
**WORLD ANTI-DOPING AGENCY
Health, Medical & Research Committee (HMRC) Meeting Minutes
September 3-4 2014**

Participants:

Prof. Arne Ljungqvist, Chair	Attending
Prof. Kamal Al-Hadidi	Attending
Dr. Alessia Di Gianfrancesco	Attending
Prof Theodore Friedmann	Attending
Prof. David Gerrard	Attending
Prof. David Handelsman	Attending
Dr. Manikayasagam Jegathesan	Attending
Dr. John Miller	Attending
Dr. José Antonio Pascual	Attending
Dr. Andrew Pipe	Attending
Prof. Gerard Saillant	Attending
Prof. Chara Spiliopoulou	Attending
Dr. Jürgen Michael Steinacker	Attending
Prof. Hidenori Suzuki	Attending
Dr. José Veloso	Attending
Prof. Jiri Dvorak	Apologies
<u>WADA Staff</u>	
Dr. Osquel Barroso	Attending
Dr. Irene Mazzoni	Attending
Dr. Olivier Rabin	Attending
Dr. Alan Vernec	Attending

Observer

Prof. Fabio Pigozzi (IUSM, University of Rome) representing FIMS.

1. Welcome and Review of the Agenda

- Mr. David Howman, WADA Director General and Prof. Arne Ljungqvist, WADA vice-President and Chairman of the Health, Medical and Research Committee (HMRC) welcomed the Committee members.
- Mr Howman thanked the members for dedicating their time and contributing with their expertise to the activities of this important WADA Committee. Mr Howman then left the meeting.

2. Review of 2015 Prohibited List, report from the List Expert Group and recommendation to the WADA Executive Committee

- The Draft of the 2015 Prohibited List, prepared by the List Expert Group (LiEG) was presented by Dr. Andrew Pipe, Chair of the LiEG. Dr Pipe reminded the Committee that the 2014 List had been modified in June 2014 following reports from the Winter Olympic Games in Sochi and the Hypoxia Inducible Factor (HIF) activators (e.g. xenon, argon) had been explicitly named on the List. The revised 2014 List came into effect on September 1 2014.
- For 2015, there were a number of modifications introduced in the List, many of which were inclusion of examples to make it more informative and explicit where justified.
- All of the LiEG proposed changes were accepted by the HMRC. It was decided that the resulting draft List would be recommended to WADA's Executive Committee for approval. The differences from the 2014 were as follows:
 1. S1. Anabolic Agents: Changes were made to reflect current scientific nomenclature; an example of testosterone metabolite was added.
 2. S2. Peptide Hormones, Growth Factors, Related Substances and Mimetics: The title of the section was changed and mimetics were added to reflect that synthetic analogs were also prohibited; the Erythropoietin Stimulating Agents group was expanded and non-erythropoietic EPO-Receptor agonists added; subdivisions were introduced, some substances re-classified and many examples added.
 3. S4. Hormone and Metabolic Modulators: Trimetazidine, originally in S6.b based on structural similarity to stimulants, was moved to S4 due to its pharmacological properties as a modulator of cardiac metabolism; AMPK activators were re-described based on current nomenclature.
 4. S5. Diuretics and Masking Agents: "Other" was deleted from the title since diuretics could not only be abused as masking agents but also for other properties such as weight loss; the last paragraph was reworded for clarity.
 5. M2. Chemical and Physical Manipulation: The term "surgical procedures" was added to the exceptions of intravenous infusions or injections permitted when medically required.
 6. S6. Stimulants: It was clarified that ophthalmic imidazole derivatives were also exceptions of permitted stimulants; phenmetrazine was moved from S6.a to S6.b because fenbutrazate (in section S6.b) could metabolize to phenmetrazine; it was clearly identified that the whole family of phenethylamines was prohibited, reflecting growing number of illegal designer stimulants derived from phenethylamine.
 7. S8: Glucocorticoids: Glucocorticosteroids were now described as glucocorticoids to reflect current medical nomenclature.
 8. P1. Alcohol: Karate was removed from this section following the request from the International Karate Federation.
 9. P2. Beta-blockers: The World Underwater Federation (CMAS) was added to this section upon their request to prohibit beta-blockers in-competition for certain disciplines.
 10. Monitoring Program: In order to detect potential patterns of abuse, telmisartan and meldonium were added to the 2015 Monitoring Program to assess potential abuse in sport. Following sufficient collection of data leading to clear conclusions, monitoring of pseudoephedrine below 150 microgram per milliliter will cease in 2015.

- Dr Pipe informed the HMRC of other issues discussed during the last LiEG meeting on 28-29 August 2014.
 1. Cannabis decision limit: the LiEG expressed their concerns that the reporting threshold of cannabis adopted in 2014 was too high to be useful to catch cheating athletes. In addition the LiEG discussed and will continue discussing new methods to distinguish recent (i.e in competition) from past cannabis consumption.
 2. Section S7 (Narcotics) would be re-examined in 2015 to see if inclusion of other pain killers would be warranted.
 3. Section S9 (Glucocorticoids) would be re-examined in 2015 to attempt to establish thresholds to distinguish permitted from prohibited routes of administration.

3. Report on the International Olympic Committee (IOC) additional funds for research.

- The Committee discussed the additional funds for research that the IOC had offered. The IOC had allocated ten million dollars for innovative scientific research projects with the condition that the contribution would be matched by the governments. The matched funds would be given to WADA for research, and governments had until November 16, 2014 to express their intention to contribute to the fund.
- The terms of administration of the funds would be negotiated after the November deadline. The HMRC considered that WADA was the best venue to review and administer the funds, given its 13 years' experience with the WADA-funded Scientific Research Program. The Committee considered it counterproductive to create a new entity to administer these funds and/or review the grants, as it would represent duplication of efforts, resources and time.
- The HMRC decided to write a letter to WADA's president Sir Craig Reedy thanking IOC for the initiative and offering any advice and support deemed necessary.

4. Review and recommendation for the 2014 research projects

- Conflict of interest was declared by Dr. Pascual for research involving IMIM, Spain. The implicated HMRC member left the meeting room while these projects were presented and discussed, and decisions on approval and funding were made.
- Prof Handelsman and Dr Pascual, the HMRC members who were part of the Program Review Panel (PRP), presented the conclusions and recommendations of the PRP to the HMRC. The PRP had met on September 2 and had reviewed the grants based on the independent external reviewers' evaluations as well as the PRP's own assessment.
- A record number of 116 research projects were received following the 2014 Call for Grants. Four research categories were included (*Detection of Prohibited Substances/Methods: Methodologies in Analytical Chemistry; Detection of Prohibited Substances/Methods: Affinity-binding and Biochemical Methodologies; Detection/Identification of Novel Doping Trends; Pharmacological Studies on Doping Substances/Methods*).
- The HMRC considered the recommendations from the PRP and discussed in more detail several applications.
- As a result, 30 projects were selected and recommended for funding.
 - For 17 projects, budgetary revisions were recommended.

- Three projects were considered important but uncertain. Therefore, pilot projects of one year duration were recommended with greatly reduced budgets, with further evaluation of the outcomes to be made at the end of the granting periods.
- Three extension projects were approved, as results from the initial proposals were sound and important for anti-doping.
- One project was approved in half because the experiments planned for the other part of the proposal had already been conducted by another research group.
- Four projects were approved but were requested to focus on particular points that were more relevant to anti-doping.
- One project had its budget reduced because expenses for new equipment were not approved.
- Two projects that were complementary were approved with the condition that the investigators collaborate and produce a single report at the end of the granting period.
- Two other projects that were complementary and from the same research group were approved with the condition that the investigators avoided overlaps and produce a single report at the end of the granting period.
- In addition to the regular call for grant, one out of a total of three reactive projects aimed at detecting xenon gas was reviewed and approved as well.
- In view of the increasing amount of grants received each year, it was proposed to slightly modify the reviewing process. It was decided that grants that WADA Science Department considered outside the themes of the call for grants would be separated and sent to the PRP for a quick review. If the PRP agreed with WADA Science Department appreciation, these grants would not be further considered. They would be subsequently presented "For your information" to the HMRC during their annual meeting, including the reason why they were not pursued.

5. Report from the TUE Expert Group

- Prof. David Gerrard, Chair of the TUE Expert Group (TUEC) gave an update on the group's activities during 2014, informing that:
 1. WADA Medical Department activities: included screening and monitoring TUEs from all over the world. In terms of diagnostic class, most TUEs from 2013 related to nervous system diseases, followed by endocrine and metabolic diseases (mostly diabetes). Regarding the drug category, glucocorticoids represented about a third of all TUEs received during 2013, followed by stimulants at 21% and hormone and metabolic modulators (most frequently insulin).
 2. ADAMS: WADA TUEC continued to stress the importance of using ADAMS for TUE applications especially in the interests of collating athlete information and working towards the mutual recognition of TUEs for elite performers at major events.
 3. TUE Physician Guidelines: the genesis of these documents is the belief that all athletes deserve consistent clinical management. Recent updates and revisions include Guidelines for the diagnosis of adrenal insufficiency, neuropathic pain (for disabled athletes), cardiovascular conditions, musculoskeletal conditions, attention deficit hyperactive disorder and inflammatory bowel disease. All documents are available on the WADA website.
 4. Paris TUEC Symposium: scheduled for 24 October this Symposium is aimed at TUEC physicians and it was being recommended that TUEC experts from all Federations should attend. The aim is to enhance collaboration, discuss difficult

issues, educate physicians and share knowledge and experience. An audience of 150 is expected and the endorsement of the French NOC and presence of Mme Fourneyron, the incoming HMR Chair will add particular significance to this important meeting.

8. Report from the Laboratory Expert Group

- Dr. John Miller , Chair of the Laboratory Expert Group (LabEG), gave an update on the LabEG activities during 2014:
 1. The regular tasks of the LabEG consisted in directing the process of accreditation and re-accreditation of anti-doping laboratories, evaluating laboratory performance in accordance with the International Standard for Laboratories and applicable Technical Documents, assessing the laboratory results of the WADA External Quality Assurance Scheme (EQAS) rounds, providing information to the laboratories to ensure better practice and better harmonization, reviewing any technical issue on the operation of the anti-doping laboratories, taking part in the WADA laboratory site visits, revising laboratory related documents and providing recommendations regarding laboratory performance to WADA decision bodies for final decision.
 2. There were thirty two WADA-accredited laboratories.
 3. There were two Probationary Laboratories:
 - i. Ankara (Turkey): currently in the process of re-accreditation after its revocation in July 2011; the final accreditation test should take place in late 2014 or early 2015.
 - ii. Doha (Qatar): the pre-probationary site visit took place in May 2014 and should start participation in WADA EQAS in September 2014.
 4. There were three Candidate Laboratories:
 - i. Rio de Janeiro (Brazil): accreditation was previously revoked in August 2013 and subsequently approved for the fast-track re-accreditation process. The laboratory moved to a newly built facility. The pre-probationary site visit took place in August 2014.
 - ii. Buenos Aires (Argentina): not much progress made, actions were constantly postponed. The government and National Olympic Committee were supportive of the establishment of the laboratory. The final decision would be made by the autumn of 2014.
 - iii. Cairo (Egypt): Excellent facilities were available but personnel had little experience. A Technical Questionnaire was to be completed by November 2014.
 5. Several site visits occurred in the past 12 months: Russian Federation (Moscow/Sochi for Winter Olympic Games), Cuba (Havana), Sweden (Stockholm), South Africa (Bloemfontein), Ankara (Turkey) (for Pre-probationary test) and Colombia (Bogota) in 2013 and Portugal (Lisbon), Spain (Madrid), Qatar (Doha) (for Pre-probationary test) and Brazil (Rio de Janeiro) (for Pre-probationary test) in 2014. There were four more visits scheduled for 2014: Ankara (Turkey) (for Final Accreditation Test), Greece (Athens), Poland (Warsaw) and possibly Romania (Bucharest).
 6. The LabEG had discussions with several directors to address laboratory issues.
 7. The LabEG expressed some reservation to WADA Standards and Harmonization Department with regards to the Technical Document on Sport Specific Analysis. That included the need of representation of a laboratory director in the decision making, the need of a pilot project and assessment of results before implementation, the need of a cost/benefit analysis and the fact that the methodologies for the analysis of some

prohibited substances were not sufficiently developed at the moment to be applied in routine analysis.

8. The EQAS was progressing as according to schedule, the number of double-blinds per year increased from 2 to 3 and Documentation Packages were requested for the first time in 2013 and were currently being assessed.
9. EQAS for blood samples were conducted in collaboration with the EQAS Provider in Switzerland and laboratories were generally performing well. Corrective actions would be required for laboratories consistently not performing at the highest levels expected. To evaluate performance, it was agreed to apply a pilot scheme: for reticulocytes and haemoglobin: 3 non-conformities (NC) in a 12 month period or 2 consecutive NCs; for other parameters: 4 NCs in a 12 month period or 3 consecutive NCs.
10. The hGH isoform test data was statistically re-evaluated with a larger dataset to determine revised decision limits by two teams of statisticians. Results were published in a top peer reviewed scientific journal and the *Guidelines for the application of the hGH Isoform Differential Immunoassays for detection of doping with hGH in sport* was amended to include the updated decision limits. Testing of hGH resumed from June 18, 2014.
11. The WADA/USADA hGH Working Group met in July to define the new strategy on the hGH Biomarker Test to be proposed for consideration by the LabEG.
12. Six revised Technical Documents (TD) were approved by WADA Executive Committee in May 2014 and were in effect as of 1 September 2014: TD2014DL (1.0) Decision Limits for the Confirmatory Quantification of Threshold Substances; TD2014EAAS (2.0) Endogenous Anabolic Androgenic Steroids: Measurement and Reporting; TD2014EPO (1.0) Harmonization of Analysis and Reporting of Erythropoiesis Stimulating Agents (ESAs) by Electrophoretic Techniques; TD2014IRMS (1.0) Detection of Synthetic Forms of Endogenous Anabolic Androgenic Steroids by GC-C-IRMS; TD2014MRPL (1.0) Minimum Required Performance Levels for Detection and Identification of Non-Threshold Substances; and TD2014NA (1.0) Harmonization of Analysis and Reporting of 19-Norsteroids Related to Nandrolone.
13. A few laboratories were facing some challenges, including financial, managerial and organizational issues, failure to implement IRMS analysis and insufficient expertise.
14. Despite some difficulties there was overall good performance and significant progress over the years by the laboratories with regards to the EQAS, even if WADA's rules were constantly becoming more stringent and more challenging.

9. Report from the Gene Doping Panel

- Prof. Theodore Friedmann, Chair of the Gene Doping Panel (GDP) summarized the discussions that took place during the GDP meeting and the recommendations from the Panel:
 1. An update on the developments from on-going projects and goals of newly approved projects was presented during the meeting. Five new projects on gene doping and related techniques were approved in 2013:
 - i. Gurdensen –Epigenetic studies of effects of steroids on number of myonuclei, histology, histone and DNA methylation in muscle
 - ii. Pitsiladis – transcriptional response to EPO administration and the effect of confounding factors such as altitude and exercise
 - iii. Chi – effect of blood storage on miRNA and mRNA profiles
 - iv. Baoutina – validation of assay to detect Adeno-Associated Virus (AAV)-mediated gene transfer of EPO

- v. Malm – follow-up studies of protein degradation patterns to test sensitivity, specificity and effect of training, sex, altitude following autologous blood transfusion.
 2. Prof. Fatima Bosch, new member of the GDP, updated the Panel on her research interests. These included gene therapy studies in diabetes mellitus using AAV vector transfer in skeletal muscle to study insulin resistance, β -cell replication and apoptosis and islet cell inflammation; AAV gene transfer into adipose tissue; and intracisternal AAV gene transfer into central nervous system for storage disease (sulfamidase in Sanfilippo diseases)
 3. Prof. Carl-Johan Sundberg, new member of the GDP updated the Panel on his research interests. These included acute, long-term changes following training in volunteers and elite athletes at a systemic physiological level as well as muscle biopsies for detection of molecular and histological studies (e.g. miRNA, DNA methylation and histone modifications, muscle fiber switching)
 4. Prof. Lee Sweeney updated the GDP on the status of clinical studies on myostatin inhibitors. There were several types of myostatin inhibitors including follistatin or follistatin-related genes which compete for the activin receptor, anti-myostatin antibodies, soluble activin receptor and N-terminal myo-propeptide. Many pharmaceutical companies were developing these drugs to treat e.g. sarcopenia, cachexia, multiple sclerosis.
- The HMRC also discussed the progress of gene doping projects approved in the past. Some of the results were promising while others had not lived up to expectations.

10. Science and Investigation Symposium:

- The HMRC was informed that a WADA-sponsored Symposium on Science and Investigations would be held in Istanbul on October 28-29, 2014. The symposium would bring together anti-doping experts, scientists working in international organizations against drug abuse and trafficking as well as customs and police investigational forces. A Declaration with the outcomes and future actions would be presented at the end of the meeting.

11. Conference with Pharmaceutical Industry

- The HMRC was informed that there would be a meeting between WADA and governmental health and sport authorities and the major pharmaceutical companies in Tokyo in January 2015. Japan Anti-Doping Agency had been very supportive of the meeting and was involved in the organization. This meeting would be a follow up to the successful meeting that took place in Paris in November 2012 between public authorities, WADA and the pharmaceutical industry, when ways of collaboration (e.g. detection of drugs under development), were discussed. An idea for the upcoming meeting would be to bring governmental drug agencies into the picture and find ways to further inform the pharmaceutical companies about use of their drugs as doping agents.

12. Report on hair analysis.

- Since the IOC showed great interest for hair analysis as an alternative matrix to conduct anti-doping tests, WADA contacted experts in the field to further explore this possibility. The HMRC was informed that a study sponsored by l'Agence Française de Lutte contre le Dopage concluded that hair analysis could not be a front line technology for doping control although it could be useful as a supportive technique. Confounding factors included the affinity of



certain drugs depending on hair color, environmental exposure to smoked drugs. etc. In addition, the sample collection is quite invasive since the hair has to be obtained close to the follicle. In view of the above, the HMRC suggested WADA to write a position paper explaining why hair analysis would doubtfully be a widely useful technique in doping control although it could be of use as an additional test for certain substances.

Any other matters

- Since the Chairmanship of Prof. Arne Ljungqvist, who had been Chair of the HMRC since the beginning of WADA, would come to an end in December 2014, the HMRC acknowledged his invaluable contribution to the world of sports and anti-doping and expressed their immense appreciation for his tenure as Chairman of the Committee for the last 14 years, wishing Prof. Ljungqvist all the best.
- Prof. Ljungqvist thanked the HMRC and WADA's office for their contribution and support, stressing how anti-doping science had evolved so much along the years, much of it due to the funding WADA had put into research through its Science grant program. Prof. Ljungqvist acknowledged the privilege of being the HMRC Chairman since 1999 and wished the future Chairman great success.

13. Next meeting

- The next HMR Committee tentative meeting was scheduled for **September 1-2, 2015**, while that of the Program Review Panel would take place on **August 31 2015**
- The meeting was adjourned.