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**WORLD ANTI-DOPING AGENCY  
Health, Medical & Research Committee (HMRC) Meeting Minutes  
September 1-2 2015**

**Participants:**

Dr. Valérie Fourneyron, Chair	Attending
Prof. Kamal Al-Hadidi	Attending
Dr. Alessia Di Gianfrancesco	Attending
Prof. Lars Engebretsen	Attending
Prof Theodore Friedmann	Attending
Prof. David Gerrard	Attending
Prof. David Handelsman	Attending
Dr. Peter Harcourt	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
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**

- Dr. Valérie Fourneyron, new Chairman of the Health, Medical and Research Committee (HMRC) welcomed the Committee members.
- Dr. Fourneyron introduced herself citing her tenure as a member of WADA Executive Committee from 2013 to 2015, representing Europe during her tenure as Minister of Sport from France. Involved in medical practice as a sport physician in different French sport teams, Dr. Fourneyron later on joined the French Ministry of Sports and helped draft the French Anti-Doping Law. Dr. Fourneyron said she was honoured to succeed Prof. Arne

Ljungqvist as Chair of the committee. She has already attended a meeting of each of WADA scientific Expert Groups, except for the Gene Doping Panel, in order to immerse herself in their operations. In addition, Dr. Fourneyron convened a meeting of all their Chairs the day preceding this meeting with the aim to improve communication and functioning between Expert Groups. Dr Fourneyron thanked the members of all Committees and Expert Groups, in particular their Chairs. Dr Fourneyron stressed the mission each Expert Group had for the List, laboratories, testing, therapeutic use exceptions and gene doping in supporting the credibility of WADA during the recent doping scandals and media exposure. Now, more than ever, there was a need to close the gap between dopers and testing. However, the Special Research Fund set up by donations from the International Olympic Committee and the governments of the world was now available. After many years of decline in the WADA Research budget due to alternative priorities, this Special Fund would inject much needed cash for research for the next 3 years. Dr Fourneyron indicated that there were high expectations that this extra funding would deliver results to tackle doping practices.

## **2. Conflict of Interest**

- Dr. Handelsman, Dr. Pascual, Dr. Harcourt and Prof. Pigozzi declared possible conflict of interests for reviewing a few research grants, as they either knew or collaborated with the principal investigators. They were asked to refrain from comments or leave the meeting room when those projects were reviewed.

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

- The Draft of the 2016 Prohibited List, prepared by the List Expert Group (LiEG) was presented by Dr. Andrew Pipe, Chair of the LiEG. Dr Pipe explained how the Stakeholders Comments to the proposed changes to the List are reviewed and discussed by the LiEG. In order to improve transparency, the LiEG proposed to respond this year to the stakeholders, outlining in general terms the process of review and answering to recurrent questions.
- For 2016, there were few modifications introduced in the List.
- 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 2015 were as follows:
  1. S2. Peptide Hormones, Growth Factors, Related Substances and Mimetics: Leuporelin replaced triptorelin as a more universal example of a chorionic gonadotrophin and luteinizing hormone-releasing factor.
  2. S4. Hormone and Metabolic Modulators: Insulin-mimetics were added to the List to include all insulin-receptor agonists; Meldonium (Mildronate) was added because of evidence of its use by athletes with the intention of enhancing performance.
  3. S5. Diuretics and Masking Agents: It was clarified that the ophthalmic use of carbonic anhydrase inhibitors was permitted.
  4. S6. Stimulants: It was clarified that clonidine was permitted.
  5. P1. Alcohol: After consideration of the Fédération Internationale de Motocyclisme's (FIM) request, this Federation was removed from the list of sports prohibiting alcohol as a doping agent.

6. Monitoring Program: Meldonium was removed from the Monitoring Program and added to the Prohibited List. Hydrocodone, morphine/codeine ratio and tapentadol were removed from the Monitoring Program following sufficient collection of data leading to clear conclusions.
- Dr Pipe informed the HMRC of other issues discussed during the last LiEG meeting on 26-27 August 2015. The HMRC members further contributed to the discussion :
    1. Section S0 (Non-approved drugs): the definition of S0 would be re-examined in 2016 in an attempt to improve it for better implementation. The difficulty to establish whether a substance was approved anywhere in the world by a regulatory agency was acknowledged. A reference to a "stringent" health authority as applied by the WHO is recommended for the future.
    2. Section S3 (Beta-2-agonists): the difficulty of establishing thresholds for different routes of administration was underestimated.
    3. Unique List: the LiEG had started to look into the possibility to implement a "Unique List" where all categories would be prohibited at all times. The advantages and disadvantages as well as the feasibility of such List would be examined in detail in 2016.
  - The HMRC discussed other issues related to the Prohibited List:
    1. Section S7 (Narcotics) would be re-examined in 2016 to consider an expansion to include other analgesics, e.g to see if inclusion of other pain killers would be warranted; whether they could be prohibited in certain sports. A Pain Management Symposium under the auspices of the IOC would take place in 2016 and its outcome would be relevant for future decisions on this category.
    2. Section S9 (Glucocorticoids): Dr Fourneyron stressed that the status quo on glucocorticoids was not satisfactory and this view was shared by all HMRC members. It was acknowledged that the establishment of thresholds to distinguish permitted from prohibited routes of administration was desirable but large administration studies would be needed and success in establishing such thresholds was not guaranteed. It was acknowledged that some local routes of administration could result in systemic distribution of the drug and Dr Fourneyron wished that this would be addressed in 2016 by the LiEG and external experts [e.g. International Olympic Committee (IOC) Medical Commission, FIMS, pharmacists] to find solutions (e.g. retroactive TUE, delayed return to competition after administration) and propose a recommendation for 2016. ACTION POINT

#### **4. Review and recommendation for the 2015 WADA Call for Scientific Research Projects**

- Dr. Fourneyron updated the HMRC on the joint IOC/ Governments Special Research Fund. The contributions had amounted to U\$S 13,000,000 of which U\$S 1,000,000 would be destined to Social Science Research. The funds would be used over a period of 3 years and was destined for "Innovative Research" that would examine alternative, bolder and more creative ways to address doping detection. The themes of research areas proposed would be presented to WADA Executive Committee during their meeting on 16 September, 2015. The funds would be allocated in two ways: a) projects from the regular WADA call for grants, falling into the Special Funds themes, would be assigned to that group; b) there would be Request for Proposals (RFP) in specific areas before the end of the year the selection of which would follow the same procedure as the regular call for grants. In addition, and as already

established, WADA would interact with the IOC in order to avoid duplications of grants funded.

- Prof Handelsman and Dr Pascual, the HMRC members who were part of the Project Review Panel (PRP), presented the conclusions and recommendations of the PRP to the HMRC. The PRP had met on August 31 and had reviewed the grants based on the independent external reviewers' evaluations as well as the PRP's own assessment.
- 110 research projects were received following the 2015 Call for Grants. Five research categories were included (*Detection of Prohibited Substances/Methods: Methodologies in Analytical Chemistry; Detection of Prohibited Substances/Methods: Affinity-binding and Biochemical Methodologies; Pharmacological Studies on Doping Substances/Methods; The Athlete's Biological Passport; Detection of Prohibited Substances/Methods: Molecular Biology, "Omics" and Miscellaneous methodologies*).
- 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. Seven of those would be supported by the Special Funds.
  - For 8 projects, budgetary revisions were recommended.
  - Two projects were considered to be potentially important but successful outcomes were considered to be 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.
  - One extension project was approved, conditional to the review of the report from previous studies that must show that substantial progress was made.
  - Three projects were approved only to study the human component of the proposal rather than the animal models.
  - One project, to validate the method on real doping control samples, was approved in part.
  - Two other projects that were complementary and from the same research group were approved with the condition that the investigators produce a unique detection method.
- Four projects that had been approved in principle for funding were not supported because they had been recently financed by other granting agencies.
- The HMRC was not supportive of the creation of consortia, where funds would be allocated on a regular and sustained basis to a group of research teams or researchers. The current stepwise approach, where the outcomes were evaluated yearly, was preferred.
- The HMRC wanted WADA to dedicate more funds to Targeted projects, where specific issues would be identified and investigators capable of addressing them would be contacted. In addition, the Chairpersons of the Experts Groups were encouraged to identify specific projects that could be funded through the Targeted projects. This would demand additional effort to the Science Department and as a consequence, more human resources may be needed.
- The HMRC was reminded that they should feel free to make suggestions to the Topics of Research Grants that will be circulated among the members for consultation before the call for grants.
- The HMRC was informed that there were 2 special projects to be funded from the science research funds involving the WADA Investigations Department.

## **5. Report from the Therapeutic Use Exemption (TUE) Expert Group**

- Prof. David Gerrard, Chair of the TUE Expert Group (TueEG) gave an update on the group's activities during 2015, informing that:
  1. Olympic Games 2016: The TueEG had already started working with the IOC Medical Commission to organize potential TUE review cases during next year Olympic Games in Rio

2. ADAMS: There had been a 60 % increase in the number of users ADAMS for TUE applications with respect to the previous year (9 new federations and anti-doping organizations). No all countries used ADAMS (e.g. USA, Australia)
3. WADA Medical Department activities: included screening and monitoring TUEs from all over the world. In terms of diagnostic class, most TUEs from January-August 2015 were related to nervous system diseases (mostly attention deficit hyperactive disorders, which continue to increase), followed by endocrine and metabolic diseases (mostly diabetes, also for hypogonadism, growth hormone) and respiratory diseases. Regarding the drug category, glucocorticoids represented about 30 % of all TUEs received from January-August 2015, followed closely by stimulants around 24 % and to a lesser extent Peptide hormones and beta-2-agonists. Seventy percent of requests came from anti-doping organizations and twenty nine from Federations.
4. TUE Physician Guidelines: most of these Guidelines usually stemmed from repeated queries from anti-doping organizations. There were 18 to-date and more would be added. Recent updates and revisions included Guidelines for anaphylaxis, growth hormone deficiency, neuropathic pain, musculoskeletal conditions, and intravenous infusions. Guidelines in progress included those for adrenal insufficiency, androgen deficiency-male hypogonadism and use of beta-blockers. Some reviews of TUE applications were very complex and challenging and ended in the Court of Arbitration for Sports as there were diverging opinions between WADA TueEG and the ADOs. Poor diagnoses of hypogonadism or adrenal insufficiency were linked to some of these cases. It was acknowledged that not all TUE Committees from anti-doping organizations or federations had the same level of proficiency to handle the TUE requests, even if the International Standard for TUE set the criteria.
5. Paris TUEC Symposium: took place in October 2015 and was aimed at TUE Committee physicians to enhance collaboration, discuss difficult issues, educate physicians and share knowledge and experience. The attendance was so high that it had to be limited. It was expected that another of these meetings would take place in 2017.

## **6. Update on the Athlete's Biological Passport**

- Dr Alan Vernec updated the HMRC on the Athlete's Biological Passport (ABP).
- The ABP was an indirect detection of doping by serial measure of biomarkers rather than by the direct detection of a prohibited substance. The longitudinal profiling using the adaptive model calculated the limits of normal physiological variations based on the athlete's own samples by a Bayesian-type algorithm. The results were further evaluated by experts. There was an Ad-hoc Committee evaluating the ABP.
- The ABP is implemented through ADAMS. Therefore, countries not using ADAMS did not implement ABP.
- To date there were 2 modules implemented (hematological and steroidal) and there had been progress on the endocrine module.
- In 2014 there were 35 federations and anti-doping organizations applying the hematological module, with about 18,000 samples tested. There had been a marked increase in the number of blood doping cases detected by the ABP in the last 4 years. The role of the experts consisted in evaluating all blood parameters and identifying any possible pathological or confounding conditions that may have impacted an athlete's analytical result.
- The steroidal module used the urine tests entered in ADAMS. All Atypical Passport Findings required appropriate Results Management. The steroidal module detected direct steroid

doping (e.g. testosterone, designer steroids) and indirect steroid doping (e.g anti-estrogens, aromatase inhibitors). Considering the genetic variations associated with steroid metabolism, the evaluation of the individual's data was very advantageous as it allowed for more sensitive detection of abuse below the population based limits.

- Overall the ABP had been a very good addition to the battery of doping control testing but it had to be improved, new and traditional tests were needed, confounding factors analysed and research in this area constituted a WADA priority. Dr. Fourneyron added that microdosing constituted a huge challenge for the ABP.

## **7. Report from the Laboratory Expert Group**

- Dr. John Miller , Chair of the Laboratory Expert Group (LabEG), gave an update on the LabEG activities during 2015:
  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, preparing and revising as needed the International Standard for Laboratories, technical documents and Guidelines and providing recommendations regarding laboratory performance to WADA decision bodies.
  2. There were 35 WADA-accredited laboratories, representing 3 more than last year, and included Brazil (Rio de Janeiro), Turkey (Ankara) and Qatar (Doha)
  3. There were no Probationary Laboratories.
  4. There were 2 Candidate Laboratories:
    - i. Cairo (Egypt): Excellent facilities were available but personnel had little experience. A Technical Questionnaire was completed in November 2014. There was an agreement in place with the Barcelona Laboratory for technical/scientific assistance.
    - ii. Santiago laboratory (Chile): Located in the Faculty of Pharmacy, University of Santiago. A technical questionnaire had been completed. There was a proposal to coordinate the testing of blood parameters with the laboratory in Montevideo (Uruguay).
  5. There were 5 new laboratory directors: Barcelona, Lisbon, Bloemfontein, Oslo and Paris (interim). Two laboratory directors were interviewed over concerns of their laboratory performances.
  6. External Quality Assessment Scheme (EQAS) performance: there were 5 false negatives reported by laboratories during the regular and double-blind EQAS rounds. Other issues identified included late reporting of results and Corrective Actions reports, insufficient quality of Documentation Packages and Corrective Action Reports. The HMRC was presented with the Point Scale for assessment of laboratory and probationary laboratory performance, where scoring is given for different failed performances and where actions to be taken for each performance and accumulated score were specified. There were also Educational EQAS that did not implicate any demerit points.
  7. Several site visits occurred in the past 12 months: Poland (Warsaw), several to Brazil (Rio de Janeiro) for pre-probationary test, progress monitoring and final Accreditation Test, several to Russian Federation (Moscow) assigned by the Independent Commission investigating corruption allegations, Doha (Qatar) for Final Accreditation

Test, Turkey (Ankara) also for Final Accreditation Test, Greece (Athens), Thailand (Bangkok), South Korea (Seoul), Kazakhstan (Almaty) and South Africa (Bloomfontein). Other visits planned for 2015 were to Romania (Bucharest), China (Beijing) , UK (London) and Brazil (Rio de Janeiro) to continue monitoring for upcoming Olympic Games

8. Technical Document of Sport-Specific Analysis: the LaEG made some suggestions to the group working on this technical document, including a coordinated collaboration between the laboratories, WADA and the World Association of Anti-Doping Scientists (WAADS).
9. Expanded testing List: in co-operation with WAADS, a comprehensive and expanded list of prohibited substances (including whenever possible known metabolites) was compiled and presently being reviewed. When completed & implemented, the laboratories will require to identify a greater range of prohibited substances. WADA and WAADS were working together to source the reference standards required. The laboratories would include these substances as soon as practical. The aim was to further harmonize testing in particular for some new or more challenging to test substances.
10. Five revised Technical Documents were approved by the Executive Committee and came into effect in January 2015: TD2015GH(1.0) Human Growth Hormone (hGH) isoform differential immunoassays for doping control analysis; TD2015IDCR(2.0) Minimum criteria for chromatographic-mass spectrometric confirmation of the identity of the analytes for doping control purposes; TD2015MRPL (1.0) Minimum Required Performance Levels for Detection and Identification of Non-Threshold Substances; TD2015NA (1.0) Harmonization of Analysis and Reporting of 19-Norsteroids Related to Nandrolone; TD2015BAR (1.0) Blood analytical requirements for the Athlete Biological Passport; Technical notes for procedures applied e.g. electrophoretic methods for EPO & GC/C/IRMS for exogenous steroids.
11. A few laboratories were facing some challenges, including financial, managerial and organizational issues, failure to implement IRMS analysis and insufficient expertise.
12. Despite some difficulties there was overall good performance and the great majority of laboratories were performing well but there was a small minority which required greater degree of monitoring and assistance.
13. Regarding WADA-sponsored research, the LaEG reviews the final reports of technical grants and make recommendations for implementation or follow-up projects.

## **8. Report from the Gene Doping Panel**

- Dr Fournayron congratulated Prof. Ted Friedmann for being awarded the prestigious 2015 Japan Prize for his contribution to Gene Therapy. The HMRC applauded Prof. Ted Friedmann for this achievement.
- Prof. Theodore Friedmann, Chair of the Gene Doping Panel (GDP) summarized the role of the Panel, the discussions that took place during the GDP meeting and the recommendations from the Panel:
  1. Role: monitor advances in genetics and their potential impact and application to sport. The GDP had expertise on gene therapy, gene editing and stem cell biology. Outside experts are invited for updates. The Panel also assisted HMRC with evaluation of grant applications and outcomes and advised WADA on implementation of new assays in testing laboratories.
  2. Specific issues discussed by external experts included stem cells use in sport, methods of gene modification and gene editing, efficacy of methods for detecting foreign viral

gene transfer vectors and foreign genes and the efficacy of molecular signatures for EPO.

3. A major step forward to an effective new screening technique for gene doping was achieved by Dr Anna Baoutina, from Australia, which constituted the first approved gene doping screening test validated by WADA laboratories that would be implemented in selected WADA testing laboratories.
  4. The impacts of the genetic revolution in sport remained to be seen, but will certainly be an issue that would grow with the development of the technology in other fields
  5. During the GDP meeting in February 2015, the Panel evaluated the overall summary of WADA research program. There were reservations and concerns regarding the slow progress in many projects. There was an update on transgene/vector detection projects of Simon/Snyder/Moullier and Baoutina groups where it was evident that, even if the approaches were similar, the Baoutina results were closer to implementation. Therefore, it was recommended to distribute this assay to several WADA-accredited laboratories for validation. There was a presentation and discussion of "genome editing" technology (by Dr. Christian Beausejour, Montreal), and update on stem cell biology (by Dr J. Gearhart). However, this latter approach did not appear to be a concern in doping due to its apparent lack of performance enhancement. There was, also, a presentation on myostatin inhibitors (by Dr L. Sweeney) as well as a discussion of progress in "omics" with a recommendation for a targeted WADA commitment to "omics" projects.
- 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. In addition, the relevance of stem cell treatment in sport was addressed. The HMRC in general agreed with the conclusions of the GDP.

## **9. Requests for Proposals (RFP)**

- Dr Olivier Rabin presented a draft template for the RFP on Autologous Blood Transfusion. The idea was to call for grants before the end of 2015. There were suggestions to shorten preliminary applications to an expression of interest and to target different hematological societies and meeting to attract proposals. It was suggested that a meeting of experts could be convened. Dr Fourneyron would present this draft during the Executive Committee meeting in mid-September. ACTION POINT.

## **10. Conference with Pharmaceutical Industry in Tokyo**

- Dr. Fourneyron informed the HMRC on the meeting between WADA, governmental health and sport authorities and the major pharmaceutical companies in Tokyo in January 2015. WADA representation included both the WADA's president Sir Craig Reddie and WADA's Director General, Mr David Howman. Japan Anti-Doping Agency was very supportive of the meeting and was involved in the organization, together with WADA, UNESCO and the Japanese Ministry of Sport. Dr Hidenori Suzuki was thanked on their behalf. This meeting was a follow up to the successful first Conference 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. The meeting was attended by many pharmaceutical companies. The importance of the need to further develop partnerships with those that can provide information on new drugs (e.g. pharmaceutical and biotechnology companies) was stressed. The number of participants was high and there was a willingness

of the participating parties to collaborate, as it was recognized that doping was a social problem.

#### **11. Involvement of experts in legal cases reviews.**

- Dr. Olivier Rabin informed the HMRC that there were an increasing number of legal cases where WADA Science and Medical Departments were solicited as experts by the Federations and Anti-Doping Organizations. WADA was trying to rely on external experts because of lack of human resources as well as the fact that WADA needed to preserve its right of appeal under the Code. The HMRC was invited to share the names of experts that could help in this task.

#### **12. Closing Remarks**

- Dr Fourneyron thanked the HMRC members for their commitment and the quality of the discussions. Dr Fourneyron also reminded that 3 members of the HMRC would finish their mandate at the end of 2015 and that if there were adequate candidates to replace those positions, to please submit the proposals by October 9, 2015.

#### **13. Next meeting**

- The next HMR Committee tentative meeting was scheduled for **August 30-31 2016**, while that of the Project Review Panel would take place on **August 29 2016**.
- The meeting was adjourned.