

**WORLD ANTI-DOPING AGENCY
Health, Medical & Research Committee (HMRC) Meeting Minutes
August 27-28 2013**

Participants:

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| Prof. Arne Ljungqvist, Chair | Attending |
| Dr. Alessia Di Gianfrancesco | 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 |
| Dr. Babette Pluim | Attending |
| Prof. Chara Spiliopoulou | Attending |
| Dr. Jürgen Michael Steinacker | Attending |
| Prof. Hidenori Suzuki | Attending |
| Dr. José Veloso | Attending |
| Prof Theodore Friedmann | By teleconference for Gene Doping Panel review |
| Prof. Kamal Al-Hadidi | Apologies |
| Dr. Jiri Dvorak | Apologies |
| Prof. Gerard Saillant | Apologies |
| <u>WADA Staff</u> | |
| Dr. Osquel Barroso | Attending |
| Dr. Irene Mazzoni | Attending |
| Dr. Olivier Rabin | Attending |
| Dr. Alan Vernece | Attending |
| <u>Observer</u> | |
| 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 and introduced Dr. José Veloso, a new HMRC member.
- 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 2013 Prohibited List, report from the List Committee and recommendation to the WADA Executive Committee

- The 2014 Draft of the Prohibited List, prepared by the List Committee (LC) was presented by Dr. Andrew Pipe, Chair of the LC. The modifications introduced were minimal because the LC believed that there were no needs for substantial changes, especially considering that the revision of the World Anti-Doping Code was going to be finalized in November and consequently different rules might be applicable. Many of the changes were on the wording of some provisions as well as on the chemical nomenclature of some compounds named on the List.
- All of the LC 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 2013 were as follows:
 1. Use of International Non-proprietary Names (INN)

With the assistance of the World Health Organization (WHO), the nomenclature of some substances on the List was updated to the INN. To help stakeholders, the previous name was retained and no substance was deleted.
 2. S1. Anabolic Agents

Changes were made to the definitions of "exogenous" and "endogenous" for purposes of clarification and accuracy.
 3. S2. Peptide Hormones, Growth Factors and Related Substances

For better comprehension, it was made clear that releasing factors were prohibited while other prohibited growth factors were listed separately.
 4. S5. Diuretics and other Masking Agents

Vasopressin V2 antagonists (vaptans) were added as an example of a subclass of diuretics.
 5. M1. Manipulation of Blood and Blood Components

For the purpose of scientific accuracy, the term allogenic was introduced.
 6. S6. Stimulants

Some drugs that metabolize to amphetamine or methamphetamine were reclassified because improved analytical techniques permit the identification of the administered drug and corresponding metabolites; MDMA and MDA were reclassified from S6.a (non-specified stimulants) to S6.b (specified stimulants) because they were now recognized as less likely to be used as doping agents; cathinone and its analogues (e.g. mephedrone, methedrone, α -pyrrolidinovalerophenone) and trimetazidine were added as examples to reflect emerging patterns of drug use.
 7. P1. Alcohol
 - a. Changes were made to the wording describing the threshold for alcohol in blood, in the interest of accuracy.
 - b. "Aeronautic" was replaced by "Air Sports" and "FITA" was replaced by its new acronym "WA" (World Archery).
 8. P2. Beta-blockers

"FITA" was replaced by its new acronym "WA" (World Archery)
 9. Monitoring Program

In order to detect potential patterns of abuse, mitragynine was added to the Narcotics class of the 2014 Monitoring Program.
- Dr Pipe informed the HMRC of other issues discussed during the LC meeting on August 22-23.
 1. Code review: the LC requested the Code Review Team to replace the name of Non-Specified/Specified Substances by Stipulated Substances because it was

confusing for many stakeholders. It was proposed that all substances that could result in higher sanctions should be Stipulated.

2. Scope of S0: the LC confirmed the usefulness of the "S0: Non-approved substances" section in the List. Nevertheless, the LC acknowledged the difficulties faced to evaluate substances that could potentially fall in this category. For example, it was difficult in some instances to determine if a substance was approved anywhere in the world. The difference between cosmetic and medical use was not always evident, as well as the use of some substances off-label. WADA was working with some pharmaceutical and biotechnology companies to try to detect early diversion of new experimental drugs for doping in sports. The LC confirmed that substances that may fall under S0 would be analysed on a case-by-case basis.
3. Cannabis decision limit: during the 2014 draft List consultation, many Federations expressed their disappointment about the way the reporting threshold of cannabis was changed without consultation, even when many of them approved of it.
4. Thyroid hormones: the LC did a review of the literature, and based on current knowledge it was decided that thyroid hormones warranted no inclusion in the List since their use would be counter-productive in sports.

3. Review and recommendation for the 2013 research projects

- A few conflicts of interests were declared before reviewing the grants (Dr Pascual for research involving IMIM, Spain; Dr Handelsman for a project submitted as co-applicant and others involving past collaborators from Australia; Dr Steinacher for a grant submitted by his research group). The implicated HMRC members left the meeting room while these projects were presented and discussed and decisions on approval and funding were made.
- Prof Handelsman and Prof Spiliopoulou, the HMRC members who were part of the Program Review Panel (PRP), presented the conclusions and recommendations of the PRP to the HMRC.
- A record number of 103 research projects were received following the 2013 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, 29 projects were selected and recommended for funding.
- For several projects, budgetary revisions were recommended.
- Two 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.
- Eight extension projects were approved, as results from the initial proposals were sound and important for anti-doping.
- Three projects were considered important but relatively unfocussed. Revised experimental designs were requested and decisions would be made based on reception of these modified proposals.
- Six projects were approved but were requested to focus on particular points that were more relevant to anti-doping.
- Two projects were approved with the condition to report the results from their previous research.
- One project was approved conditional to the confirmation by the researcher that the grant had not been funded by another granting institution.

4. Update on Code Review and International Standards (IS)

- The HMRC was informed on several aspects discussed during the World Anti-Doping Code review:
 1. List:
 - a. It was proposed that the 3 criteria for considering prohibiting a substance or method remained the same.
 - b. As discussed in item 2, there was a request to change the definition of Specified/Non-Specified substances
 2. Laboratories:
 - a. There would be a distinction between WADA Accredited laboratories, that would perform all the doping control tests, and the WADA Approved laboratories that would only perform tests for the hematological module of the Athlete Biological Passport.
 - b. The statute of limitation would be increased to 10 years.
 - c. Reanalysis B Sample: If there was not enough quantity of sample A, then sample B would be opened and if the athlete would not be available to presence the opening, the laboratory would designate an independent witness.
 - d. Presumptive Analytical Finding (PAF) for beta-2-agonists or glucocorticosteroids: recommendation for the laboratory to proceed to the confirmation analysis without inquiry about the existence of a TUE for.
 - e. Test reports and ADAMS reporting: the name of the competition and the Results Management Authority would only be added if provided by the Testing Authority.
 3. Therapeutic Use Exemption (TUE):
 - a. The TUE competence of International Federations (over International-Level Athletes), of National Anti-Doping Organizations (over Athletes below international level), and of Major Event Organizations (over participants in their Events) would be confirmed and it would be clarified that ADOs will be required to recognize TUEs granted by others if they comply with ISTUE.
 - b. In case of disagreement, WADA would decide and may charge the 'losing' party a fee to cover costs of review.
 - c. WADA may wish to review other TUE decisions for compliance with ISTUE.
 - d. Retroactive TUE would only be granted:
 - (a) for emergency treatments;
 - (b) in exceptional circumstances when there was no time to apply in advance;
 - (c) when the athlete is not International or National-Level;
 - (d) when WADA and the ADO involved agree to do so.
 4. Other:
 - a. It was proposed that sanctions for grave offenses be increased from 2 to 4 years.

5. Strategy for development of network of Anti-Doping Laboratories

- The HMR was presented with WADA' s Executive Committee recommendations on the strategy for development of the anti-doping laboratory network:
 1. Restrict the maximum number of laboratories to 40 for the next five years.
 2. Future approval based upon the needs in various regions of the world.
 3. No additional laboratories to be approved in Europe (exception: re-accreditation of Turkey), Oceania, North America and Central America.

4. Support the finalization of the Qatar laboratory application and the re-accreditation of the Malaysia laboratory but no further laboratories in Asia.
 5. Support two additional laboratories in Latin America.
 6. Strengthen the analytical capability of South Africa's laboratory and support one more new laboratory in the northern part of Africa (preferably Cairo) and examine if a third laboratory could be developed in the central region of Africa.
 7. Find non-compliant if any signatory to the Code uses non-WADA accredited laboratories for analyzing samples.
 8. Any new laboratory will only be approved in a country where there is a robust and compliant anti-doping program.
 9. Support usage of existing laboratories for major events, rather than developing a costly satellite laboratory.
 10. Develop blood analysis capacity in countries or areas of the world having limited or no blood analytical capability.
- The HMRC endorsed all the proposals for recommendation to the Executive Committee. In addition the HMRC proposed to look for ways to strengthen the collaboration between laboratories especially for new techniques.

6. Reporting pathological results

- Dr Alan Verneq informed the HMRC that some physicians and stakeholders were concerned that there was no process to report analytical results potentially associated with pathologies that were found in the course of anti-doping testing.
- WADA investigated this issue but the ISL said that WADA laboratories should only analyze for anti-doping purposes.
- In addition most laboratories did not employ physicians and generally no physician was involved in planning tests through results management.
- There would be many challenges related, for example, to the use of assays and methods in doping control that have not been approved for clinical diagnosis, the existence of dissimilar regulations in different countries, the mechanism to notify athletes (e.g. confidentiality, responsibility, liability), the timing of notification, etc.
- Very rarely the results may be indicative of a known pathology, such as early testicular cancer (elevated hCG) or haematological abnormalities as detected by the Athlete Biological Passport (ABP). There exist WADA Guidelines for reporting and managing hCG findings where the athlete would be advised to undergo clinical investigations. The haematological module of the ABP has a process where the specialists may alert the Athlete via the Anti-Doping Organization if pathology is suspected.
- A series of processes and principles were summarized in a paper for the consideration of the HMRC, which was accepted by the group.

7. Report from the TUE Committee

- Dr David Gerrard, Chair of the TUE Committee (TUEC) gave an update on the TUEC activities during 2013, informing that:
 1. TUE screening: There was a lack of universal use for reporting TUEs in ADAMS (only 62% of stakeholders). The most commonly Prohibited Substances for TUEs were glucocorticosteroids (for allergies, asthma, chronic inflammatory conditions) and stimulants (most for ADHD)
 2. The TUEC received a few requests to review the TUE decisions taken by International Federations.
 3. The TUEC had thoroughly reviewed and updated some of Medical Information to Support the Decisions of the TUEC [e.g. ADHD, musculoskeletal injuries, androgen deficiencies, female-to-male sex reassignment, intrinsic sleep disorders (Narcolepsy/Cataplexy), GH (adults),

cardiovascular conditions] and also created some new documents (e.g. Transgender issues).

4. The TUEC investigated and discussed the mechanisms of transient low pituitary dysfunction secondary to trauma, mainly in contact sports.
5. There was a fruitful Regional TUE Seminar in Tokyo, Japan, where 27 Asian NADO/RADOs participated with the goal of enhancing effective management of the TUE process. Emphasis was made on using ADAMS for incorporating TUE information.
6. There will be a TUEC's Chair Symposium in Paris, in October 2014 to clarify the medico-legal aspects of the new ISTUE and enhance the dialogue and exchange of knowledge between International Federations and NADOs.
7. For Veterans and Masters athletes, there was no international accord and no obligation to request TUEs according to the ISTUE. The TUEC considered that it would not be logistically possible to cover all the TUEs of veteran athletes.

8. Report from the Laboratory Committee

- Dr. John Miller , Chair of the Laboratory Committee (LabC), gave an update on the LaC activities during 2013:
 1. The LaC was composed of Christiane Ayotte (resigned in June), Wilhelm Schänzer, Terence Wan, Francesca Rossi, Alan Squirrel, Steven Westwood, John Miller, Jordi Segura, and Tiia Kuuranne .
 2. The regular tasks of the LaC consisted in reviewing results from the External Quality Assessment Scheme (EQAS), review corrective action reports, review Documentation packages from analytical results, score overall performance of the laboratories, review compliance with the International Standard for laboratories (ISL) and update the regulations (e.g. ISL, Technical Documents, Guidelines).
 3. There were 32 WADA-accredited laboratories.
 4. The Mexico City laboratory successfully completed the probationary phase of WADA accreditation and became the latest laboratory accredited.
 5. The 3 Candidate Laboratories:
 - i. Doha (Qatar): should be ready for the pre-probationary site visit and the analysis of blind EQAS samples before the end of 2013;
 - ii. Ankara (Turkey) laboratory was currently in the process of re-accreditation;
 - iii. Buenos Aires (Argentina): not much progress had been made
 6. Laboratories under suspension/revocation due to ISL non-compliances: Tunis (Tunisia) and Rio de Janeiro (Brazil).
 7. Several visits occurred in the past year at the Moscow's laboratory. Following a site visit from WADA, some improvements were observed but several corrective actions need further completion, so a new deadline to resolve outstanding corrective actions was established and another site visit would be done in early September.
 8. The EQAS was progressing as usual but the number of double-blinds per year increased from 2 to 3 and their Documentation Packages were requested for the first time in 2013.
 9. EQAS for blood samples were conducted in collaboration with an EQAS Provider in Switzerland and laboratories were generally performing well. To evaluate performance it was proposed 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 GH isoform test data was being statistically re-evaluated with a larger data set to determine decision limits by two teams of statisticians. Results will be published and the Guidelines amended accordingly.
 11. Endogenous Anabolic Androgenic Steroid Technical Document
 12. Following a CAS case, a larger data set for determining the decision limits for the GC/C/IRMS analysis was requested. The TDEAAS previously approved (March 2013) by the LaC divided the technical document in two parts: a) one dealing with the

steroid profiling which is essential for the Athlete's Biological Passport (ABP); b) the second exclusively for the GC/C/IRMS analysis. The proposed limits may have to be changed when a larger data set will be established from population data sets. A request had already been made to the ten laboratories considered to be the most experienced to supply this data. After completion of the work, it will be submitted to an appropriate peer reviewed scientific journal. In the meantime, the current technical document 2004 should be applied

13. Substances newly added to the 2014 List may be incorporated in the 2014 EQAS scheme.
14. The Executive Committee decision to raise the threshold for carboxy-THC from 15 ng/mL to 150 ng/mL had an immediate negative impact for the laboratories, since time is required to re-validate the methodology and estimate the uncertainty of measurement (MU). In addition, the LabEG expressed their disappointment for not having been consulted before a decision was taken by the Executive Committee.

9. Report from the Gene Doping Panel

- Prof. Theodore Friedmann, Chair of the Gene Doping Panel (GDP) summarized by teleconference the recommendations of the Panel, composed of Theodore Friedmann, Odile Cohen-Haguenaer, Hidde Haisma, Lee Sweeney and Perikles Simon:
 1. An update on the developments from on-going projects and goals of newly approved projects was presented during the meeting. Of special interest:
 - a. Very promising results of a WADA-sponsored pilot study by a commercial provider using chemically modified aptamers to identify protein biomarkers of hGH administration.
 - b. Invited speaker Dr. Yannis Pitsiladis reported impressive progress in transcriptomic analysis of athletes treated with erythropoietin. In the view of the GDP, it was one of the most promising proofs of the concept of a genetic signature for doping detection.
 - c. Advances with the meta-analysis of data from different studies on hGH treatment of athletes
 - d. Encouraging results for the prototype assays for direct transgene detection.
 2. Dr Darryl D'Lima, invited by teleconference, prepared an update on the use of cellular regenerative materials and methods including stem cells and other cells. Dr. D'Lima reported that cell-transplantation methods had been used in very high profile athletes but that there was little or no evidence of efficacy or of safety.
- The HMRC stressed that it was reassuring that WADA research projects related to gene doping were well advanced and promising.

10. Status of grant 09C18MA

- The HMRC reviewed the status of grant 09C18MA "Validation of genomic signatures associated with autologous transfusions". The award of this grant was conditional to obtaining promising results from grants "Investigation of indirect markers of autologous blood transfusion in peripheral blood samples" and its extension "Confirmation of differentially expressed genes associated with autologous transfusion". Unfortunately those grants did not produce any candidate markers, so the HMRC considered that no satisfactory progress had been made and decided to cancel the award of grant 09C18MA.

11. Information on "No Lie MRI"

- The HMRC was presented with a summary of the method "no Lie MRI". According to the inventors, the method consisted in determining through MRI different brain patterns that would indicate that a person was lying. It was being used in justice to obtain additional

evidence of a crime. The method was discussed by the HMRC. Based on the data available it appeared that the method could be quite accurate but for anti-doping it would be very difficult to validate, since some athletes truly believed that doping was not an offense. In addition, it was not clear which neurons were activated and maybe other brain activities would produce similar patterns. It was agreed that the method was better than a polygraph. The HMRC concluded that if the method was proven to be efficacious for crime prosecution, it will eventually find its way in anti-doping in the future. No immediate action to be taken by WADA.

12. Any other matters

- Since the Chairmanship of Prof. Arne Ljungqvist's, who had been Chair of the HMRC since the beginning of WADA, could come to an end in December 2013, the HMRC acknowledged his invaluable contribution to the world of sports and anti-doping and wished him all the best.
- Prof. Ljungqvist thanked the HMRC and WADA's office for their contribution and support and acknowledged the privilege of being the HMRC Chairman since 1999.

13. Next meeting

- The next HMR Committee tentative meeting was scheduled for **September 3-4, 2014**, while that of the Program Review Panel would take place on **September 2, 2014**
- The meeting was adjourned.