WORLD ANTI-DOPING AGENCY
play true

WORLD ANTI-DOPING AGENCY
Health, Medical & Research (HMR) Committee Meeting Minutes
August 25-26 2011

Participants:

Prof. Arne Ljungqvist, Chair	Attending
Prof. Kamal Al-Hadidi	Attending
Dr. Richard Budgett	Attending
Prof. Eduardo De Rose	Attending
Dr. Alessia Di Gianfrancesco	Attending
Prof. Theodore Friedmann	Attending
Prof. David Handelsman	Attending
Dr. Manikayasagam Jegathesan	Attending
Prof. Per Wiik Johansen	Attending
Prof. Ichiro Kono	Attending
Dr. José Antonio Pascual	Attending
Dr. Babette Pluim	Attending
Dr. Anik Sax	Attending
Prof. Chara Spiliopoulou	Attending
Dr. Jiri Dvorak	Apologies

WADA Staff

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

- Prof. Arne Ljungqvist welcomed the Committee members.
- One new member of the HMR Committee, Prof. David Handelsman and two new ex-officio HMR members, Dr. Richard Budgett (Chair, List Expert Group) and Dr. Anik Sax (Chair, TUE Expert Group) were introduced.
- The Agenda was approved.

2. Conflict of Interest - policy and implementation:

- Mr Jean–Charles René, of the Norton Rose law firm presented the new WADA policy on Conflict of Interest.
- The policy was adopted in order to ensure transparency and to avoid all appearance of Conflict of Interest in the agency's activities, also for research grant allocations.
- The policy applied to all WADA employees, expert group and committee members.

- Mr René explained that a Statement of Independence and Interest form would have to be completed and signed each year. In this form, any facts or circumstances which could call into question an individual's independence or impartiality in the eyes of WADA stakeholders or the public should be disclosed in writing.
- Mr René said that the statements would be made available to the chairs of each of the Committees to ensure that if a conflict arises, the person in conflict could be excluded from the discussions if necessary.
- Mr René explained that there was an extra provision for the HMR Committee members due to their involvement in the review process for funding of research grants. In this regard, a CV should be submitted prior to the appointment to the HMR Committee indicating employment, memberships, positions held in other organizations/institutions, shares held in relevant companies, engagements and associations during the last 5 years. In addition, indirect associations e.g. involvement of family members in particular organizations/institutions/companies, collaborators, should be declared as well. It was clarified that only what was relevant to the grant funding process should be disclosed.
- Every person should be free of undue influence or other factors that may lead to a conflict of interest.
- Mr René added that a HMR Committee member would have to step out during the review and discussion of any grant that he/she or any collaborator/colleagues applied for. This should be written in the Minutes of the meeting. In addition, the independent external reviewers would also be subjected to the same policy.
- It was noted that it was likely that the signature of the statement would be done months prior to the grants submission and reviews. Therefore the grant applicants would not be known *a priori*. In that event, it was recommended to sign the statement in general terms and to deal with the particular cases once they occurred.
- Mr René concluded his presentation and left the meeting.

3. Review of 2012 Prohibited List, report from the List Expert Group and recommendation to the Executive Committee

- The 2012 Draft of the Prohibited List, prepared by the List Expert Group (LiEG) was presented by Dr. Richard Budgett, Chair of the LiEG. Dr. Budgett noted that the LiEG had received 90 pages of comments from the stakeholders. All the LiEG proposed changes, listed below, were accepted by the HMR Committee and it was decided that the resulting draft List would be recommended to WADA's Executive Committee for approval. The changes were as follows:
    1. S0 (Non-Approved Substances) was moved under "Prohibited Substances" to clarify that it did not include "Methods".
    2. More examples were added to S0 and the scope of the section was broadened by replacing "i.e." with "e.g.". The HMR Committee ratified that any substance included in section S0 was a specified substance and that this point should be clearly explained in the Summary of Major Modifications and Explanatory Notes, published concomitant with the Prohibited List.
    3. The IUPAC name of bolandiol (estr-4-ene-3β, 17β-diol) was included in S1.a (Exogenous AAS).
    4. Three metabolites of DHEA (7α-hydroxy-DHEA, 7β-hydroxy-DHEA and 7-keto-DHEA) were added as examples to S1.b (Endogenous AAS) and the list of metabolites of endogenous AAS (but not the endogenous AAS themselves) was made an open list.
    5. Formoterol by inhalation up to a maximum daily therapeutic dose of 36 micrograms was included as an exception in the prohibited beta-2-agonists section. It was clarified that if more than 30 ng/mL formoterol was detected in urine, the *Athlete* would have to undergo a controlled pharmacokinetic study to show that the abnormal result was the consequence of the use of a therapeutic

inhaled dose. The HMR Committee considered whether it was necessary to keep the urinary threshold values of formoterol and salbutamol on the List and concluded that they were educative for the *Athletes*.

6. The title of S4 was modified from "Hormone Antagonists and Modulators" to "Hormone and Metabolic Modulators" to reflect the addition of a new subsection on cellular metabolism. The HMR Committee discussed and concluded that anti-estrogenic substances should remain prohibited for women as they can be used with anabolic steroids or precursors for performance enhancement.
7. Peroxisome Proliferator Activated Receptor δ (PPARδ) agonists (e.g. GW 1516) and PPARδ-AMP-activated protein kinase (AMPK) axis agonists (e.g. AICAR) were re-categorized as substances that modify cellular metabolism and therefore they were moved from M3 (Gene Doping) to S4.
8. Section S5 (Diuretics and other Masking Agents): Felypressin used in dental anesthesia was added as an exception to the inclusion of products having a similar effect to desmopressin
9. Catheterisation was removed as an example of prohibited physical manipulation in M2.1 because it was recognized that it may be necessary for medical purposes. It was clarified that catheterisation remained prohibited if it was used to tamper or attempt to tamper with the integrity of a sample or sample collection.
10. In M2.2, the volume and frequency of intravenous infusions and/or injections was clarified as being greater than 50 mL per 6 hour period.
11. PPARδ agonists and AMPK axis agonists were re-categorized in S4.5 to enable a more precise definition of Gene Doping.
12. The note on adrenaline in the S6.b section (Specified Stimulants) was clarified with respect to its use in local administrations.
13. At the request of Federation Internationale des Quilleurs (FIQ), prohibition of alcohol was excluded from Ninepin and Tenpin Bowling.
14. Bosbsleigh and Skeleton (FIBT), Curling (WCF), Modern Pentathlon (UIPM), Motorcycling (FIM), Sailing (ISAF), Wrestling (FILA) were removed from the list of sports in which beta-blockers were prohibited, following the re-evaluation of their prohibition made by WADA and the concerned federations.
15. The summary of Monitoring Program statistics was presented to the HMR Committee. There was a significant decrease in the number of samples containing concentrations of pseudoephedrine greater than 150 µg/mL. The number of samples with urinary concentrations of caffeine greater than 12 µg/mL continued to increase in 2010. The number of cases of bupropion increased in 2010 as well. The number of other monitored drugs remained stable.
16. Finally, in order to detect potential patterns of abuse, the following substances were added to the 2012 Monitoring Program: a) In-competition: nicotine, hydrocodone, tramadol; b) Out-of-competition: glucocorticosteroids.

4. Review and recommendation for the 2011 research projects

- Members of the HMR Committee responsible for organizing the peer-review process presented a summary of the evaluations received from the external independent reviewers in their field.
- Eighty two research projects were received following the 2011 Call for Grants. Four research categories were included (*Detection of Prohibited Substances/Methods: classic methodologies in analytical chemistry; Detection of Prohibited Substances/Methods: immunological and biochemical methodologies; Detection/Identification of novel doping trends; Pharmacological studies on doping substances/methods*).
- A ranking of projects within each category was made and 35 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 at the end of the granting periods.
- One extension project was approved with the condition that the Final report from a previous project was received.
- Two projects were considered important but relatively unfocussed. Revised experimental designs were requested and decisions would be made based on reception of these modified proposals.
- One extension project was approved but was requested to focus on particular points in order to demonstrate applicability for antidoping.
- One project had considerable overlap with a previously WADA funded project; therefore WADA would request the principal investigator to only carry out the complementary part of the project.
- One project was approved but the budget was cut because WADA would attempt to establish a collaboration with a pharmaceutical company to obtain the reference material.
- One project was not approved based on the results of the initial grant but could be reconsidered if the principal investigator addresses specificity issues.
- One project was approved only in part as other aims had already been addressed by other published studies.
- One follow-up collaborative project addressing detection of gene doping was approved.
- A few conflicts of interests were declared while reviewing some grants (Dr. Jose Antonio Pascual for research involving IMIM, Spain; Dr. David Handelsman for one project involving a past collaborator from Australia; Prof. Arne Ljungqvist for a project originating from the Karolinska Institute, Sweden; Prof Theodore Friedmann for projects submitted by two of his collaborators). The implicated HMR Committee members left the meeting room while these projects were presented and discussed and funding decisions were made.
- The HMR Committee would like to follow the outcomes of the research program. To this end, a presentation to be made to the Executive Committee in November was requested to be distributed to the HMR Committee members- ACTION POINT

5. Grant review program 2012

- The HMR Committee was informed that the reviewing process of future WADA Call for Grants had been modified. The process would be structured as follows:
    1. Submitted grants would undergo the usual reviewing by external independent reviewers (EIR).
    2. A second reviewing level would be created: the Project Review Panel (PRP). This panel would be composed of a number of external independent experts, selected members of the HMR Committee and WADA Science Management members.
    3. The PRP would meet previous to the HMR Committee meeting, integrate the review from the EIRs together with the PRP's evaluation, score/rank the grant applications and make a recommendation of the grants to be funded.
    4. The PRP would then present their recommendations to the HMR Committee at its annual meeting for endorsement.
    5. Final approval would be done as usual by WADA Executive Committee.

6. Selection of candidate laboratories for accreditation

- Dr. Olivier Rabin updated the HMR Committee on the candidate antidoping laboratories:
    1. In May 2009, WADA Executive Committee accepted 3 of 10 candidate laboratories to continue with WADA Laboratory Accreditation Process: Argentina (Buenos Aires), Mexico (Mexico City) and Qatar (Doha).
    2. These laboratories were making progress but had not been accepted yet in the probationary phase of WADA accreditation.

3. During the Panamerican Games in Guadalajara, a satellite laboratory of the WADA-accredited Barcelona anti-doping laboratory would be in charge of performing anti-doping analyses. The WADA-approved satellite laboratory would be using the facilities and instrumentation of the Mexico City's laboratory. The Mexican personnel would be working under the management and direct supervision from their Spanish colleagues. In May 2011, the Executive Committee assigned the responsibility on recommendation of candidate laboratories to the HMR Committee. The new list of candidate laboratories included: Belarus (Minsk), Bulgaria (Sofia), Egypt (Cairo), Hungary (Budapest), Indonesia (Jakarta), Iran (Tehran) and Ukraine (Kiev).

- The HMR Committee decided that for future accreditations, priority should be given to laboratories whose accreditation had been revoked (i.e. Malaysia, Turkey), as these already had the infrastructure, expertise and minimum required number of samples. In addition, it was suggested that interactions should be continued with other candidate laboratories and site visit should be planned in Minsk (Belarus).

7. Athlete's Biological Passport (ABP)

- Dr. Alan Vernec gave an update on the Athlete's Passport and informed that:
    1. The ABP Hematological Module had been published in December 2009 and the Operating Guidelines were being reviewed and modified. In this regard, there had been a meeting of hematology experts in February and another with key anti-doping organizations in June.
    2. Further feedback from stakeholders would be sought.
    3. The importance of ADAMS in the operation of the ABP was stressed, including whereabouts, laboratory results, ABP software analysis, information to and from experts and intelligent targeting.
    4. At the moment, ADAMS was prioritizing the whereabouts, so the integration of other elements was delayed.
    5. There were still some data protection issues to clear with certain European countries.
    6. Approximately 30 anti-doping organizations were integrating the ABP but they were at different stages of development.
    7. The steroid and endocrine modules were still under development.

8. Update for need for a B-sample

- Prof. Arne Ljungqvist updated the HMR Committee on the status of the discussion for the need of a B-sample. Following the recommendation by the HMR Committee, Prof Ljungqvist informed that the 2013 Code Review process would deal with this proposal. Whenever necessary, the HMR Committee would be consulted.

9. Status of stem cells

- The HMR Committee discussed the status of stem cells and concluded that if they were used to treat injuries and did not enhance performance beyond normal recovery, the method would not be considered prohibited. Nevertheless the subject would be discussed more in-depth by the LiEG and the Gene Doping Panel in 2012.

10. Update on the agreements with the pharmaceutical/biotechnology industry

- Dr. Olivier Rabin informed the HMR Committee that there had been substantial progress in the collaboration with industry. In this regard, there had been agreements signed with the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), GlaxoSmithKline (GSK) and Hoffmann–La Roche and more were expected in the future

including with the biotechnology industry. WADA envisaged organizing a high profile conference with the industry in the near future.

11. Report from the TUE Expert Group

- Dr Anik Sax, Chair of the TUE Expert Group (TUE-EG) gave an update on the TUE_EG activities during 2011:
    1. The group had a new member, Dr. Susan White and the 7 medical doctors in the EG had different backgrounds.
    2. Until the 25th of August 2011, 463 TUE had been selected through "intelligent" screening. This screen was done through ADAMS and aimed to detect clinical "red flags" (e.g. substance, route of administration, duration). The TUE-EG would then make a decision based on the information, i.e. request more information, close the file or start a formal review.
    3. So far in 2011, 60% of TUE had been granted by International Federations and 40% by NADOs.
    4. Glucocorticosteroids and beta-2-agonists each constituted 31% of granted TUE, followed by stimulants (12%), peptide hormones, growth factors and related substances (9%), diuretics and masking agents (6%), narcotics (5%), beta blockers (2%), cannabinoids (1%), enhancements of oxygen transfer (1%), hormone antagonists and modulators (1%) and endogenous anabolic steroids (1%).
    5. Most of the asthma medication TUE were granted for formoterol (56%) followed by terbutaline (12%) and prednisolone (8%).
    6. Article 10.2 (Review of TUE decisions by WADA) of the International Standard for TUE was more stringently applied.
    7. Documents of Medical Information (MI) to support TUE Committee decisions continued to be developed and updated. Although not mandatory, this enabled standardization of TUE granted and provided assistance to the TUE Committees. To-date there were 15 MI published, which were regularly reviewed; these included MI for asthma, post infectious cough, platelet rich plasma (PRP), a new edition for attention deficit hyperactive disorder (ADHD), IV infusions and androgen deficiency/hypogonadism which were going to be published shortly and arterial hypertension, which was being updated.
    8. There were still ongoing discussions on the duration of TUE for common chronic medical conditions like arterial hypertension, diabetes, heart disease, chronic inflammatory bowel disease.
    9. The TUE-EG praised WADA's Medical Department for their dedication and professionalism

12. Report from the Laboratory Expert Group

- Dr. Toni Pascual, Chair of the Laboratory Expert Group (LaEG), gave an update on the LaEG activities during 2011:
    1. The regular duties of the LaEG consisted in reviewing the anti-doping laboratories results from External Quality Assessment Scheme (EQAS) rounds, corrective action reports, documentation packages, overall performance, International Standard for Laboratories (ISL) compliance and sharing of knowledge.
    2. For the EQAS rounds the new scheme was already implemented and comprised 3 rounds of blind EQAS per year (6 samples each) and 2 samples of double-blind EQAS per year.
    3. The Penang (Malaysia) and Ankara (Turkey) laboratories had their accreditation revoked due to recurrent analytical deficiencies and reporting mistakes, while the one in Tunis (Tunisia) had its accreditation suspended.
    4. The Almaty (Kazakhstan) laboratory received its WADA accreditation.

5. Four laboratories nominated new directors: Dr. Catrin Goebel, (Sydney, Australia); Dr. Peter van Eenoo (Gent, Belgium), Dr. Jesus Muñoz-Guerra (Madrid, Spain) and Dr. Ileana Vajiala (Bucharest, Romania).
6. The anti-doping laboratory in Salt Lake City encountered some technical problems and a new director was expected to be nominated before the end of 2011. The laboratory was currently being tutored by the Oslo (Norway) accredited laboratory.
7. The Mexico DF (Mexico) laboratory pre-probationary phase was in progress. The accreditation process had stopped because of the preparations for the Panamerican Games in Guadalajara taking place in October 2011. Doping control during the games would be performed by a satellite facility of the Barcelona (Spain) laboratory. The Mexico DF laboratory was fully equipped and planned to continue its progression towards the accreditation process right after the Games.
8. The Doha (Qatar) laboratory was not ready for the pre-probationary phase; they were finishing building the laboratory and part of the personnel were training first in Penang and later on in Barcelona; a new technical director had been appointed and they had established an agreement with the Barcelona laboratory for tutoring; the laboratory would probably be ready for accreditation in late 2012.
9. The pre-probationary phase of the Buenos Aires (Argentina) laboratory was progressing slowly. It was being tutored by the Madrid laboratory with some input from Barcelona. The LaEG was monitoring the situation and would propose deadlines before re-considering the present candidacy.
10. The revised ISL was being circulated at the time and the major new points included were the independence of the anti-doping laboratories from their NADOs, contract disclosure, re-sealing of samples for long term storage and re-testing and specificity of immunoassays.
11. Technical documents (TD): the TD2010NA:"Harmonization of analysis and reporting of 19-norsteroids related to nandrolone" was being circulated for consultation; there were confounding factors due to the use of certain contraceptives; two sections of the TD2010EAAS on steroid profile (reporting of screening values for the variables of the steroid profile and performance of IRMS analysis) were under development and the hCG guideline on "Reporting and Managing Human Chorionic Gonadotrophin (hCG)" findings was undergoing a final round of discussion among experts prior to its publication.
12. Detection of plasticizers: earlier in 2011, Prof. J. Segura presented the results of his project which aimed at detecting metabolites of plasticizers as a proof of blood transfusion. The concentration of plasticizers increased very markedly after transfusion and this increase was detectable for 1-2 days. However, other reports suggested that environmental exposure to plasticizers could constitute a confounding factor. Therefore the follow-up project was not approved by WADA. Instead, information on plasticisers was being gathered by some laboratories on routine doping samples.
13. Minimum Required Performance Levels (MRPL): the LaEG was reviewing the document since the limits of detection of many laboratories were below the MRPL and continued decreasing. The aim was to determine if it was necessary to harmonize values across all laboratories.
14. hGH detection, indirect markers: the LaEG was expecting additional information from the research team, including the first draft of the guidelines for performance of the assays and interpretation the test results, before making its recommendation for approval of the hGH biomarker test by WADA.
15. Regarding education and communications activities related to laboratories, there had been a session on measurement uncertainty during the Cologne Workshop plus the Laboratory Director's meeting. In addition, there was a proposal to have a training session for laboratory directors on how to proceed during a Court case.

13. Report from the Gene Doping Panel

- Prof. Ted Friedmann, Chair of the Gene Doping Panel (GDP), summarized the recommendations of the Gene Doping Panel:
    1. The Panel proposed to review the definition of Gene Doping on the Prohibited List by transferring the last point (agents that alter gene expression e.g. PPARδ-agonists and PPARδ-AMPK axis agonists) to another section, as these did not purely constitute "gene doping".
    2. During the GDP meeting in February, Prof. Perikles Simon and Dr. Richard Snyder presented results from their assays developed to directly detect gene doping. The benefits/shortfalls of each technique were discussed by the GDPl and follow-up projects were supported. Following extensive negotiations, the two groups submitted a consolidated joint project that was approved by the HMR Committee during the review and recommendation for the 2011 research projects.

14. Next meeting

- The next HMR Committee meeting was scheduled for **August 21-22, 2012.**
- The meeting was adjourned.