forum for the exchange of information about the research and measurement service delivery programmes and other technical activities of the CC members and observers, thereby creating new opportunities for collaboration.

In order to carry out its responsibilities, the CCQM currently has eight Standing Working Groups and three ad hoc Working Groups.

Standing Working Groups:

- Organic Analysis Working Group (OAWG)
- Gas Analysis Working Group (GAWG)
- Inorganic Analysis Working Group (IAWG)
- Electrochemical Analysis Working Group (EAWG)
- Bioanalysis Working Group (BAWG)
- Surface Analysis Working Group (SAWG)
- Key Comparisons and CMC Quality Working Group (KCWG)
- Strategic Planning Working Group (SPWG).

Ad hoc Working Groups:

- Ad hoc Working Group on the Mole
- Ad hoc Steering Group on Microbial Measurements (MBSG)
- Ad hoc Working Group on CMC Generation, Formatting and Presentation.

3. Strategy

The CCQM strategy document was first published on 23 May 2013, with a revised version published on 30 January 2014. The detailed list of CCQM comparisons for the period 2013-2023 was updated and published on 1 July 2014.

The strategy addresses the diverse and challenging nature of metrology in chemistry and biology and the evolving and expanding measurement service and hence comparison needs in this area. It foresees the execution of 19 CCQM comparisons annually for the period 2013-2023 to cover measurement service comparison needs for NMI standards and measurement services in chemistry and biology. The CCQM strategy responds to three key challenges:

1. the requirement to develop and maintain an effective, efficient and manageable programme of comparisons to underpin the broad range of measurement standards and capabilities at NMIs;
2. the need to deal with new, emerging and evolving fields;
3. the need to improve the efficiency of the CMC generation and review process and optimize their presentation and formatting in the fields of chemistry and biology.

Progress has already been made in each of these three areas.
In order to develop a manageable programme of comparisons, the CCQM Working Groups are developing a core capability approach to key comparisons, where the key comparison benchmarks NMI performance for a core capability. The performance of a NMI in a limited number of these comparisons, covering different capabilities required to deliver services, can then be used to underpin a very broad range of measurement standards and capabilities at NMIs. This has allowed the CCQM to limit its requirement for comparisons despite an ever increasing portfolio of measurement services to be compared. The strategic planning of comparisons has also allowed long-term plans to be developed by the CCQM, as well as advice on which CCQM comparisons are most effectively coordinated by the BIPM for the NMIs.

Realizing agreement on statistical analysis of comparison results to enable the rapid completion and publication of comparison reports was identified by the CCQM as a potential area for improvement. Further guidance on calculating the KCRV and its uncertainty were published by the ad hoc CCQM Working Group on the KCRV in 2013 (CCQM/13-22). Having completed its task the ad hoc WG was closed.

Each of the CCQM Working Groups has adapted its comparison programme to meet the needs of its member NMIs. Additionally, the CCQM has responded to the growing number of NMIs developing metrology in biology programmes. This has involved:

a. the establishment of an ad hoc Steering Group on Microbial Measurements, which has undertaken its first studies on comparability of methods for microbial identification and quantification;
b. planning for the potential sub-division of the Bioanalysis Working Group into expertise-based sub groups (e.g. proteins, nucleic acids, cells), to increase efficiency in the planning and execution of comparisons and effectiveness of working group activities, and to better reflect the breadth of the biosciences and their metrology needs;
c. modifying the name of the CCQM to include reference to metrology in biology, to better reflect the scope of activities undertaken by the CC.

Requirements to improve the efficiency of the CMC generation and review process and optimize their presentation and formatting in the fields of chemistry and biology were acknowledged in the CCQM strategy document. They are being addressed by the CCQM ad hoc Working Group on CMC Generation, Formatting and Presentation, which developed and reviewed (in 2013/2014) answers to a questionnaire on CMCs, with comprehensive feedback from 32 out of a total of approximately 70 institutes with declared activities in metrology in chemistry and biology under the CIPM MRA. The working group is currently developing proposals for the structure of CMCs in the chem/bio field, and these are expected to input into the general review of the CIPM MRA planned for 2015.

4. Activities and achievements since the last meeting of the CGPM

4.1. Comparisons and CMCs

In the period 1 September 2011 to 15 July 2014 an additional 877 CMCs in areas covered within the scope of the CCQM have been published in the BIPM key comparison database, bringing the total number of Chem/Bio CMCs published to 5718. During the same three year period the CCQM has approved and published the results of 35 comparisons (29 key comparisons and six stand-alone pilot studies), a further 20 comparisons are currently in progress, either in the measurement or reporting phase.
The CCQM Key Comparison and CMC Quality Working Group has coordinated the systematic review of Chem/Bio CMCs that are over five years old since 2010. Systematic review of already published CMCs has now covered eight (at least partially) of the 15 major service categories covered by CCQM activities.

4.2. Impact studies of CCQM activities and achievements in the CCQM WGs

The impact of the range of activities covered by the CCQM has been described by providing ten example impact case studies in the 2013-2023 CCQM Strategy Document. The examples chosen provide information on the benefits and impact of internationally equivalent measurement in the areas of:

- Healthcare
- Environmental and climate change monitoring
- Food analysis and safety
- Energy
- Advanced manufacturing
- Redefinition of SI units.

The achievements of the CCQM WGs have centred on their delivery of comparisons, and notable progress in these has included:

- A ten-fold improvement in the equivalence of standards for methane in air, a major greenhouse gas, demonstrated in 2013 in CCQM-K82 in comparison to ten years previously. The equivalence of standards is now comparable with the data quality objectives set by the World Meteorological Organization – Global Atmosphere Watch (WMO-GAW) for atmospheric monitoring. The limiting factor for the accuracy of these standards was identified as the challenge in achieving accurate measurements of trace methane in nitrogen, a topic where further development in measurement techniques is foreseen.

- Demonstration of previously unknown instrument and procedure dependency of measurement results for Practical Sea Salinity, as revealed by the results of CCQM-P142. These potential sources of bias were previously unobserved by the oceanographic community, as their current calibration and measurement salinity rely on a single type of instrument and seawater standard. Accurate and precise measurements of seawater salinity are used by the oceanographic community for long-term monitoring of the environment. The measurement issues revealed by the CCQM study are being studied further through international collaborations both within the Joint Committee on Seawater (JCS), endorsed by The International Association for the Properties of Water and Steam (IAPWS) and the Scientific Committee on Oceanic Research/the International Association for the Physical Sciences of the Oceans (SCOR/IAPSO), and the EAWG.

- Dramatic advances have been made during the past seven years by NMIs/DIs in undertaking inorganic speciation analysis which is a key measurement service for research in nutrition, health and cancer diagnosis/treatment. These advances were clearly illustrated by the results reported for CCQM-K107/CCQM-146 in 2013. Using isotope dilution mass spectrometry, the participants achieved measurements of Se methionine in human serum at a concentration of 25 µg/kg with a KCRV uncertainty of about 2.5 % whilst working with the limited sample size (about 1 ml) typical for this type of clinical application. This should be compared with CCQM-P86 in 2006 where participants reported measurements of the same analyte in a less demanding yeast
matrix, provided as tablets in large pharmaceutical packs, at a concentration of 575 mg/kg (i.e. 23,000 times higher than CCQM-K107) with a relative standard deviation of about 8%.

- Recent completion the first cell measurement comparison (CCQM-P102) demonstrating equivalence in capability in flow cytometric measurement of CD4+ cell concentrations, and documenting the associated measurement uncertainty. Measurement of CD4-positive (CD4+) T-cells is an essential tool for the laboratory monitoring of HIV infected patients. The final report was circulated to a number of interested stakeholders including WHO, INSTAND, EQUALIS and DGKL.

- Coordination of a series of strategic key comparisons, planned by the Organic Analysis Working Group liaising with the BIPM Chemistry Department, to underpin organic purity assessment. This measurement area is critical for the traceability of the highest order calibrants used across a large number of sectors, and essential for the preparation of the matrix materials that NMIs and DIs produce as accuracy control materials. The comparisons have entailed in-depth analyses of indirect and direct purity analysis techniques permitting the BIPM and NMIs to draft an IUPAC Guidance Document on Purity Assessment techniques which will be highly valuable to the analytical chemistry community.

- Benchmarking for the first time the accuracy of thin functional alloy film composition measurement, through the pilot study and subsequent key comparison (CCQM-P108 and K129), to address stakeholder needs for traceable, repeatable and reproducible measurement methods in advanced manufacturing, specifically in the fields of electronic devices, data storage devices and energy harvesting.

4.3. Redefinitions of the SI units

The CCQM has followed up on its statement from 2011 ‘on the need for further consultation over the possible redefinition of the mole’, with the organization of two workshops on the topic in 2012 and 2014. In 2012, IUPAC was invited to reconfirm their statements in support of the redefinition of the mole in 2009, which they did. In 2014, the CCQM invited a selection of authors who had published papers against redefinition to give presentations at the workshop to explain their views. The CCQM has been invited to make a presentation on the redefinition of the mole at a meeting of the American Chemical Society, and members of the CCQM are active in the recently established IUPAC project entitled ‘A critical review of the proposed definitions of fundamental chemical quantities and their impact on chemical communities’, which will undertake a critical review of the definitions for the quantity amount of substance and its unit, mole, as well as the related unit of the quantity mass.

NMIs that are CCQM members have carried out measurements of silicon isotope ratios in silicon samples being used in the Avogadro project, which is contributing to the redefinition of the kilogram. The mass spectrometric approaches used were presented and methods discussed in a CCQM IAWG workshop on the Avogadro and other related mass spectrometric measurements (2011).

The use of dimensionless quantities in the biosciences and chemistry, and the common use of pseudo units to represent the unit 1, led the CCQM to request the development of further guidance on use of units in this area by the Consultative Committee for Units (CCU). The ad hoc WG created by the CCU in 2014 to address this issue includes CCQM experts from both the chemical measurement and bioanalysis fields.
4.4. Technical workshops on specific areas of measurement science in chemistry and biology

The CCQM working groups have organized fourteen technical workshops over the period to transfer knowledge on new measurement techniques and best practice. The topics and highlights of these were:

- Gas standards for atmospheric measurements (2011), concentrating on the collaboration between the CCQM and the WMO in atmospheric measurements, especially in greenhouse gases;
- A Workshop on Microbiology Measurements for Food Safety (2011), which led to the development of two study focus areas: microbial quantitation and molecular identification. Both focus areas have yielded promising initial studies including a manuscript on measurement uncertainty for microbial DNA sequence identity;
- The Avogadro project and related mass spectrometry (2011) highlighted the key contribution of inorganic spectroscopy for isotopic analysis and molar mass determination of the Si spheres required for SI unit redefinitions;
- New and specialized measurement techniques (with invited expert laboratories, 2011) highlighted two key issues in inorganic instrumental analysis: the need to provide metrological underpinning for rapidly evolving new areas, such as laser ablation inductively coupled plasma mass spectrometry (ICP-MS), and the continued requirement for existing techniques such as neutron activation analysis (NAA) and gas analysis of metals;
- Clinical and bio-analysis (2011) highlighted the important contribution being made by CCQM participants in developing advanced analytical techniques essential to clinical and healthcare research;
- Inorganic research projects in the European Metrology Research Programme (EMRP) (2012) presented research outputs of interest to the global network provided by the CCQM;
- Biomeasurement in support of the clinical diagnostics community (2011) discussing measurement research being undertaken to address the significant challenges of protein and nucleic acid biomarker measurement and RM development for clinical diagnostics including cardiac troponin, infectious diseases and methylation standards for cancer prognostics;
- Measuring molecular adsorption at the solid-liquid interface (with the International Union for Vacuum Science, Technique and Applications (IUVSTA), 2012), highlighting the requirement to develop metrologically underpinned methods of surface chemical analysis with relevance to manufacturing of reliable biosensing devices for clinical diagnostics;
- Mass spectrometry and molecular structure metrology research underpinning the development of bio and chemical reference material and NMI measurement capabilities (2012), highlighting new generation (ion mobility, HDX, CE-MS, FFF) mass spectrometric capabilities of the NMIs applied to the challenge of complex protein characterization and structural measurement;
- SI traceable elemental calibration (2012) highlighted the challenges of providing SI traceable inorganic measurements;
- Carbon dioxide and methane isotope ratios standards (with the International Atomic Energy Agency (IAEA) and the BIPM, 2013), highlighting the developments in optical methods for isotope ratio measurements from traditional mass spectrometric methods and the requirements for new certified reference materials for their calibration;
Bio and Chemical Measurement Research Challenges and New Developments (2013) describing emerging techniques (super-resolution microscopy, dPCR, CARS/SHG, NMR) primarily focused towards accurate single molecule measurement and purity determination;

New measurement techniques in gas metrology (2013), to share the information on the latest techniques of gas analysis and standards preparation;

Isotope ratio measurements of the light elements (with invited expert laboratories, 2014) highlighted the need for SI traceability of isotopic delta values and measurement research which is working towards this long-term goal.

In addition, a workshop on the achievements and future challenges for the CCQM was organized in 2013 to coincide with the twentieth anniversary of the formation of the CC, and to provide a discussion forum for input into the CCQM strategy document. Advances made through CCQM activities in isotope dilution methods for organics, purity analysis, neutron activation analysis for inorganics and digital PCR for DNA quantification were highlighted. The potential for applying new measurement techniques and standards in the field of forensics was presented.

4.5. Dissemination of CCQM activities
The CCQM has undertaken to improve processes for dissemination of information. As of 2012, the CCQM has started to disseminate its decisions and actions within the two weeks following the plenary session, with the reviewed report of the plenary meeting published typically within four months following the meeting. In addition, increasing the number of publicly available presentations and reports is foreseen.

4.6. Challenges and difficulties
Three main challenges have been identified for the CCQM in the strategy development process and actions are under way to address these (see Section 3).

The CCQM, with responsibility for metrology in chemistry and biology, arguably covers fields of measurement science that are as broad as, or broader, than all the other CCs combined. The CCQM has managed this by developing a measurement expertise-based working group structure. The meetings of working groups have often been collocated in order to maximize synergy and cross-fertilization between them. The interest in and success of the activities of the CCQM working groups has resulted in more than 200 scientists attending these meetings. Accommodating meetings of the working groups now poses a challenge both for the BIPM and NMIs. This issue is being addressed by the CCQM SPWG, with proposals to reduce the number of working groups that meet simultaneously in one location at any one time, and that the main meetings of the working groups will not coincide with the plenary session. A new meeting schedule for the CCQM WGs is planned to be implemented in 2016.

The CCQM has historically organized a considerable number of pilot studies, and on occasion invited guest laboratories to participate, where their participation would add scientific value to the study. The continued interest from potential guest laboratories in participating in these studies together with concerns to ensure that the results of the studies are used appropriately has led the CCQM to develop a formal process for requesting, reviewing and accepting guest laboratory participation in pilot studies. The process was approved by the CIPM for implementation by all CCs.
5. **Outlook in the short and long term**

The scope of the CCQM is very diverse and complex and should provide for evolving and expanding measurement service needs. Specific examples of important issues and trends in various sectors that are likely to drive the development of NMI services are given below. Future CCQM comparisons would then be selected to establish the international equivalence of these measurement standards and services:

- **Healthcare**: Reference measurement systems for diagnostics, traceability of quantitative measurements of nucleic acids, proteins, polysaccharides and cells to the SI including high accuracy purity assessment; systems biology support (e.g. combined ‘omic’ approaches covering lipids/cells/genes/proteins…) including interactions in immune systems; measurements to support bio/pharmaceutical identity, quality, safety and efficacy.

- **Food safety and nutrition**: Residue and contaminant quantification, microbial identification and quantification, nutrient quantification, food constituent labelling, food provenance.

- **Environment**: Reference measurement systems for: Long-term global, direct and remote monitoring of greenhouse gases; development of emission controls on toxic and reactive gases from industrial activities to atmosphere and the workplace; particulates and nanoparticles; semi-volatile organic compounds in indoor and urban air including real-time analysis of composition; isotope ratio measurements for sensitive environmental studies; water quality.

- **Energy**: Diversification in the supply of energy gases (e.g. biogas, coal mine methane, shale gas); dissolved gas in water (e.g. methane and methane hydrates); emerging hydrogen economy (e.g. measurements of impurities in hydrogen); usable energy from bio-waste; industrial biotechnology (harnessing sustainable microbial energy); chemico-physical properties of biofuels; state of health and charge of energy storage systems (e.g. batteries in the automotive sector); injection of non-conventional gases into existing gas grids; alternative technologies in photovoltaic systems.

- **Advanced materials**: Development of metrologically underpinned characterization tools and protocols for analysis of nano-structured surfaces, nano-particles. Research towards traceability of toxicity measurements will focus on chemical and biological characterization of nano-particles; development of new materials with functional surfaces including, biomaterials, metamaterials, and hybrid materials; electrochemical sensors to monitor and feed-back on the performance of smart materials; embedded chemical sensors in intelligent buildings.

- **New technological requirements**: The range and complexity of analytes covered by the CCQM is expected to expand. This will require technological developments including the development of primary calibrators and reference measurement systems for new and more complex analytes and the development of an international metrological infrastructure for biological measurements.
Annex: CC Data

CCQM set up in 1993
President: W. E. May
Executive secretary: R.I. Wielgosz
28 members and 12 observers

Membership:

Meetings since the 24th CGPM meeting:
19-20 April 2012 / 18-19 April 2013 / 10-11 April 2014
Full reports of the CCQM meetings:

8 Working Groups:
- Organic Analysis (OAWG);
- Gas Analysis (GAWG);
- Inorganic Analysis (IAWG);
- Electrochemical Analysis (EAWG);
- Bioanalysis (BAWG);
- Surface Analysis (SAWG);
- Key Comparisons and CMC Quality (KCWG);
- Strategic Planning (SPWG);

3 ad hoc Working Groups:
- ad hoc Steering Committee on Microbiological Measurements (MBSG);
- ad hoc WG on the Mole;
- ad hoc WG on CMC Generation, Formatting and Presentation

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<th>In progress</th>
<th>Planned [to 2015]</th>
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<td>CCQM key comparisons (and supplementary comparisons)</td>
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<td>CC (stand-alone) pilot studies</td>
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<td>8</td>
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<td>CMCs</td>
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<td>5718 CMCs in 67 service categories Increase of 877 CMCs since 1 September 2011</td>
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