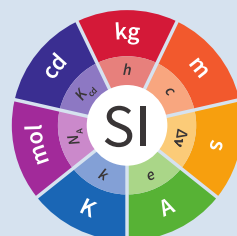


BIPM-WADA Workshop: Standards Metrology in support of Anti-Doping Analysis

1st edition 2016



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BIPM-WADA Workshop: Standards and Metrology in support of Anti-Doping Analysis

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1. Introduction

A joint BIPM-WADA Symposium on Standards and Metrology in support of Anti-Doping Analysis was held on 28 and 29 September 2016 at the BIPM in Sèvres, France. In addition to WADA Science Department and BIPM staff, participants included invited parties from WADA-accredited laboratories, National Metrology Institutes (NMIs) and representatives from the clinical chemistry and laboratory medicine communities. A total of 95 scientists from 35 countries registered for the meeting.

The rationale for organizing the Symposium was to bring together experts from both communities to review the recent developments in chemical metrology and in anti-doping science in order to:

- Facilitate the development of new tools and strategies for the harmonization of analytical practice applied to the fight against doping in sport;
- Explore possibilities for the application of the expertise of NMIs in the provision of reference measurement systems to the particular challenges required to underpin and further develop anti-doping analysis.

2. Aims

The aims of the symposium were:

- to assess current needs and emerging priorities for the provision of reference materials and reference measurement systems to support activities in anti-doping analysis;
- to discuss the implementation of inter-laboratory comparisons to demonstrate equivalent measurement results for quantitative and qualitative analysis for prohibited substances and endogenous markers;
- to share knowledge on the latest approaches used in NMIs, clinical chemistry and anti-doping laboratories for the detection and quantification of chemical and biological analytes in urine and blood matrices.

3. Programme of the Symposium

The Symposium was officially opened by Mr Thierry Braillard, the French Secretary of State for Sport, attached to the Minister of Urban Affairs, Youth and Sport with additional contributions by the Chair of the WADA Health and Medical Research Commission, Dr Valerie Fourneyron, and by the Director of Special Projects at NIST, Dr Richard Cavanagh.



Figure 1 — Official Opening (L. to R: Dr Olivier Rabin, M. Pierre Soubelet, M. Thierry Braillard, Dr Valérie Fourneyron, Dr Martin Milton, Dr Robert Wielgosz, Dr Richard Cavanagh (standing))

The opening session was followed by six technical sessions with presentations focused on:

- Reference material requirements for anti-doping analysis;
- Measurement uncertainty of determinations of threshold substances;
- Roles of comparisons and EQAS studies;
- Measurement systems for quantitative biomolecule analysis;
- Measurement support for qualitative analysis.

The Symposium speakers were drawn equally from the anti-doping laboratory community and from NMI or clinical chemistry reference laboratories. The presentations from the anti-doping community were focused on the measurement challenges and practical aspects relevant to their field, whilst the presentations by speakers from the reference measurement community were tailored to the linkage of higher order reference measurements and good practice in metrology which were relevant to the specific challenges and requirements of anti-doping analysis.

The full programme for the Symposium is reproduced in Appendix 1. The various speaker presentations are available from a [dedicated area](#) on the BIPM website.

In addition to the Symposium, a press conference and Q&A session on anti-doping measurement was held separately in the Grand Salle of the BIPM with participation by Dr Valérie Fourneyron, Chair, WADA Health, Medical and Research Committee; Dr Martin

Milton, Director, Bureau International des Poids et Mesures; Dr Olivier Rabin, WADA Senior Director, Science; and Dr Robert Wielgosz, Director of the BIPM Chemistry Department.



Figure 2 — Press Conference, Grande Salle BIPM (L. to R: Dr Martin Milton, Dr Robert Wielgosz Dr Olivier Rabin, Dr Valérie Fourneyron)

4. Outcomes and Recommendations of the Symposium

The Symposium concluded with a review and summary of the measurement issues raised within the course of the two days of talks. As a result, actions were agreed upon and collaborations identified as opportunities to deliver further metrological support for anti-doping analysis. There was a high level of satisfaction expressed with the quality of the individual presentations and the excellence of the scientific work described, as well as with the depth of the constructive discussions accompanying each session.

In terms of the availability of pure substance reference materials covering the “small” organic compounds that make up the bulk of the Non-Threshold substances on the WADA List of Prohibited Substances and Methods, it was felt by the majority of participants that many current needs were suitably addressed. The remaining areas of need identified for pure substance materials included:

- substances recently added to the list of Threshold Substances (e.g. formeterol), which require a fully characterized and documented CRM;
- long-term (Phase I and II) metabolites of exogenous doping compounds, particularly anabolic steroids, which are required to extend the detection window for these substances;
- compounds under development by pharmaceutical companies which are potentially open to abuse for purposes of doping.

Given the need at times for fit-for-purpose, suitably characterized reference materials to rapidly respond to the emergence of new types of doping compounds, it was suggested that there would be value if NMIs could either develop “quick response” service of this type or could provide guidance to laboratories as to the minimum requirements to undertake for an “in house” characterization.

The need to establish and make readily available a standardized summary of the current reference material needs and priorities of the anti-doping community was emphasized. Previous experience had shown that direct contact with the laboratories did not yield sufficient response, and in any case the information obtained was not readily made available to other parties. It was proposed that WADA establish, through consultation with the anti-doping laboratories and the World Association of Anti-Doping Scientists (WAADS), a prioritized and periodically updated list of reference material requirements that could be made available by the BIPM to the NMI community to aid in the development of their work programmes.

Another common theme of the discussions was recognition that there is a commonality of interest between the technical challenge for the provision and support of reliable measurements in laboratory medicine, in the detection of doping with peptides and proteins and for the delivery of the Athlete Biological Passport programme. In this regard the availability of EQAS comparisons organized in the clinical chemistry area that are relevant to the detection of analytes monitored in doping analysis should be investigated, with a view to the potential participation of anti-doping laboratories in suitable comparisons.

The important role of NMIs to provide a reference measurement infrastructure to underpin existing and emerging analytical challenges in anti-doping analysis was emphasized repeatedly in the course of the discussions. There is a need for reference procedures for the quantitative measurement of biomolecules, in particular hGH and IGF-1. The development of higher-order reference methods for the measurement of these compounds in urine and serum, based on quantitative LC-MS methods would provide multiple advantages over the immunoassay-based methods currently provided by the commercial IVD manufacturers, and

could serve to support a switch to the use of direct LC-MS based routine measurements in the future.

In addition to the provision of reference materials and higher-order reference methods NMI support in the form of guidance and knowledge transfer to anti-doping laboratories on good metrological practice in such areas as method validation, quality control, the use of reference materials and the estimation of the measurement uncertainty of results would also be highly valued.

The presentations on best practice for the MU assignment of Threshold substance measurements provided clear examples in the anti-doping context of both “bottom-up” and “top-down” approaches tailored to the requirements of the WADA Technical Document on Decision Limits. Similarly, useful examples were presented on establishing the LOD of qualitative methods for screening and confirming the presence of Non-Threshold substances. It was noted in the discussions in each session that there would be significant value if a document could be prepared capturing these examples in a form that could be used by anti-doping laboratories and stakeholders for educational and informational purposes.

It was recognized during the discussions that it will always be a challenge to provide the resources, in terms of staff and funding, required to allow an individual NMI to develop materials and methods intended for use by a small network of laboratories spread world-wide. It was hoped that the high public and political visibility of anti-doping analysis at both the national and international level and the advantage of heightened interest associated with the Olympic Games would assist in supporting the necessary funding for existing programmes and for the establishment of new ones. Possibilities for direct technical exchange and collaboration between anti-doping laboratories and NMIs in order to strengthen the metrological infrastructure should be investigated. The recent collaboration in Brazil between INMETRO and LADETEC during the Rio Summer Olympic Games provided a good example of this type of collaboration.

The potential for the funding of specific projects and collaborations between NMIs and anti-doping laboratories for the provision of measurement standards and methodology through WADA Research Grants, the USOC Partnership for Clean Competition and other nationally funded anti-doping research programmes should also be actively investigated.

5. Recommendations and Actions

1. Establish a Priority List of Anti-Doping Reference Material Requirements

Action for WADA:

- Produce in consultation with WAADS and the anti-doping laboratories a prioritized list of pure substance and matrix CRMs requirements including needs for:
 - Prohibited List analytes currently lacking a suitable pure substance RM;
 - Threshold Substances;
 - phase II/III and LTMs of anabolic steroids;
 - peptides/proteins;
 - matrix materials for method validation and quality control;
 - reference materials for gene doping.
- Institute a mechanism to review and update this list on a regular basis

Action for BIPM:

- When available, distribute and promote the CRM Priority List within the NMI community
- Provide feedback to WADA and the anti-doping laboratories

2. Scan for opportunities to utilize existing accuracy based EQAS for measurands relevant to doping analysis in blood/serum

Action for WADA:

- Review currently available higher level EQAS schemes in clinical chemistry for their relevance to the biomolecules that can be used for doping and make the results available to anti-doping laboratories

3. Raise awareness in Member States of the need for Measurement Standards (CRMs) in support of Anti-Doping Analysis

Action for BIPM:

- Report to NMI Laboratory Directors, RMOs and at the Member State level on the outcomes of the Symposium and promote interest in the need for Measurement Standards (CRMs) in support of anti-doping analysis with an emphasis on the high level of public and political visibility of these programmes
- Encourage in NMIs in the Asia/Oceania region to seek opportunities to develop programmes to support the anti-doping testing for the next three Olympic Games, which have all been awarded to cities located in East Asia.

Action for WADA:

- On occasions involving high-level contact with representatives of national governments and sport federations, encourage the allocation of resources to the local NMI to allow them to undertake programmes that support anti-doping analysis.

4. Make use of NMI expertise, Anti-doping laboratories and Laboratory Medicine reference laboratories to develop measurement standards and methods for analytes with relevance to anti-doping analysis

Action for WADA and BIPM:

- Encourage and facilitate further opportunities for collaboration and information sharing amongst their communities.

5. Produce documented examples of MU assignments for educational/informational purposes

Joint action for WADA and BIPM:

- In consultation with the individual presenters, prepare a guidance document for the MU assignment of Threshold Substances based on the examples reported at the Symposium

6. Share best practice on procedures to optimize knowledge transfer between laboratories

Action for WADA:

- Consider further the visiting scientist programmes that have been implemented between NMIs and the BIPM as a potential model for optimizing knowledge transfer between WADA-accredited laboratories.

7. Produce summary of recommended practice for LOD calculations

Joint action for WADA and BIPM:

- In consultation with the individual presenters, prepare a guidance document on terms, theory and best practice for the estimation of the LOD for Non-Threshold substances

Appendix 1. Symposium Agenda and List of Speakers

Agenda for BIPM-WADA Symposium 28-29 September 2016

STANDARDS AND METROLOGY FOR ANTI-DOPING ANALYSIS

Day 1 Wednesday 28th September

Official Opening

| | |
|------------|---|
| 9.00-9.05 | Opening of the meeting (Dr Robert Wielgosz) |
| 9.05-9.15 | Opening Address by the Minister of State for Sport, attached to the Minister of Urban Affairs, Youth and Sport (Mr Thierry Brailard) |
| 9.15-9.25 | Reply by the Director of the BIPM (Dr Martin Milton) |
| 9.25-9.35 | Address by the Chair of WADA Health and Medical Research Commission (Dr Valérie Fourneyron) |
| 9.35-9.45 | Address by the Director of the Office of Special Programs, NIST (Dr Richard Cavanagh) |
| 9.50-10.20 | <i>Group Photograph /Coffee Break</i> |

METROLOGY FOR ANTI-DOPING ANALYSIS: CURRENT ISSUES

Session 1 Metrology Needs and Reference Material requirements for Anti-Doping Analysis Co-Chairs: Lindsey Mackay/John Miller

| | |
|-------------|---|
| 10.20-10.40 | Overview of WADA activities and viewpoint on metrology (John Miller – WADA Lab Expert Group) |
| 10.40-11.00 | Overview of CCQM activities in organic and bioanalysis (Robert Wielgosz – BIPM) |
| 11.00-11.20 | Reference Materials for Doping Analysis (Lindsey Mackay—NMIA, Australia) |
| 11.20-11.40 | Metrology support for doping analysis at the Rio Olympics (Bruno Garrido—INMETRO, Brazil) |
| 11.40-12.00 | (Certified)RM requirements – availability and gap analysis (Peter van Eenoo – DoCo Lab, Belgium) |
| 12.00-12.30 | Discussion 1 —© RM priorities for WADA Code compliance and accreditation |
| 12.30-13.00 | <i>Press Conference (Grand Salle, Pavillon de Breteuil)</i> |
| 12.30-14.00 | <i>Lunch</i> |

Session 2 Measurement Uncertainty (MU) of Determinations of Threshold Substances (TS)

Co-Chairs: Robert Wielgosz/Peter van Eenoo

- 14.00-14.20 “Bottom up” (GUM) approaches to MU assignment for organic analytes (**Chris Mussell—LGC, UK**)
- 14.20-14.40 “Top-down” approaches to MU assignment of Threshold Substance determinations (**Peter van Eenoo—DoCo Lab, Belgium**)
- 14.40-15.00 Practical Implementation of the GUM (**Antonio Possolo—NIST, USA**)
- 15.00-15.30 **Discussion 2**—“Best (Fit-for-purpose) practice” for assigning and applying MU for TS results
- 15.30-16.00 *Coffee Break*

Session 3 **Roles of Comparisons and EQAS studies in Measurement Systems**

Co-Chairs: Steven Westwood/Victoria Ivanova

- 16.00-16.20 CCQM Key comparisons and NMI measurement services for EQAS providers (**Lindsey Mackay—NMIA, Australia**)
- 16.20-16.40 EQAS in clinical chemistry: Linking routine analysis to reference laboratory results (**Anja Kessler—RfB, Germany**)
- 16.40-17.00 Expanding the role and use of WADA EQAS studies and results (**Thierry Boghosian—WADA**)
- 17.00-17.30 **Discussion 3** – Enhancing the value of WADA EQAS studies for anti-doping analysis

Day 2 **Thursday 29th September**

METROLOGY FOR ANTI-DOPING ANALYSIS: EMERGING ISSUES

Session 4 **Measurement systems for quantitative biomolecule analysis – Part 1**

Co-Chairs: Robert Wielgosz/Osquel Barroso

- 9.00-9.20 WADA Isoform assay for detecting and reporting doping with hGH (**Martin Bidlingmaier—Endocrine Laboratory, LMU Munich, Germany**)
- 9.20-9.40 Reference measurements for hGH (**Andre Henrion—PTB, Germany**)
- 9.40-10.00 Biomarker assay for hGH and the role of IGF-1 measurements (**David Cowan – Doping Control Centre, King’s College London, UK**)
- 10.00-10.20 Reference measurements for IGF-1 (**David Bunk—NIST, USA**)
- 10.20-10.30 **Discussion 4** – Measurement systems for quantitative protein analysis
- 10.30-11.00 *Coffee Break*

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|------------------|--|
| Session 5 | Measurement systems for quantitative biomolecule analysis—Part 2 Co-Chairs: Lindsey Mackay/Peter van Eenoo |
| 11.00-11.20 | Realising traceable, comparable results for steroid hormone analysis (Hubert Vesper—Centre for Disease Control, USA) |
| 11.20-11.40 | Measurement issues for detection by GC-IRMS of doping with steroids (Thomas Piper—Sport University Cologne, Germany) |
| 11.40-12.00 | Accreditation assessment of GC-IRMS (Detlef Thieme—IDAS, Germany) |
| 12.00-12.20 | Dealing with bias in measurements of endogenous substances (Elvar Theodorsson—Clinical and Experimental Medicine, University of Linköping, Sweden) |
| 12.20-12.40 | Detection systems for gene doping (Anna Baoutina—NMIA, Australia) |
| 12.40-13.00 | Discussion 5 – Standards and Metrology for Emerging Analytical Challenges |
| 13.00-14.00 | <i>Lunch</i> |
| Session 6 | Measurement support for qualitative analysis Co-Chairs: Steven Westwood/Detlef Thieme |
| 14.00-14.20 | Determining and controlling the LOD of methods for qualitative organic analysis (Steve Ellison—LGC, UK) |
| 14.20-14.40 | Detection of doping with peptide non-Threshold Substances (Mario Thevis -Sport University Cologne, Germany) |
| 14.40-15.00 | Determination of the decision limit CC- α and detection capability CC- β for analytical methods based on mass spectrometry (Corinne Buisson -AFLD, France) |
| Session 7 | Workshop Summary and Recommendations Panel to lead discussion |
| 15.00-15.30 | Discussion 6 —Review of recommendations for metrology support of anti-doping analysis |
| 15.30-15.45 | Summary of Workshop and Recommended Outcomes Co-Chairs: Olivier Rabin, WADA/Robert Wielgosz, BIPM <i>Coffee Break and Close</i> |

Appendix 2. Group Photograph



Document Control

Authors:



