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**WORLD ANTI-DOPING AGENCY  
Health, Medical & Research Committee Meeting Minutes  
August 27-28 2019**

**Participants:**

Health, Medical & Research Committee (HMRC)

Prof. Dr. Uğur Erdener, Chair	Attending
Prof. Wayne Derman	Attending
Prof. Alessia Di Gianfrancesco	Attending
Dr. Lenka Dienstbach-Wech	By teleconference
Prof. Lena Ekström	Attending
Prof. Lars Engebretsen	Attending
Prof. David Gerrard	Attending
Prof. David Handelsman	Attending
Dr. Audrey Kinahan	Attending
Prof. Margo Mountjoy	Attending
Dr. Aya Nakitanda	Attending
Prof. Maria Orbetzova	Attending
Dr. José Antonio Pascual	Attending
Prof. Christian Strasburger	Attending
Prof. Hidenori Suzuki	Attending
Prof. Ye Tian	Attending
Dr. Terence Wan	Attending

WADA Staff

Dr. Osquel Barroso	Attending
Dr. Irene Mazzoni	Attending
Dr. Marcia MacDonald	Attending
Dr. Olivier Rabin	Attending
Dr. Alan Vernece	Attending

Observers

- Prof. Christiane Ayotte (INRS, Montreal, Canada) representing the World Association of Anti-Doping Scientists (WAADS)
- Prof. Fabio Pigozzi (IUSM, University of Rome) representing the Fédération Internationale de Médecine du Sport (FIMS).

Apologies

- Prof. Theodore Friedmann
- Dr. Timothy Armstrong, World Health Organization (observer)

## 1. Welcome and Review of the Agenda

- Mr. Olivier Niggli, WADA Director General, welcomed the Health, Medical and Research Committee (HMRC), highlighting the importance of this Committee and their challenging activities.
- Mr. Niggli pointed out that the List Expert Group (LiEG) had very good suggestions on how to enrich the Prohibited List process. He also noted that Scientific Research is a key WADA activity, but funds had been limited in recent years due to budgetary restraints. Mr. Niggli hoped that more resources would be available in the near future. Finally, he stressed the importance of maintaining and supporting the network of high-quality doping control laboratories which were crucial for the fight against doping.
- Mr. Niggli thanked the HMRC and left the meeting.
- Dr. Uğur Erdener, Chairman of the HMRC, welcomed the Committee, indicating that there were two newly appointed members: 1- Prof. Wayne Derman, Director and Chair of the Institute of Sport and Exercise Medicine, Department of Surgical Sciences at Stellenbosch University in South Africa, Co-Director of the International Olympic Committee Research Centre of South Africa and member of the International Paralympic Committee Medical Commission and 2- Dr. Lenka Dienstbach-Wech, Surgeon in Frankfurt, Germany, Chair of the World Rowing Federation (FISA) Athletes Commission and former rowing champion.
- Prof. Theodore Friedmann, Chairman of the WADA Gene and Cell Doping Panel and Professor at the University of San Diego was absent for personal reasons.
- Subsequently, all the other Committee members introduced themselves:
  - Prof. Dr Uğur Erdener, Chairman of the HMRC, Professor in ophthalmology and surgeon, member of the International Olympic Committee (IOC) and Chair of the IOC Medical Commission as well as President of World Archery. In addition, Prof. Dr Erdener serves as a WADA Executive Committee (ExCo) and Foundation Board member;
  - Prof. Alessia Di Gianfrancesco, Professor in Pharmacology and member of the Italian National Anti-Doping Organization and of the Therapeutic Use Exemption (TUE) Committee of FIBT and UCI;
  - Prof. Lena Ekström, pharmacologist and toxicologist, from the Division of Pharmacology at the Karolinska Institute in Sweden,
  - Prof. Lars Engebretsen, sports physician, Professor in Orthopedics and Head of IOC Medical Sciences;
  - Prof. David Gerrard, Chairman of the WADA TUE Expert Group, specialized in internal and sports medicine at the University of Otago, former Olympic swimmer;
  - Prof. David Handelsman, endocrinologist at the ANZAC Research Institute and Department of Andrology, Concord Hospital in Australia and involved in anti-doping for more than 13 years;
  - Dr. Audrey Kinahan, Chair of the WADA LiEG and pharmacist, assessor of the Irish and European Medicines Regulation authorities;
  - Dr. Margo Mountjoy, sports medicine physician, member of the IOC Medical Commission and FINA Sports Medicine Committee, and former international synchronized swimmer.
  - Dr Aya Nakitanda, physician and former Olympic swimmer, currently Head of the national antidoping program at the Uganda Olympic Committee, board member for the Africa Zone V Regional Antidoping Organization (RADO) and member of Uganda Swimming Federation Medical Committee;

Prof. Maria Orbetzova, MD, PhD, Head of Clinic/Department of Endocrinology and Metabolic Diseases, «Sv.Georgy» University Hospital, Vice-Dean Education, Medical Faculty, Medical University of Plovdiv, Bulgaria.

Dr. José Antonio Pascual, Senior Researcher at the IMIM in Barcelona with long experience in anti-doping;

Prof. Christian Strasburger, endocrinologist, Chief of Clinical Endocrinology at the Department of Medicine of Charité-Universität, Berlin, and developer of the growth hormone isoforms test;

Prof. Hidenori Suzuki, pharmacologist and President of the Japan Anti-Doping Agency (JADA);

Prof. Ye Tian, researcher and former Head of CHINADA;

Dr. Terence Wan, chemist, Chief Advisor, Doping Control of the Hong Kong Jockey Club and Chairman of the WADA Laboratory Expert Group (LabEG).

- Finally, the observers introduced themselves: Prof. Christiane Ayotte representing the World Association of Anti Doping Scientists (WAADS) and Director of the Montreal anti-doping laboratory and Prof. Fabio Pigozzi, physician in internal medicine, representing the Federation International de Medecin du Sport (FIMS).
- Prof. Erdener noted that this would be a very important year for WADA, as the World Conference would be taking place in Poland in November, a new President will be elected and the revisions to the World Anti-Doping Code and the international standards would be reviewed for final approval. In addition, the new governance rules would come into effect in 2020, limiting the number of years that a member could be part of WADA standing Committees.

## 2. Conflict of Interest

- Dr. Pascual declared possible conflicts of interest for a few research grants from IMIM (Barcelona) that he would identify in due time and leave the room for the discussions and decisions.

## 3. Review of 2020 Prohibited List, report from the List Expert Group (LiEG) and recommendation to the WADA Executive Committee

- The Draft of the 2020 Prohibited List, prepared by the LiEG, was presented by Dr. Audrey Kinahan, Chair of the LiEG. The draft List was circulated to about 2,900 stakeholders from May to July, aiming to make little changes on the draft, if any, in August. The changes proposed were as detailed below:
  - a) S1. Anabolic Agents:
    - The sub-division of anabolic androgenic steroids (AAS) into '*a. exogenous*' and '*b. endogenous*' was removed and all AAS were joined into one class, S1.1: Anabolic Androgenic Steroids. This change was originally proposed by members of the HMRC during the 2018 HMRC meeting. The prohibited substances in S1 did not change but two additional examples (methylclostebol and 1-epiandrosterone) were included. This change was made to reflect the fact that all anabolic agents when administered exogenously were prohibited and harmonized the presentation of S1 with other classes of the List, which did not distinguish endogenous from exogenous origin. The determination of the substances' origin (i.e. whether they are of endogenous or exogenous nature) is, as before,

regulated in the corresponding technical document TD2019IRMS or any other applicable technical document (e.g. TD2019NA) or Technical Letter.

- In addition, LGD-4033, classified under S1.2 Other Anabolic Agents, was also listed by another commonly used name, ligandrol.

Prof. Handelsman considered that the changes introduced were in the right direction but did not go far enough. In this regard, he had proposed that the section should be called "Androgens" instead of anabolic agents. There are anabolic agents which are not androgenic and the List really refers to steroidal and non-steroidal androgens. Prof. Handelsman stated that the distinction into anabolic vs androgenic was simply mistaken. In addition, it also created a subclass S1.2 in which SARMs were listed separately although they were just non-steroidal synthetic androgens. In addition, Prof. Handelsman considered that the List should be indexed according to a chemical database (e.g. CAS, ChemSpider, PubChem) to remove any ambiguity about the structures and common names. The comments would be relayed to the LiEG for further consideration.

b) S2: Peptide hormones, growth factors, related substances and mimetics:

- Argon was removed from the Prohibited List because it was considered that it did no longer meet the criteria for inclusion.
- The word "signalling" was added to "TGF- $\beta$  inhibitors" to better reflect the predominant mechanism of action of the listed substances. It now reads "TGF- $\beta$  signalling inhibitors", which affect among other functions, the hematological mechanisms.
- The HMRC reiterated that Platelet-Rich-Plasma preparations were not prohibited if no growth factors were added to it.

c) S4: Hormone and metabolic modulators:

- Bazedoxifene and ospemifene were added as additional examples of selective estrogen receptor modulators.

d) M2: Chemical and physical manipulation:

- The wording was changed to clarify that the context of protease prohibition referred only to the tampering of samples. In this regard, it clarified that topical and systemic use of proteases were not prohibited.

e) M3: Gene doping: with the help of the Gene and Cell Doping Panel chaired by Prof. Friedmann, several changes were introduced:

- Classes M3.1 and M3.2 were combined, since the effects of gene doping on gene expression could be produced by technologies other than gene editing.
- "Transcriptional, post-transcriptional or epigenetic regulation of gene expression" were changed to "gene expression by any mechanism" to

encompass a wide range of mechanisms without exhaustively listing all steps at which gene expression may be altered.

- "Gene silencing" and "gene transfer" were added as further examples of gene doping methods.
- "Polymers of" was removed to reflect standard scientific terminology for nucleic acids.
- Regarding stem cells, it was reiterated in the Explanatory Note that non-transformed stem cells, used alone (with no growth factors or other hormones added) for the purpose of healing injuries were not prohibited, as long as they returned the function of the affected area to normal and did not enhance it.

f) S6: Stimulants:

- Octodrine (1,5-dimethylhexylamine) was added as an example of Specified Stimulants since it was recently found in some dietary supplements.
- It was clarified that the administration of imidazole derivatives was not prohibited when the routes of administration were dermatological, nasal or ophthalmological.

g) S7: Narcotics:

- It was clarified that all optical isomers were prohibited (e.g. levomethadone).

h) S8: Cannabinoids:

- The wording was updated for greater clarity as requested during the HMRC meeting in 2018, but the substances prohibited were not changed. All natural and synthetic cannabinoids were prohibited including any preparation from cannabis or any synthetic cannabinoid. Natural  $\Delta^9$ -tetrahydrocannabinol (THC) and synthetic THC (e.g. dronabinol) remain prohibited. All synthetic cannabinoids that mimicked the effects of THC also remain prohibited. This will also be reflected in a Question & Answer (Q & A) on the List posted in WADA website.
- It was reiterated in the Explanatory Note that cannabidiol (CBD) was not prohibited. However, since some CBD products extracted from cannabis plants may also contain THC that could result in a positive test for a prohibited cannabinoid, athletes should be warned to be cautious.

i) Monitoring Program:

- Ecdysterone was included in the Monitoring Program to assess patterns and prevalence of misuse. While other ecdysteroids exist, most data (especially concerning effects on athletic performance) and stakeholder comments centered around ecdysterone, and consequently it was added to the Monitoring Program for 2020.

- The LiEG was exploring the possibility of collecting information for the Monitoring Program by allowing the laboratories to analyze stored data from routine doping control analysis. This would require a change in the Code. The HMRC was favorable to the suggestion, so this would be proposed to the Code Review Working Group.
  
- j) The draft 2020 List was put into consideration and approved by the HMRC. This draft would be presented to the WADA ExCo for approval on September 23, 2019.
- Dr Kinahan informed the HMRC of subjects to be discussed by the LiEG in 2020, some of which were ongoing projects.
  - a) Glucocorticoids (GC) Working Group (GCWG):
    - The GCWG, composed of experts in GC pharmacokinetics, pharmacodynamics, dose equivalents, ergogenicity and analytical chemistry and urinalysis, held their 2<sup>nd</sup> and 3<sup>rd</sup> meetings in December 2018 and March 2019.
    - During the first two meetings, all members agreed that the current reporting limit of 30 ng/mL was not adequate for all GC. In addition, it was determined that it would be difficult to establish unique urinary thresholds or to correlate ergogenicity and dose due to the different pharmacokinetics, potency and routes of administration. A new approach was proposed, based on the amount of GC required to mimic a fixed percentage increase in the body's natural daily cortisol production. When the administration of exogenous GC exceeded the upper range of normal physiological cortisol by more than an established percentage, that dose would be considered to be potentially performance enhancing.
    - During the March 2019 meeting, the proposal was pilot-tested using a 20% cortisol threshold and GC doses and routes of administrations that were known to have either no effect or a positive effect in performance. In all cases the calculations were adequate to classify performance enhancing from non-performance enhancing routes and doses.
    - The results of the pilot test were presented to the LiEG during their 11-12 April meeting and the principle was well accepted.
    - The GCWG continued working with other GC and routes of administration. The results were presented during the 22-23 August LiEG meeting. These results also showed that local GC injections (e.g. intra-articular, peri-articular) produced cortisol levels equivalent to systemic prohibited routes.
    - The HMRC discussed the proposal and requested some clarifications. Overall, the Committee agreed that the task was very complex, but supported the rational and standardized model of comparing the different routes and doses through cortisol daily dose equivalents. The HMRC encouraged the GCWG to continue with their task. Future actions would include to do similar calculations with other GC and finally integrate these results with those from published and unpublished excretion studies done with different GC and routes of administration. The final aim was to re-evaluate the current prohibited routes of administration and/or establish different thresholds/reporting limits for different routes and GCs, with the objective of providing a concrete proposal to the LiEG leading to a better regulation on GC control.

b) “Strategic Thinking” on the LiEG activities:

- During the 31 January 2019 meeting, the LiEG engaged in discussions on how to make the List process better. There were three main topics: i) to strengthen the existing decision-making processes; ii) to communicate the contents/changes of the List better, and iii) to encourage more reactions from stakeholders.
- A proposal covering these 3 topics was prepared by the LiEG for the 11-12 April meeting and presented to WADA Executive Management. The proposal was well received.
- Subsequently, WADA management engaged in internal discussions to determine how to address the proposals from the LiEG “Strategic Thinking” and an update was presented to the LiEG during the 22-23 August 2019 meeting.
- Regarding the process to include or exclude substances and methods from the List, the LiEG had developed some defined procedures in the past. WADA reviewed them and made suggestions on how to improve some sections.
- Regarding how to better communicate the contents of the List, as well as to improve the Explanatory Notes and Questions & Answers (Q & A) on WADA’s website, WADA was receptive to introduce changes to make these documents more user-friendly, explainable and instructive. This could include engaging an expert in science communication to make the List more appealing.
- Dr. Rabin indicated that this was a work in progress, but the proposal gained support from different sectors at WADA. It was envisioned that while some changes could be implemented for the 2021 List, others would require more time.
- The HMRC was pleased with the initiative and noted that the List should indeed be made simpler for athletes. In addition, the HMRC encouraged the List EG to consider physician education on the List as well, to improve understanding and compliance, similar to what the TUE EG did around the Medical Guidelines for TUE.
- The HMRC thanked Dr. Kinahan for her presentation and the extensive work done by the LiEG.

#### **4. Review and Recommendation for the 2018 WADA Call for Scientific Research Projects**

- Dr. Rabin re-iterated that the funds available for scientific research were limited and WADA had approached private sources, but there was nothing concrete yet. Prof. Erdener evoked the possibility of a renewal of the Special Fund established in 2015 with equal contributions from the IOC and the governments. This will be further considered in the coming weeks.
- Prof. Handelsman and Dr. Pascual presented the conclusions and recommendations of the Project Review Panel (PRP) to the HMRC. The PRP, formed by three HMRC members, two external scientists and staff from WADA’s Science & Medicine Department, met on August 26 and reviewed the grants based on the independent external reviewers’ evaluations (three per application) as well as the PRP’s own assessment; in total each application was reviewed by 12 different individuals.

- Investigators from 22 different countries and 4 continents submitted 53 research projects to WADA in 2019. The number of proposals received this year was considerably less than other years.
  - Theme A - 16 projects were submitted in the category "Detection of Prohibited Substances/Methods: Methodologies in Analytical Chemistry"
  - Theme B - 6 projects were submitted in the category "Detection of Prohibited Substances/Methods: Affinity-Binding and Biochemical Methodologies"
  - Theme C - 13 projects were submitted in the category "Pharmacological Studies on Doping Substances/Methods"
  - Theme D - 11 projects were submitted in the category "The Athlete's Biological Passport"
  - Theme E - 7 projects were submitted in the category "Detection of Doping 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, 19 projects were selected and recommended for funding. Ten (10) of those would be supported by the Special Research Funds.
  - For 6 projects, budgetary revisions were recommended.
  - For one project, it was requested that only peptides known or suspected to be performance enhancing should be analyzed. The HMRC highlighted the importance of this project, as there as a proliferation of new doping peptides coming from the black market.
  - For one project, it was requested that only examples of substances of different classes should be tested with a new equipment, to evaluate if sensitivity was improved.
  - For another project, the use of serum rather than plasma or dried blood spots should be prioritized.
  - For one project targeting the production of reference materials for sulfated metabolites, it was recommended to target long-term metabolites.
  - For one project, it was suggested, if possible, to utilize a different collection procedure while, for another, to use a different route of drug administration.
  - For one project, it was requested that the elucidation of the chemical structures should be prioritized over the other parts of the grant.
  - The budget of one project was slightly increased because there was a request to add more experiments.
  - For one grant, the HMRC requested to add the comparison between the proposed method and the one currently used.
  - For a follow-up project, it was requested that only long-term stability experiments should be done to consolidate and validate previous results.
  - For one project, it was requested that more detail of the experiments should be provided.
  - One project submitted in 2018 had the budget drastically cut. However, not all experiments could be covered with that funding, so the difference needed in the budget was restored this year.
  - All the other projects were funded as submitted.
  - Two follow-up projects were considered, but the initial grants had not been finished and reported. Therefore, they were not funded because the outcomes of the previous grants were unknown.
- The HMRC would submit the recommendations for funding of the 19 projects during the ExCo meeting on 23 September 2019.

## 5. Special call for grants:

- ❖ Update on markers of erythropoiesis stimulating agents and hypoxia:
  - Dr. MacDonald informed the HMRC that the Special Grant on Markers of Erythropoiesis Stimulating Agents and Hypoxia, approved late in 2017, was well advanced and samples had been collected. The metabolomic analysis was expected to start in summer 2019 while the proteomics was still to be determined.
  
- ❖ Special call for grants on Artificial Intelligence (AI) Application in Anti-Doping:
  - Dr. Rabin updated the HMRC on the special call for grants on AI.
  - As reported in 2018, WADA, in conjunction with the Fonds de Recherche du Quebec (FRQ), which depends from the government of the Province of Quebec, issued a Special Call for Grants on the application and impact of AI in anti-doping and by extension, other areas of society.
  - The primary interest was on analytical techniques and application of AI to identify use of prohibited substances and/or actions suggesting attempts to bypass anti-doping rules (e.g. performance, associations).
  - The Call for Grants was posted on 24 May 2018 and the deadline was 5 October 2018 and a total of 10 research projects were submitted.
  - The application review process was similar to that followed for the regular WADA call for grants, i.e. grants were reviewed by the WADA Science Department and the FRQ, where it was determined that 8 of the submitted proposals fulfilled the requirements of the call for grants. The grants were sent to three independent external reviewers.
  - In parallel, a Project Review Panel (PRP) was constituted and met on 13 February 2019. Three grants were pre-selected for further discussion with the research teams, which took place in mid-April 2019. These three proposals covered the call for grants from different angles: one proposed a broad use of anti-doping data, another focussed on the steroid module of the Athlete Biological Passport (ABP) and the third addressed legal and sociological aspects.
  - Two teams resubmitted revised versions of their grant applications and were recommended for funding to the HMRC and then approved by WADA ExCo by circulatory vote on 12 July 2019.
  - The third proposal needed additional discussions and was finally agreed that access to data would be limited to those data uploaded in ADAMS by stakeholders who agree to participate, and anonymization would be done on site at WADA by a third party to ensure the highest degree of privacy protection. In addition, expenses were reviewed and justified, and some aspects of ownership and access to intellectual property of the product were confirmed.
  - The HMRC discussed the merits of this innovative grant and the usefulness of the proposed outcomes. The HMRC agreed that the project had great potential and therefore recommended it to WADA ExCo for funding. The final decision would take place on 23 September 2019.

## 6. 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 2019.

- a) TUE monitoring in ADAMS: TUE monitoring was a key element of WADA's mandate and TUEs were monitored and screened by WADA following a prioritization algorithm. In 2018 there was an 18% decrease in the number of TUEs reported in ADAMS with respect to 2017. However, the figures from 2017 were inflated because of a backlog of data already accumulated in previous years. It is possible that the maximum number of new TUE submissions per year may have been reached.
- b) TUE by class: Glucocorticoids had the highest number of TUEs requested, mainly for inflammation, asthma, followed by stimulants, mainly for ADHD, which showed marked regional differences e.g. very few in Asia, very predominant in North America. Hormone and metabolic modulators were 3<sup>rd</sup>, mainly for insulin, followed by diuretics and masking agents, beta-2-agonists and peptides hormones.
- c) TUE Physician Guidelines: The TUEEG also worked on the annual update of the Medical Guidelines. Some of them had only minor changes (e.g. ADHD) while others were extensively revised (e.g. GH).
- d) TUE Checklist: The TUEEG also finished developing the TUE Checklist. This very useful tool was meant for athletes to bring to their physicians to ensure that they had the necessary information to submit a complete TUE. The Checklist was uploaded onto WADA's website and translated into 6 languages.
- e) TUE Reviews and Appeals: Some examples of TUE reviews recently undertaken by the TUEEG were presented to the HMRC. These included instances where decisions of NADOs or IFs to grant TUEs were reversed based on the ISTUE, e.g.: for the use of GH, since the diagnostic criteria were not met; for the use of a beta-blocker, because the treatment was not appropriate for the athlete's condition; for the use of testosterone for a 20 year-old cyclist, because the diagnosis was weak. In other cases, WADA reversed the rejection of a NADO or IF to grant a TUE, e.g.: a retroactive TUE for the use of an ADHD medication; a TUE for the use of medicinal marijuana or for the use of insulin.
- f) TUE module in ADAMS next generation: the TUE module is being completely redone in the next generation of ADAMS. The project started in April 2019 in conjunction with stakeholders (e.g. ADO managers and physicians) and in consultation with the TUEEG.
- g) E-Learning for Medical Professionals: the platform was completely revamped with updated material, originating from external and internal experts. It included an IOC Pre-Games module. It was developed by an external supplier and it is mobile friendly. It will be launched on the WADA ADeL platform in late 2019.
- h) Other activities:
  - a. The International Standard for TUE was being updated with the participation of 2 external and 1 internal lawyer, 1 external physician, the TUEEG and WADA Medical section staff of the Science and Medicine Department.

- b. Publications: there were two publications related to TUE, one addressing the use of glucocorticoids in sport (published) and the other rebutting the concept that athletes with TUE won more medals at the Olympic Games (in progress).
  - c. TUE support: it was provided to NADOs and IFs as well to other WADA departments for compliance in audits and corrective action reports as well as for communications with stakeholders, legal and investigations issues.
- i) The HMRC discussed the presentation and was particularly impressed by the usefulness of the TUE Checklist.
  - j) The HMRC thanked Dr. Gerrard and congratulated the TUEEG for their work.

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

- Dr. Terence Wan, Chair of the LabEG, gave an update on their activities during 2019:
  1. The WG was mainly composed of anti-doping laboratory scientists, analytical chemists and standard and measurement scientists.
  2. The key activities of the LabEG consisted in directing the process of accreditation and re-accreditation of anti-doping laboratories, assessing laboratory compliance and performance in accordance with WADA laboratory standards [International Standard for Laboratories (ISL), Technical Documents (TD), Technical Letters (TL) and Laboratory Guidelines (LG)], evaluating laboratory results from the WADA External Quality Assessment Scheme (EQAS), reviewing technical issues related to the operation of WADA accredited laboratories, reviewing selected WADA-funded research projects and providing recommendations for implementation, revising as needed the ISL, TDs, TLs and LGs and providing recommendations regarding laboratory compliance and performance to WADA decision bodies for final decisions.
  3. Since the previous HMRC meeting (Aug 2018), the LabEG held 3 meetings (November 2018, March 2019 and June 2019).
  4. There were currently 31 WADA-accredited laboratories, including those under suspension: Helsinki (Finland) self-suspended its anti-doping activities up to 15 February 2020 due to relocation and control by a new organization, and the National Dope Testing Laboratory (New Delhi, India), suspended for 6 months since August 2019. There was 1 probationary laboratory (Lisbon, Portugal). Three laboratories were reinstated: Bloemfontein (South Africa) in September 2018, Bucharest (Romania) in April 2019 and Stockholm (Sweden), partial suspension lifted in August 2019.
  5. There were 3 WADA-approved laboratories for blood testing in support of the Athlete Biological Passport (ABP): Egyptian Doping Control Laboratory (Cairo, Egypt), National Anti-Doping Laboratory (Moscow, Russia) and Lancet Laboratory (Nairobi, Kenya) and 1 candidate laboratory: King Faisal Specialist Hospital and Research Centre, (Riyadh, Saudi Arabia). For harmonization of analyses of blood samples in support of the ABP, all WADA accredited and approved laboratories must exclusively use the Sysmex XN-Series Automated Hematology Analyzer.
  6. There were 3 candidate anti-doping laboratories: Cairo, Egypt, a candidate for 6 years and therefore the LabEG requested the provision of a satisfactory business plan as a condition to maintain candidate status; Almaty, Kazakhstan, which was in the process of ISO/IEC 17025 re-accreditation and Bogotá, Colombia, which requested a delay in the re-accreditation process due to missing reference materials.

7. The WADA-approved ABP Laboratory in Auckland (New Zealand) was closing operations due to their decision not to acquire the new Sysmex equipment and the WADA-accredited laboratory in Mexico City (Mexico), was probably closing as well, pending final decision by the Mexican authorities.
8. In May 2019, WADA ExCo removed the candidate status of the Anti-Doping Analysis Laboratory of the University of Chile (Santiago, Chile) due to a lack of progress and support after several years.
9. There were several interviews with newly appointed Laboratory Directors who pointed out several challenges, like the relationship with their NADO and support from anti-doping authorities, the availability of human and financial resources, the low number of samples analyzed annually, lack of availability of reference materials and outdated laboratory instrumentation.
10. The new WADA ISL, version 10, approved by WADA ExCo in May 2019, would come into force on 1 Nov 2019 but would be short-lived because it would be further reviewed and edited to be consistent with the 2021 World Anti-Doping Code. The ISL Working Group would undertake the additional revision starting in September 2019.
11. Six Technical Documents were revised and published between September 2018 and August 2019: TD2019DL (Decision Limits for the Confirmatory Quantification of Threshold Substances), TD2019CG/LH (Reporting and Management of Urinary Human Chorionic Gonadotrophin (hCG) and Luteinizing Hormone (LH) Findings in Male Athletes), TD2019IRMS (Detection of Synthetic Forms of Endogenous Anabolic Androgenic Steroids by GC/C/IRMS), TD2019NA (Harmonisation of Analysis and Reporting of 19-Norsteroids Related to Nandrolone), TD2019MRPL (Minimum Required Performance Levels for Detection and Identification of Non-Threshold Substances) and TD2019GH (Human Growth Hormone (hGH) Isoform Differential Immunoassays for Doping Control Analyses). Most revisions were minor and most of the TDs were modified to account for the changes made in the new TD2019DL and to update the formula for adjusting thresholds or concentrations in samples with high urinary specific gravity.
12. Two Technical letters, providing guidelines to report tetroquinol and tulobuterol were issued as well.
13. The EQAS included 3 rounds of 5 blind urine samples annually for the Regular EQAS (2 already completed, the other scheduled for October), 5 urine samples for the double-blind EQAS, which were identically presented as an athlete's samples and distributed to laboratories by Testing Authorities on behalf of WADA, 2-3 rounds for the Educational EQAS to harmonize the identification and reporting of substances and monthly rounds of EQAS for blood samples.
14. On site laboratory assessments were done for varied reasons: e.g. preparation for upcoming major events, prior to entry into process of accreditation or final evaluation of accreditation for global anti-doping or ABP testing, non-compliant performance in EQAS or in routine operations, ISL/TD infringements, LabEG evaluation and decision, post suspension visits and as part of WADA's continuous laboratory monitoring activities. There were 8 site visits to laboratories since the last HMRC meeting, including New Delhi, Bangkok, Barcelona, Bucharest, Tokyo, Ankara, Havana and Stockholm.
15. The LabEG also reviewed reports of 9 selected research projects related to new laboratory methodologies and possible implementation in anti-doping laboratories, improvements in substance detection, detection of new markers for the ABP, synthesis of reference material and excretion studies to define beta-2-agonist thresholds. Recommendations were communicated to the relevant research groups and the information was disseminated to all laboratories when appropriate.

16. The HMRC discussed the activities of the LabEG. A key element for the survival of a laboratory was the support from the government in terms of resources. It was expected that not all laboratories would be able to afford the complexity of doping control analysis.
17. The HMRC thanked Dr. Wan for the update and congratulated the LabEG for their work.

## 9. Report from the Gene and Cell Doping Panel

- Prof. Friedmann, Chair of the Gene and Cell Doping Panel (GCDP), provided a summary of the activities of the Panel in a report presented by Dr. MacDonald.
  1. The GCDP was composed of scientists working in different areas of gene therapy, including cancer, muscle disease and performance, blood diseases, stem cells and gene transfer and manipulation.
  2. The role of the Panel consisted in monitoring advances in genetics and their potential impact and application to sport, assisting the HMRC with the evaluation of grant applications and the review of progress reports of WADA-funded studies, advising WADA on the implementation of new assays in testing laboratories and preparing and publishing commentaries on doping. When needed, the GCDP invited testimony from outside experts.
  3. The major discussion items discussed in recent years by invited guests included updates on detection of transgenes and gene transfer vectors, transcriptomic molecular signatures for EPO, nucleic-acid based drugs in development to target myostatin, stem cell and stem cell grafting applications in sport, genome editing, genetically modified/edited plants and telomerase modification.
  4. Salient points discussed in the 2019 meeting included reviewing the definition of gene and cell doping for the LiEG and the potential role of DNA sequencing in doping detection.
  5. With regards to the definition of gene doping, the GCDP discussed a publication by Jacob Shekow (J. Law Biosci. 2018, 5 (3): 786) where gene doping was defined as needing to be *"intentional, expected to be permanent, specific alteration of the DNA sequence of the cellular genome, for a clinical purpose"*. The proposed definition was considered by GCDP to be inappropriate and not applicable to doping, so an alternative wording was proposed and sent to the LiEG for consideration.
  6. There was an extensive discussion on DNA sequencing methods for doping detection. Dr. Anna Baoutina, from Australia and Dr. Hidde Haisma, from the GCDP and Ms. Jard Mattens, from University of Utrecht were invited to present the results from their studies. Dr. Baoutina's was an ongoing project using PCR-based enrichment of exon-exon junction sequences or other exon elements of target genes used for doping for library preparation and sequencing while Dr. Haisma's study was based on hybrid capture of exon-exon sequences of the target genes for sequencing. Ms. Mattens' was a pilot study that used targeted sequencing for detecting Epo cDNA using a Cas9-transposase fusion protein and sgRNA that bound selectively to Epo cDNA, and was considered to be less mature than the other approaches. Drs Baoutina's and Haisma's projects had made impressive progress but needed validation, so they were to be invited to apply for follow-up studies including in vivo validation of the methods.
  7. In the meanwhile, the efforts were focused to implement Dr. Baoutina's PCR assay in time for the 2020 Tokyo Olympic Games.
- The HMRC thanked Dr. MacDonald for the presentation on behalf of Prof. Friedmann

## 11. Alternative matrices for doping control analysis:

- Dr. Rabin introduced the subject on the advantages and disadvantages of using doping control matrices different from urine and blood. He reminded that at present, only urine and blood were accepted matrices and that any other matrices could be used to support the results of an Adverse Analytical Finding but not to override it. WADA frequently received research proposals to use other matrices like saliva, hair, breath, sweat, and these were almost systematically not considered to be a priority. Examples included detection of clenbuterol in hair, perfluorocarbons in breath. Saliva was discussed by the HMRC in the past but did not have support due to the abundance of confounding factors. Sweat may be problematic due to contamination. Dried blood or urine spots were not considered to be alternative matrices since the biological fluids were the ones approved for doping control analysis. The questions posed to the HMRC was to whether WADA should give more consideration to alternative matrices, at least at the research level.
- Several of the HMRC members gave their opinion. Prof. Handelsman believed there could be a place for the use of hair analysis. Prof. Ayotte mentioned that hair would only be useful for chronic administrations and if it was a matter of sensitivity, none of the other matrices would compare to urine or blood. Dr. Verneec noted it could be useful to distinguish the cases where a unique exposure was claimed. Dr. Barroso raised the fact that drugs stuck to hair differently depending on the colour and thickness. Dr. Wan noted that hair analysis is used in horse racing doping control, but even the follicle could become contaminated and there was no consensus on how to clean the hair. Dr. Pascual added that hair was always accessible to tampering. Prof. Ayotte proposed that WADA should convene a working group that should look into the published literature and recommend whether the results would be defensible in court. There was not much support for saliva: it could only be used for certain hormones but it could be easily contaminated with blood, and the collection required that the person didn't eat for a certain period of time. Breath would be limited to a few substances and could be contaminated with saliva, which in turn could be contaminated with blood.
- In summary the HMRC recommended to look more into hair analysis, implicating the LabEG and a special working group, but for the moment, disregard the other alternative matrices.

## **12. Information on low-level Adverse Analytical Findings**

- Dr. Barroso updated the HMRC on the activities of the Working Group addressing low concentration Adverse Analytical Findings (AAF). A number of stakeholders were critical that the sensitivity of the analytical methods had improved so much that laboratories could detect infinitesimal quantities that would not be meaningful for doping. It was very advantageous for anabolic steroids but more problematic for other drugs like diuretics. Supplements were also blamed for some of the AAF but many wondered if that should not incentivize stakeholders to ask the authorities to better control the supplement industry. It was less clear on how to deal with water or food contamination.
- Prof. Ayotte, also a member of the Working Group, noted that SARMs were present in many supplements, originating from the black market, so it was dangerous for the health of the athletes. Many of the long-term metabolites of anabolic steroids were always excreted at very low concentrations, so that did not indicate the real initial dose. In this regard, Dr. Kinahan pointed out that in a spot urine it was not possible to know if the initial dose was low or the low concentration was indicating the end of the excretion of a normal dose.
- Dr. Rabin noted that there was more support to deal with cases of contaminated meat or medications. In some rare cases, it could be water contamination as well.
- The Working Group would continue their work and attempt to come up with guidelines for at least some cases of possible contamination.

### **13. Any other business:**

- There was a request that WADA distribute to the HMRC members the published articles originating from WADA-funded projects.

### **14. Closing Remarks**

- Prof. Erdener thanked the HMRC members and WADA staff for a very productive and intense meeting and for all their contributions.

### **15. Next meetings**

- The next meetings were scheduled for **26 August 2020 for the Project Review Panel and 27-28 August 2020 for the Health, Medical and Research Committee.**
- The meeting was adjourned.