WORLD ANTI-DOPING AGENCY
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WORLD ANTI-DOPING AGENCY
Health, Medical & Research Committee (HMRC) Meeting Minutes
August 21-22 2012

Participants:

Prof. Arne Ljungqvist, Chair	Attending
Prof. Kamal Al-Hadidi	Attending
Prof. Eduardo De Rose	Attending
Dr. Jiri Dvorak	Attending
Dr. Alessia Di Gianfrancesco	Attending
Prof. Theodore Friedmann	Attending
Prof. David Handelsman	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. Richard Budgett	By teleconference for List review
Dr. Manikayasagam Jegathesan	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

- 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 the two new members, Prof. Jürgen Michael Steinacker and Prof. Hidenori Suzuki.
- 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.
- The Agenda was approved.
- Prof. Ljungqvist gave an overview of the recent London Olympic Games, pointing out their success from a sports and an anti-doping perspective. Prof. Ljungqvist indicated that the anti-doping program was broad, including doping control before and during the competition and through intelligence and information. Several athletes were excluded before the

competition and over 5,000 doping control tests were conducted during the pre-Olympic period and the Olympic Games.

2. Review of 2013 Prohibited List, report from the List Committee and recommendation to the Executive Committee

- The 2013 Draft of the Prohibited List, prepared by the List Committee (LC) was presented by Dr. Richard Budgett, Chair of the LC, who joined the meeting by teleconference due to his duties linked to the London Paralympic Games, in preparation at the time. Most of the LC proposed changes was accepted by the HMRC Committee and some modifications were introduced. 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): it was clarified that veterinary products only refer to substances not approved for human use.
2. The IUPAC names of several Anabolic Androgenic Steroids were reviewed with the assistance of IUPAC and the appropriate changes were introduced for:
    - danazol ([1,2]oxazolo[4',5':2,3]pregna-4-en-20-yn-17α-ol)
    - ethylestrenol (19-norpregna-4-en-17α-ol)
    - furazabol (17α-methyl[1,2,5]oxadiazolo[3',4':2,3]-5α-androstan-17β-ol)
    - methasterone (17β-hydroxy-2α,17α-dimethyl-5α-androstan-3-one)
    - prostanozol(17β-[(tetrahydropyran-2-yl)oxy]-1'H-pyrazolo[3,4:2,3]-5α-androstane)
    - tetrahydrogestrinone(17-hydroxy-18a-homo-19-nor-17α-pregna-4,9,11-trien-3-one)
    - trenbolone (17β-hydroxyestr-4,9,11-trien-3-one)
    - prasterone (dehydroepiandrosterone, DHEA, 3β-hydroxyandrost-5-en-17-one).
3. Etiocholanolone was added to the S1.b section as an example of testosterone metabolite.
4. Insulins were moved to S4.5.a (Metabolic Modulators) because it was considered a more appropriate category based on their mechanism of action.
5. The non-prohibited status of Platelet Derived Preparations (except intravenously) was re-iterated in the Explanatory Notes as a reminder to stakeholders.
6. The permitted delivered (inhaled) dose of formoterol was increased to 54 micrograms over 24 hours for emergency treatment. As a consequence, the urinary threshold was increased to 34 ng/mL, a value suggested by the drug manufacturer. The HMRC decided to raise the threshold to 40 ng/mL to have a wider safety margin that would minimize the impact of inter-individual variability in formoterol urinary concentrations.
7. For clarity, it was noted that all optical isomers (d- and l-) where relevant, were prohibited in sections S3 (beta-2-agonists) and S6 (Stimulants).
8. "Local application" of felypressin was changed to "Local administration" in S5 for clarity.
9. Morphine was removed from the last paragraph of S5 as it was not a substance subject to threshold limits in the List, so a TUE would always be required to use in-competition.
10. To enable a more precise definition of Gene Doping, M3.1 was been reworded as suggested by the gene Doping Panel.
11. Methylsynephrine was added as a different name for oxilofrine in S6 (Stimulants).
12. Boules (CMSB), Bridge (FMB), Ninepin and Tenpin Bowling (FIQ) and Powerboating (UIM) were removed from the list of sports in which beta-blockers were prohibited. This decision was a consequence of consultations, research and discussion with the concerned federations and other stakeholders.

13. In order to detect potential patterns of abuse, tapentadol was added to the 2013 Monitoring Program "In-competition".

- Dr Budgett informed the HMRC of other issues discussed during the LC meeting on August 16-17.
    1. Code review: the main discussions dealt on the possibility of having a unique List where substances and methods were prohibited at all times, or to keep the current format; whether performance enhancement should be mandatory to include a substance or method in the List; the division of stimulants into specified and non-specified classes. The LC weighed the pros and cons of the different options, and would inform the WADA Executive Committee.
    2. Return to competition after glucocorticoid injections: studies were still ongoing to determine the adequate time when glucocorticoids were washed out from the system after administration.
    3. Nicotine: collection of data must continue before any conclusion could be reached.
    4. Cannabis decision limit: it was acknowledged that it was possible that an athlete could test positive for cannabinoids in-competition even if the consumption was out-of-competition. LC was addressing this issue and there were several possibilities, including doing a screening on saliva as a first step or taking 2 blood samples. The LC concluded it would not be useful to raise the threshold in urine because of the inter-individual variability in excretion patterns. The HMRC requested WADA to compile all the Adverse Analytical Findings reported, including the concentrations reported and how they were dealt with in terms of results management and sanctions in an attempt to better approach the problem.
    5. The teleconference with RB concluded.
- The HMRC discussed the method of UV blood irradiation (see Section 8). As a result the title and the body of the M1 section were changed to encompass all kinds of manipulations of blood and blood components. As a consequence, M2.3 was deleted, as it would now be included in the revised M1 category.

3. Review and recommendation for the 2012 research projects

- As an introduction, the HMRC was reminded of the procedure for the new grant reviewing process, implemented for the first time in 2012. The reasons for this new process were the harmonization with WADA Social Science grant program and better time management of the HMRC meeting, since not all the HMRC members were involved with the review process. Changes included the establishment of a Program Review Panel (PRP) composed of external experts and members of the HMRC and WADA management. The PRP was in charge of discussing the evaluations of the external independent reviewers, adding their own assessment and propose to the HMRC the grants to be funded. The PRP recommendation would then be discussed by the HMRC, who would make a consolidated proposal to WADA Executive Committee, who, as always, would make the final decision. As a consequence of this lengthier process, the call for grants was opened (November 2011) and closed (February 2012) earlier than in the past, the external reviewers did their evaluations between March and May, the outcomes were compiled by WADA Science Department and sent to the PRP and HMRC members in June and the PRP met the day before the HMRC meeting. The HMRC was informed that the PRP, who was meeting for the first time ever, was very focused and efficient.
- Members of the HMRC who were part of the PRP presented the conclusions and recommendations of the PRP to the HMRC.
- Seventy one research projects were received following the 2012 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 26 projects were selected and recommended for funding.
- For several projects, budgetary revisions were recommended.
- Four 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.
- Seven 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 that additional control groups were added.
- One project was approved if the researcher confirmed that he had no conflict of interest with a particular industry.
- One project was approved under the condition it provided the preliminary data generated with a grant from another institution.
- A few conflicts of interests were declared while reviewing some grants (Dr Pascual for research involving IMIM, Spain; Dr Handelsman for project involving a past collaborator from Australia; Dr Pigozzi for a grant submitted by his research group). The implicated HMRC members left the meeting room while these projects were presented, discussed and funding decisions made.

4. Delayed grants and late final reports: consequences on follow-up grants

- The HMRC was informed that in some cases there was a long delay between the award of the grant by WADA and the signature of contract with the grantee. The main reasons were the grantees' requests to change WADA standard contract and/or obtaining the local ethics committee approval. The HMRC decided that if there was no feedback from the principal investigator after 9 months of the grants award, the grant would be automatically forfeited. The grantee should be warned in advance of these conditions i.e. in the letter of award and possibly in the contract. Special circumstances should be taken into account at the criterion of WADA management. In addition the HMRC was informed that several ongoing grants were late and in some cases it was difficult to obtain the final reports. In that case the HMRC decided that if a researcher was late with a progress report for a project and applied for a new grant, the funds would be retained until the late report was received and approved. In case a researcher was unresponsive following several reminders, the Chairman of the HMRC would be consulted whether the grant should be terminated.

5. Report from the TUE Committee

- Dr Andrew Pipe, Chair of the TUE Committee (TUEC) gave an update on the TUEC activities during 2012, informing that:
    1. <u>TUE screening</u> was ongoing and that due to human resource issues, the screening of TUEs was prioritized based on high risk substances. TUE screening efforts were hampered because many Anti-Doping Organizations did not use ADAMS, the tool used by WADA to do the screening. There was a significant decrease in the number of TUE applications in ADAMS since inhaled salbutamol and salmeterol were no longer prohibited. This number, however, remained unaltered when similar changes for inhaled formoterol were introduced.

2. An athlete requested WADA to review the TUE decision taken by his International Federation. WADA overturned the Federation's decision.
3. The TUEC reviewed TUE duration for each medical condition and extended the period up to 8 years, which coincided with the time period where the data is kept in ADAMS.
4. Over the past year, the TUEC had thoroughly reviewed some of Medical Information to Support the Decisions of the TUEC (e.g. Attention Disorder/Hyperactivity Disorder, Anaphylaxis, Arterial Hypertension, Growth Hormone, Inflammatory Bowel Disease, Narcolepsy-Cataplexy, Hypogonadism) but also created some new documents (e.g Transgender issues).
5. The TUEC discussed in detail the International standard TUE during their past meeting and would continue the discussions in the future in preparation for the Code and Standard revision.

6. Report from the Laboratory Committee

- Dr. Jose Antonio Pascual, Chair of the Laboratory Committee Expert Group (LaC), gave an update on the LaC activities during 2012:
    1. The LaC was composed of Jose Antonio Pascual, Christiane Ayotte, Wilhelm Schänzer, Terence Wan, Francesca Rossi, Alan Squirrel, Steven Westwood, John Miller; Jordi Segura, president of WAADS, was an observer.
    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 Standards for laboratories (ISL) and update the regulations (e.g. ISL, Technical Documents).
    3. There were 33 accredited laboratories around the world; Tunisia had been fully suspended and Rio had been suspended for the IRMS technique.
    4. Laboratory status: Barcelona had a satellite laboratory for the Pan Am Games, as the accreditation of the Mexico Laboratory had not been completed; the previously-accredited Malaysia laboratory expressed their wish to re-initiate accreditation procedures; the London laboratory opened a satellite laboratory in Harlow, UK, for the Olympic Games; the laboratory in Prague ceased their activities due to lack of resources.
    5. There were several new laboratory directors: Dr Daniel Eichner (Salt Lake City, USA), Prof Mohamed Kallel (Tunis, Tunisia); Dr Rodrigo Aguilera (Lisbon, Portugal), Dr Valentin Mihai Pop (Bucarest, Romania); Dr Magnus Ericsson (Stockholm, Sweden). It was pointed out the WADA had no power or responsibility in the choice of laboratory directors.
    6. The Rio laboratory had been suspended for IRMS procedures and was currently improving the method with the assistance of the Cologne laboratory. It was expected that it would be re-instated in the near future. They were building new facilities for the Olympic Games (2016) but progress had been slow.
    7. The Tunis laboratory was suspended after accumulating penalty points; there were problems at the accreditation and managerial levels and several corrective actions were being worked on after a site visit. They were getting assistance from the Paris and Madrid laboratories.
    8. The Mexico Laboratory had continued with the process of accreditation and had successfully passed the pre-probationary test; it was currently in probationary phase which was expected to be finished by the end 2012; it was anticipated that full accreditation would occur by mid-2013.
    9. The laboratory building in Doha was almost completed and instrumentation should be received in the next months; they had named a new director in 2011, Dr Costas Georgakopoulos (former Athens laboratory director) and already hired Senior Scientists experts in different analytical techniques.

10. The laboratory in Buenos Aires ceased its pre-probationary phase and was expected to return in the future once a new facility was built, but the timeline was uncertain.
11. Other laboratories seeking candidate status: Minsk (Belarus), Cairo (Egypt) and Kiev (Ukraine).
12. Several ISL modifications came into effect on January 2012 including laboratory independence from Anti-Doping Organizations, reanalysis of samples in other laboratories, long-term storage, anonymization and disposal of samples, re-sealing and re-testing of samples, time elapses between analysis of A and B samples, and WADA right to review laboratory documentation e.g. contracts with third parties.
13. Some technical documents would come into effect in the near future: a) TD2013MRPL, in effect on January 2013; changes included reduced MRPL to improve performance, reducing the analytical differences between laboratories, ways to deal with specific problematic substances (e.g. clenbuterol, octopamine); TD2012DL, in effect on October 15 2012; changes included the introduction of a decision limit for formoterol and glycerol and the changes of some measurement uncertainties; TD2013EPO, in effect on January 1 2013; changes included the adoption of IEF and SDS analysis, a mandatory immunopurification, new criteria for blood and urine analysis and the inclusion of new analogues (e.g. hematide, EPO-FC); TD2013EAAS: in the process of being developed, it would probably be ready by year's end and would include reporting the steroid profile for all samples and start the endocrine module of the biological passport.
14. A number of Guidelines were also developed, including a) human Chorionic Gonadotrophin (hCG) (implemented in September 2011) guidelines for results management (e.g. confirmation of intact hCG, reporting threshold, alert for clinical investigations in case of atypical findings); b) the Athlete Biological Passport (in effect in April 2012), including the implementation of the Haematological Module, testing requirement, transport, instrumentation check and quality assessment; c) Elevated T/E ratios and endogenous steroids (in effect in October 2011) complementing the TD2004EAAS to harmonize reporting of abnormal steroid profiles, covering endogenous boldenone production and defining atypical findings, results interpretation and follow-ups; d) Application of the GH markers method (in effect in June 2012 for a limited number of experienced laboratories).
15. Lastly, the Educational-communication activities of the LaC included the Laboratory Director's meeting and a proposal to have a training session for laboratory directors on how to defend a case in Court.

7. Report from the Gene Doping Panel

- Prof. Theodore Friedmann, Chair of the Gene Doping Panel (GDP), summarized the recommendations of the Panel, composed of Theodored Friedmann, Odile Cohen-Haguenauer, Hidde Haisma, Lee Sweeney and Perikles Simon:
    1. The Panel proposed to review the definition of Gene Doping on the Prohibited List by including miRNA and siRNA methods; therefore, subsection M3.1 would read "The transfer of polymers of nucleic acids or nucleic acid analogues"
    2. The GDP reviewed the progress of the research grants linked to gene doping.
    3. There were two expert presentations on Stem Cells, one by Dr Darryl D'Lima from the Scripps Institute in San Diego, California, USA and another by Dr Paul Martineau from McGill University, Montreal, Canada, who explained that there were different types of stem cells e.g. Mesenchymal stem cells, capable of differentiating into different tissues (bone, cartilage, muscle, neurons); placental stem cells; muscle stem cells; induced pluripotent cells (iPS). Suspicion was expressed that stem cell therapy was increasingly used by athletes for treatment of injuries. There were almost no clinical trials and in some cases few pre-clinical studies; however lesions in animal models studies were performed in ways that did not really recapitulate the injuries in real-life sports. The experts and GDP concluded that for now there were no elements of performance enhancement in the treatments that were being used and were merely

therapeutic treatments for injury repair. Nevertheless, the potential of reprogramming stem cells to produce growth factors that would go undetected or to increase pain threshold existed so it was necessary to continue monitoring the technology closely.

- The HMRC further discussed the issue and emphasized that they did not oppose the use of stem cells for injury recovery. Regarding gene doping, the HMRC stressed that it was reassuring that WADA already had an assay in development to detect gene transfer.

8. Discussion on UV blood irradiation

- The HMRC discussed the method of UV blood irradiation with the participation of Mr David Howman. The method consisted in aspirating 50 mL of venous blood into a 50 mL syringe, irradiating the blood in a quartz cuvette with UV-C light and re-injecting the blood into the circulation. The whole session lasted about 10 minutes. It had been used in Germany for many decades and more recently by Dr Franke in a number of elite athletes. In Germany, such methods did not need to be scientifically proven as long as they did not harm the patients.
- Dr Ljungqvist indicated that the International Olympic Committee had prohibited this method since 2002, when the Austrian skiing team was found with paraphernalia for this procedure and was sanctioned.
- The HMRC reviewed section M1, subsection 1.1 and section M2, subsection 2.3 of the Prohibited List. It was concluded that M1.1 was prohibiting blood manipulation from the point of view of the performance enhancing effect of the method, while M2.3 was prohibiting blood manipulation from a process perspective. The HMRC thought it sensible to encompass both types of manipulation under a same section.
- There were many methods for blood manipulation for which the efficacy was unknown. It would probably not be possible to establish the usefulness of each of these procedures and to be aware of all the methods and their variations available.
- As a consequence the HMRC decided to change the title and the body of the M1 section to encompass all kinds of manipulations of blood and blood components. As a consequence, M2.3 was deleted, as it would be now included in the revised M1 category which prohibited administration of any blood products or intravascular manipulations.

9. Reporting Pathological Results

- The HMRC discussed how to proceed with pathologies that were discovered through a doping control. It was reminded that it was not in WADA mandate to use doping control results as a health check-up; however it seemed it was a professional responsibility to inform the athlete of any sign of a disease. It was acknowledged that there may be problems with privacy issues, so the HMRC asked WADA management to look into the legal consequences of reporting pathological results. It was suggested to maybe target some parameters that would indicate serious pathologies, for example hCG, abnormalities in red or white blood cells. Clear guidelines based on the findings should be given as of when to inform the athlete. As a starting point the HMRC asked WADA to compile the number of hCG Adverse Analytical Findings reported in the last years (ACTION POINT). Once the compilation was ready, the HMRC would re-discuss the issue.

10. Abuse of painkillers.

- Dr Dvorak informed that FIFA had published a series of papers that during the Football World Cup, 70% of athletes administered non-steroidal anti-inflammatory drugs, 5-15% used narcotics including sleeping pills and many others administered pain killers. Even during the

Under-17 championships there was an abuse of these types of drugs. The trend had been stable for more than 10 years. Several HMRC members added that there were similar tendencies in other sports. The HMRC questioned whether this was a doping issue or a medical one, related to abuse of medication but in any case WADA should try to help finding solutions. It was recognized, however, that injury was part of sport and use of painkillers was in part a consequence of this, especially with the ever-increasing frequency of games/competitions. Dr Dvorak proposed to create a working group with Dr Alan Vernec (WADA Medical Director) and the International Olympic Committee Medical Commission to look for solutions.

11. Next meeting

- The next HMR Committee meeting was scheduled for **August 27-28, 2013.**
- The meeting was adjourned.