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WORLD ANTI-DOPING AGENCY
Health, Medical & Research Committee (HMRC) Meeting Minutes
August 29-30 2017

Participants:

Dr. Uğur Erdener, Chair	Attending
Prof. Alessia Di Gianfrancesco	Attending
Prof. Lena Ekström	Attending
Prof. Lars Engebretsen	Attending
Prof Theodore Friedmann	Attending
Prof. David Gerrard	Attending
Prof. David Handelsman	Attending
Dr. Manikayasagam Jegathesan	Attending
Dr. Audrey Kinahan	Attending
Dr. Margo Mountjoy	Attending
Dr. José Antonio Pascual	Attending
Dr. Orlando Reyes	Attending
Prof. Jürgen Michael Steinacker	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. Olivier Rabin	Attending
Dr. Alan Vernec	Attending

Observers
Prof. Fabio Pigozzi (IUSM, University of Rome) representing FIMS.
Prof. Peter Van Eenoo (DoCoLab, Ghent University, Belgium) representing WAADS

1. Welcome and Review of the Agenda

- Dr. Uğur Erdener, new Chairman of the Health, Medical and Research Committee (HMRC) welcomed the Committee members and introduced himself. Dr Erdener said that he took over the Chair position in January 2017. Dr Erdener is a Professor in ophthalmology and Surgeon, a member of the International Olympic Committee (IOC) and Chair of the IOC Medical Commission as well as President of World Archery. In addition, he serves as an Executive Committee and Foundation Board Member of WADA.
- Dr Erdener welcomed the new HRMC members Prof. Lena Ekström, from the Division of Pharmacology at the Karolinska Institute in Sweden, specialized in anabolic steroid research

and Prof. Ye Tian, researcher and former member of CHINADA. Subsequently, all the other Committee members, introduced themselves:

Prof. Alessia Di Gianfrancesco, Professor in Pharmacology and Member of the Therapeutic Use Exemption (TUE) Committee of the Federation Internationale de Bobsleigh et de Tobogganing;

Prof. Lars Engebretsen, Professor in Orthopedics and Head of Medical Sciences at the IOC;

Prof Theodore Friedmann, Chairman of the WADA Gene and Cell Doping Panel and Professor at the University of San Diego;

Prof. David Gerrard, Chairman of the WADA TUE Expert Group, specialized in internal and sports medicine at the University of Otago;

Prof. David Handelsman, endocrinologist at the ANZAC Research Institute and Department of Andrology, Concord Hospital in Australia;

Dr. Manikayasagam Jegathesan, Deputy President and Chairman of the Medical Committee of the Olympic Council of Malaysia;

Dr. Audrey Kinahan, Chair of the WADA List Expert Group and pharmacist, assessor of the Irish and European Medicines Regulation authorities;

Dr. Margo Mountjoy, sports medicine physician and Professor at McMaster University, with long experience in anti-doping;

Dr. José Antonio Pascual, Senior Researcher at the IMIM in Barcelona;

Dr. Orlando Reyes, sports doctor and member of the Instituto Colombiano del Deporte;

Prof. Jürgen Michael Steinacker, Professor of Sports Medicine at the University of Ulm;

Prof. Christian Strasburger, clinical endocrinologist and member of the German National Anti-Doping Agency;

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

Dr. Terence Wan, chemist, Head of the Racing Laboratory of the Hong Kong Jockey Club and Chairman of the WADA Laboratory Expert Group.

- Finally, the observers introduced themselves: Prof. Peter van Eenoo from the World Association of Anti-Doping Scientists (WAADS) and Director of the Ghent anti-doping laboratory and Prof. Fabio Pigozzi from the International Federation of Sports Medicine (FIMS).

2. Conflict of Interest

- Profs. Pascual and Handelsman declared possible conflicts of interest for the time of the reviewing a few research grants, as they knew or collaborated in the past with the principal investigators; Prof Strasburger declared a potential conflict of interest since he was co-founder of the company that developed the growth hormone (GH) isoform test; Prof Van Eenoo declared that some colleagues from his laboratory had applied for grants and Prof Friedmann indicated that he had applied for a grant. It was decided that for the general discussion they could remain in the room but for specific discussions on those projects and the final decision they would be asked to leave the meeting room.

3. Review of 2018 Prohibited List, report from the List Expert Group (Li EG) and recommendation to the WADA Executive Committee

- The Draft of the 2018 Prohibited List, prepared by the Li EG, was presented by Dr. Audrey Kinahan, Chair of the LiEG. The draft List was circulated to about 3,000 stakeholders in April

and 227 comments were received; some were very valuable but not all could be incorporated and will be considered for future revision. The changes proposed were as detailed below:

a) S0: Non-approved drugs: no changes made. There had been a proposal to narrow the scope of S0 to prohibit drugs which were not approved by WHO's definition of Stringent Regulatory Authorities rather than any regulatory agency in the world (a difficult task to verify), since countries with lax regulatory controls could approve marketing of drugs based on reduced safety and efficacy standards and which could be used for doping purposes. However, it was considered that the narrowed S0 definition was too restrictive and would pose a burden of proof on the athletes. The matter remained under further consideration.

b) S1: Anabolic steroids: there were new examples of exogenous anabolic steroids and SARMs added and the renaming of an anabolic steroid by its international non-proprietary name (INN).

c) S2: Peptide hormones, growth factors, related substances and mimetics: the whole section was reviewed and restructured for clarity and accuracy. ARA290 was removed from the Innate Repair Receptors section as it was considered that it did not fulfill the inclusion criteria in the List, being neither an EPO nor affecting erythropoiesis. There were many examples of GnRHs, GH secretagogues, GHRHs, GHRPs and new growth factors added. There was evidence that small hGH fragments (eg AOD9604) were being abused so they were added in the GH subsection. Dr Kinahan re-iterated that platelet-rich plasma preparations were not prohibited unless prohibited substances like growth factors or hormones were added. There was a request of the HMRC to the Li EG to revisit the literature on this procedure in 2018. ACTION POINT.

d) S3: Beta-2-agonists: the wording on dosing parameters of salbutamol was refined to make it clear that divided doses of salbutamol may not exceed 800 micrograms over any 12 hours. Tulobuterol was added as example. Dr Kinahan also noted that there were ongoing studies to define urinary thresholds to distinguish therapeutic inhaled administration of procaterol and vilanterol from other routes of administration or supratherapeutic doses.

e) S4: Hormone and metabolic modulators: SR9009 was added as an AMPK activator example.

f) S5. Diuretics and other masking agents: glycerol was removed from the Prohibited List because the information published in scientific articles since 2012 showed that the magnitude of glycerol-derived effects influencing the athlete's plasma volume and parameters of the Athlete Biological Passport (ABP) was minimal.

g) M1: Manipulation of blood and blood components: no changes proposed

h) M2: Chemical and physical manipulation: the permitted volume and timing of intravenous infusions were changed from no more than 50 mL per 6-hour period to no more than a total of 100 mL per 12-hour period since this change should not impact the ABP parameters. In addition, to reflect medical practice, "hospital admissions" was changed to "hospital treatments" and "clinical investigations" was clarified as "clinical diagnostic investigations".

i) M3: Gene doping: with the help of the Gene and Cell Doping Panel chaired by Prof. Friedmann, the definition of gene doping was updated to reflect new technologies (e.g. gene editing).

j) S6: Stimulants: 1,3-dimethylbutylamine was added as example. The HMRC requested to add more cathinone derivatives as examples but it was noted that many of these substances appeared and rapidly disappeared from the market due to high toxicity or poor efficacy. Therefore WADA was working closely with the United Nations Office of Drugs Control (UNODC) to target the more common and persistent drugs.

k) S7: Narcotics: no changes were introduced.

l) S8: Cannabinoids: the section was slightly structured to reflect new cannabimimetics in the market; in this regard examples of traditional Spice compounds were deleted since their consumption had declined and were less relevant as examples. Those substances remained prohibited nevertheless. Synthetic and pure cannabidiol was no longer considered prohibited as it did not have psychoactive activity, but the oil remained prohibited as it contained tetrahydrocannabinol.

m) S9: Glucocorticoids: a number of commonly used glucocorticoids were added as examples.

n) P1: Alcohol: Alcohol was removed from the List after several years of consultation with the affected Federations, as it was considered that it did not fulfill the inclusion criteria in the List. The Federations were asked to include alcohol in their sports rules if it was a safety concern in their sport.

o) P2: beta-blockers: as a result of removing Alcohol, beta-blockers became section P1.

p) Monitoring Program: Bemitil was added because of its increased use as declared in doping control forms. Hydrocodone was added to see current patterns of use.

q) The draft 2018 List was put into consideration and approved by the HMRC. This draft would be presented to WADA Executive Committee for approval on September 24, 2017.

- Dr Kinahan informed the HMRC of other issues discussed during the last LiEG meeting on 24-25 August 2017. The HRMC members further contributed to the discussion :
    a) Glucocorticoids (GC) Working Group (GWG):
        - GC are widely used in medicine since they are effective and cheap. The current reporting value (MRPL = 30 ng/mL) for an Adverse Analytical Finding (AAF) may not be adequate to distinguish prohibited systemic and permitted local injections. In 2016, the proposal for prohibiting all GC injections for a 72 h period before competition was not supported by a majority of the stakeholders that responded to the draft 2017 List consultation. Therefore, in August 2016 the HMR Committee requested the Li EG to enlarge the GWG to try to get a solution for issues surrounding the use of GC.
        - Problems to address included the overlap of urinary concentrations between local injections and systemic use, TUE burden of prohibiting GC that were commonly used in sport and complications with Results Management.
        - The Experts in the WG were Dr. Richard Budgett (Li EG), Dr. Martine Duclos (Centre Hospitalier Universitaire, Clermont-Ferrand, France), Dr. Peter Harcourt (Li EG), Dr. Audrey Kinahan (Chair, Li EG), Dr. Katja Mjøsund (TUE EG), Francesca Rossi (Cycling Anti-Doping Foundation), Dr. Martial Saugy (CHUL, Switzerland), Dr. Christian Strasburger (HMRC) and Mr. Nick Wojek (UKAD). WADA staff was composed of Adam Klevinas (Legal Manager), Andrew Slack (Medical Manager), Dr. Alan Vernec (Medical Director).
        - The GWG discussed different aspects of GC in sport and issued a report that contained 14 recommendations that affected different levels of WADA management and Expert Groups, including laboratory issues, results management, TUEs, education, investigations and sports specific analysis. These recommendations, as well as the publication of the report, are subject to further discussion.
        - The HMRC discussed the recommendations from the GWG.
        - It was noted that the issue of the overlap between systemic and local injections had not been dealt with. In this regard, as in the previous HMRC meeting, there were opinions that if local and systemic routes of administration had similar pharmacokinetics and excretion profiles and levels, then local injections should also be prohibited.
        - It was acknowledged that intra-articular injections caused adrenal suppression indicating a systemic effect. However, according to the literature the performance enhancing (PE) glucocorticoid effects were obtained using relatively high systemic doses for short periods which had prominent mood elevating effects.
        - A retroactive TUE was also something to consider.
        - It was concluded that the recommendation to establish thresholds based on PE doses of GC would require a clear definition of the doses and potency of the different GC which would require a heavy investment in research from WADA. A new WG with expertise in analytical and research aspects as well as endocrinology and pharmacokinetics should be formed. The HMRC also decided that all the different recommendations should be directed to the appropriate WADA established Expert Groups or where needed a new WG should be formed.

b) Narcotics:

- Dr Kinahan informed the HMRC that the Li EG formed a WG to determine whether Narcotics had a place in the List. The conclusion from the WG was that there is limited information that narcotics were PE so there were considerations on whether it could be removed from the List.
- The Li EG was however divided on the issue with both removal and status quo supported, based on the 3 WADA Code criteria used to consider a substance prohibited.

c) Unique List:

- The LiEG continued exploring the possibility to have a Unique List with substances prohibited at all times.
- Their initial proposal considered to prohibit Stimulants at all times. A Li EG WG on Stimulants had reviewed all the drugs in the category and believed they could be useful for doping when used out-of-competition as well. There could be a need to develop thresholds for some of them if they were of common use. Issues like supplement contamination and increase in TUE applications should be considered as well
- As mentioned in section b) above, Narcotics could be considered for removal from a Unique List according to the Li EG.
- Cannabinoids status was also questioned since the current high threshold for THC already made their prohibition rather meaningless. Cannabimimetics could be prohibited at all times as stimulants.
- The Li EG also proposed that GC would be prohibited at all times but there were some suggestions to prohibit them sports specifically.
- Beta blockers would be part of a Unique List.
- The Li EG requested guidance from the HMRC to define which would be the next steps and whether the Unique List should be proposed to stakeholders.
- The HMRC discussed the Li EG recommendations on the Unique List. It was noted that it was too premature in the present form to put it into consideration to stakeholders. In addition, there was little desire among the HMRC members to remove categories from the List. In particular, it would seem irresponsible to remove narcotics when the world was facing an opioid abuse crisis related to fentanyl and derivatives, although it could be misinterpreted as not social responsible. In addition, GC abuse could do serious damage to the athlete and should remain prohibited.
- In addition, it seemed somehow contradictory to propose a Unique List and prohibit certain categories only in certain sports.
- In conclusion, the Committee believed that the HMRC members needed more time to study and process the information on the Unique List. Since there was no urgency, it was decided that a general overview would be presented during one of the next WADA Executive Committee meetings to seek for feedback and reaction. ACTION POINT.
- The HMRC congratulated Dr Kinahan for all the GWG thorough work.

4. Review and recommendation for the 2017 WADA Call for Scientific Research Projects

- Profs. Handelsman and Pascual presented the conclusions and recommendations of the PRP to the HMRC. The PRP comprising two HMRC members, two external scientists and WADA's Science Department had met on August 28 and had reviewed the grants based on the independent external reviewers' evaluations (three per application) as well as the PRP's own assessment so that each application was reviewed by 10 different individuals.
- Investigators from 23 different countries and 4 continents submitted 85 research projects to WADA in 2017.
    - Theme A - 32 projects submitted in the category "Detection of Prohibited Substances/Methods: Methodologies in Analytical Chemistry"
    - Theme B - 7 projects submitted in the category "Detection of Prohibited Substances/Methods: Affinity-Binding and Biochemical Methodologies"
    - Theme C - 11 projects submitted in the category "Pharmacological Studies on Doping Substances/Methods"
    - Theme D - 22 projects submitted in the category "The Athlete's Biological Passport"
    - Theme E - 13 projects submitted in the category "Detection of Doping Substances/Methods: Molecular Biology, Omics and Miscellaneous Methodologies"
- The HMRC considered the recommendations from the PRP, proposed funding additional grants and discussed in more detail several applications. As a result, 29 projects were selected and recommended for funding. Thirteen (13) of those would be supported by the Special Funds. Overall the funding for research had been substantially reduced over the years and was at a minimum in 2017 but this was in part compensated by the remaining of the Special Funds.
    - For 18 projects, budgetary revisions were recommended.
    - 6 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.
    - For one project, it was requested that metabolic studies should only be done when a new substance was identified in the tested supplements.
    - The funding for one study was increased because an additional Certified Reference Material was requested.
    - For one pharmacokinetic study, it was requested to extend the collection period of the samples.
    - One project was revised to compare results of whole blood and dried blood spots, while in another a comparison between results in blood and urine was requested.
    - For one project, the in vitro part was not funded because the relevance to anti-doping was limited.
    - In one project, there was a request to compare the effects on performance of 2 pain killers with different mechanism of action.
    - In another study, there was a request to use the newest fungicides in the market and concentrate on the therapeutic doses.
    - For another project, there was a request to detail the experimental procedure since it was vague.

- Two projects that were complementary and from collaborating researchers were approved and merged but part of it was not funded since it was not a priority.
- For one project, the HMRC was interested in one marker of red blood cells aging but not another.
- For one project, a reduction of personnel was requested since it far exceeded the needs of the study.
- All the other projects were funded as submitted

- The HMRC would recommend the funding of the 29 projects during the Executive Committee meeting on September 24 2017.

5. Special call for grants on Markers of Erythropoiesis Stimulating Agents (ESA) and Hypoxia:

- In February 2017, WADA issued a special Request for Proposals (RFP) to detect by proteomics and metabolomics specific markers of erythropoiesis stimulating agents that were not affected by altitude exposure.
- Nine grants were received, evaluated by external reviewers and a PRP specifically convened for this call for grants and two were retained as the best proposals. However, both required improvements.
- The revised proposals were resubmitted by the investigators and the PRP made their recommendation to the HMRC during the present meeting.
- The HMRC still found some limitations in the design of the studies and requested further clarifications on the part of the PRP. It was expected that the PRP would address the criticisms and once evaluated, the HMRC would make a final recommendation by email consultation.

6. Improving the research grant submission:

a. Proposal for information included in Project Description

- During the reviewing process, it was noted that some proposals did not have the needed information needed for a thorough evaluation. In some cases, the project appeared important and useful but was difficult to evaluate. WADA Science Department proposed to add a number of subsections e.g. methods, conditions, subjects, treatments, statistical analysis, endpoint, to guide the applicants to provide additional information.
- The HMRC approved this proposal.

b. Proposal for Ethics self-assessment for research grant applications.

- Since inception, WADA grant application forms requested that the researchers provided their local Institution Review Board (IRB) ethics approval at the time the project was submitted to WADA.
- In many instances, the investigators believed they did not need ethics approval even if they were working with human material, including urine.
- In addition, in the last few years it was apparent that it had been more difficult for investigators to obtain the ethics approval beforehand. In some cases, the investigators had to pay for the review, so they would not incur in the expense unless they knew that the grant was approved. In other instances, the IRB would not grant an approval before a formal approval by WADA.

- In order to offset this problem, WADA Ethics Panel drafted a questionnaire that should be included in the application form. This brief ethics self-assessment was meant to serve as a reminder to applicants to address potential ethics issues in their proposal. It did not replace the requirement for local IRB ethics review or any legal compliance obligations from the country of origin nor WADA independent ethics review, which was mandatory for all grants using human subjects or human material. WADA also requested Animal Welfare approval in case of animal studies.
- The questionnaire was reviewed by the HMRC and after some slight modifications, the proposal was approved.

7. Report from the Therapeutic Use Exemption (TUE) Expert Group

- Prof. David Gerrard, Chair of the TUE Expert Group (TUE EG) gave an update on the group's activities during 2017, informing that:
    1. TUE EG and Medical Team composition: The Expert Group was composed exclusively of clinicians. Due to the increase in TUE submissions, a new TUE Manager was recruited by WADA to assist with monitoring and assessment
    2. ADAMS: There continued to be an increase in the use of ADAMS by the stakeholders during the previous year because there was more acceptance of its use. National Anti-Doping Organizations (NADO) constituted 82 % of ADAMS users. It was not known how many organizations did not use ADAMS but there were some solutions available to address this issue, like the WADA Code Compliance Questionnaire.
    3. TUE: Glucocorticoids had the highest number of TUE requested, followed by stimulants (mainly for ADHD), hormone and metabolic modulators (mainly for insulin), diuretics and masking agents and beta-2-agonists, peptide hormones, growth factors and related substances and finally anabolic androgenic steroids, narcotics and beta-blockers. There was a considerable number of unnecessary TUE submissions, e.g. for inhaled salbutamol.
    4. TUE Physician Guidelines: The TUE EG also worked on the annual update of the Medical Guidelines, the earliest of which was developed 10 years ago. These documents provided diagnostic guidelines as the basis of a satisfactory TUE application. Despite these Guidelines, many TUE applications were incomplete or contained errors. In addition, new Guidelines were being developed.
    5. TUE Reviews and Appeals: Some examples of TUE reviews recently undertaken by the EG were presented to the HMRC. These included instances of the reversal of several decisions by NADO or International Federations (IF) that had approved the use of testosterone or stimulants or metabolic modulators in the treatment of a number of clinical conditions across different sports. The basis for rejection included poor documentation, unsatisfactory explanation and inadequatediagnostic details. The percentage of refused TUE applications was approximately 5 %.
    6. WADA TUE Symposium: This would be held in Helsinki on 21-23 September 2017. The organization of the meeting had the support of the Finnish NADO and Government. The expected attendance was around 200 physicians, and the Symposium topics included updated clinical guidelines, educational cases, medico-legal precedence, networking and harmonisation.
    7. The HMRC discussed some related issues. There seemed to be some regionalization in the different treatments (for example ADHD), so there was a need for harmonization. Also, it was agreed that physicians should always

provide evidence that "Permitted" drugs had been trialed before resorting to the use ofprohibited alternatives.

8. Report from the Laboratory Expert Group

- Dr. Terence Wan, Chair of the Laboratory Expert Group (Lab EG), gave an update on the Lab EG activities during 2017:
    1. The WG was mainly composed of anti-doping laboratory scientists, analytical chemists and standard and measurement scientists.
    2. 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 (ISL) and applicable Technical Documents (TD), assessing the laboratory results of the WADA External Quality Assessment 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, reviewing selected WADA-funded research projects taking part in the WADA laboratory site visits, preparing and revising as needed the ISL, TD and Guidelines and providing recommendations regarding laboratory performance to WADA decision bodies.
    3. There were 32 WADA-accredited laboratories, including 4 currently under suspension (Los Angeles, Bogota, Mexico and Lisbon). Madrid and Doha had served the suspension and were re-accredited while Almaty and Bloemfontein accreditation had been revoked.
    4. There were 3 WADA-approved Athlete Biological Passport (ABP) only laboratories to perform analysis of blood samples: Bloemfontein laboratory (South Africa); Antidoping Centre Moscow (Russia) and Labtests Auckland Limited (New Zealand).
    5. There were 2 Candidate Laboratories: a) Cairo (Egypt): the NADO was developing very slowly and this delayed the laboratory access to accreditation. b) Santiago laboratory (Chile): the laboratory submitted a Business Plan, which was reviewed by the Lab EG and recommendations were communicated to the laboratory.
    6. There were 15 site visits to the laboratories since the last HMRC meeting, including Almaty (2), Seoul (2), Tokyo, Bloemfontein, Ankara, Lisbon, Doha, Madrid, Rome, Mexico, Bogota, Beijing, and Los Angeles. The reasons were varied: e.g. upcoming major events, non-compliant performance, ISL/TD infringements, to gain ABP testing approval, probationary phase or general laboratory evaluation
    7. The EQAS in urine included 3 rounds of 5 blind samples for the Regular EQAS, 5 samples for the double-blind EQAS, which were identically presented as an athlete's samples, 1-3 rounds for the Educational EQAS and monthly rounds of EQAS for blood samples.
    8. The WADA EQAS List WG was established to finalize the 2018 document containing the extensive list of substances to be tested by laboratories, including target metabolites and substances newly incorporated in the 2018 Prohibited List. The EQAS List was updated frequently.
    9. The ISL was being updated to e.g. further harmonize with the TDs, general improvement, clarify requirements of laboratory performance, align with the newly-revised ISO/IEC 17025 and include the *ad-hoc* WG recommendations regarding Laboratory Accreditation.
    10. Several TD were updated and approved: TD2017NA (Harmonization of analysis and reporting of 19-Norsteroids related to nandrolone); TD2017 CG/LH - (Reporting and Management of Urinary Human Chorionic Gonadotrophin (hCG) and Luteinizing Hormone (LH) Findings in Male Athletes); TD2017 MRPL (Minimum Required Performance Levels for Detection and Identification of Non-Threshold Substances);

TD2017 DL (v1 and v2) (Decision Limits for the Confirmatory Quantification of Threshold Substances); and TD2017 LDOC (Laboratory Documentation Packages). Three technical letters, which were instructions on very specific topics for laboratories, were issued as well.

11. The Lab EG also reviewed reports of 9 selected research projects related to new laboratory methodologies, improvements of detection methods, synthesis of reference material and detection of new substances, metabolites and markers.
12. An *ad-hoc* WG on laboratory accreditation was formed at the request of the WADA Foundation Board (FB) to undertake a review of the current system of accreditation. A preliminary report was presented to WADA's FB in May 2017 and in July 2017 WADA launched a stakeholder consultation process to review the recommendations made by the WG.
13. The HMRC discussed the future of accredited laboratories. It was recognized that most laboratories were performing extremely well and quality was essential. Independence of the laboratories from governmental organizations, including NADO, was imperative. The site visits were essential to assure e.g. best methods, knowledge, laboratory security. The HMRC recognized that the Lab EG was doing an incredible job and that more resources were needed to continue with this top level performance

9. Report from the Gene and Cell Doping Panel

- Prof. Theodore Friedmann, Chair of the Gene and Cell Doping Panel (GCDP) summarized the role of the Panel, the discussions that took place during the GCDP meeting and the recommendations from the Panel:
    1. The Panel 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. When needed, the GCDP invited testimony from outside experts. In addition, they assisted WADA HMRC committee with the evaluation of WADA grant applications and progress reports of WADA-funded studies in this field as well as advising WADA on implementation of new assays in testing laboratories.
    2. Previous invited guest included updates on detection of transgenes and gene transfer vectors, transcriptomic molecular signatures for EPO, pharmaceuticals affecting myostatin, stem cell and stem cell grafting applications in sport, genome editing, genetically modified/edited plants and telomerase modification.
    3. Salient points discussed in the last meeting included revising the definition of Gene Doping, an overall summary of the WADA research program for gene-related studies, discussion on the implementation of the direct gene doping test and ethical aspects of Gene Doping testing.
    4. The GCDP discussed use of stem cells in sport and reiterated that despite the claims, there was no proven repair of injury or enhanced function following their use.
    5. Gene editing was also discussed and was being followed closely. Its rapid advance as a potential gene therapy tool prompted the GCDP to include it in the Gene Doping definition.
- The HMRC agreed in general with the conclusions of the GCDP in that gene doping did not appear to represent an immediate threat but new developments should be closely followed to avoid potential abuse as well as harm.

10. Update on the Athlete Biological Passport

- Dr Alan Vernec updated the HMRC on the Athlete Biological Passport (ABP) program.

- The use of the ABP as well as the number of cases continued to increase in the last year.
- WADA ABP group was working on ways to do more strategic testing that included parameters such as risk, athlete, performance. An outcome of this would be a Performance Module that could be incorporated to the ABP.
- There were several Athlete Passport Management Units (APMU) formed by experts in the passport. The purpose was to be consulted by laboratories to evaluate ABP results that could trigger an atypical ABP.
- The ABP Experts Group consisted of specialists in hematology, anabolic steroids, endocrinology and analytical chemistry.
- A Blood Stability Score was established to evaluate the stability of samples that could not be analysed immediately. It was determined that if samples were kept at 4 C the degradation would be minimal and the time to a valid analysis could be increased up to 72 hours.
- There was a pilot project for the Endocrine Module to follow the GH isoforms tested longitudinally to see if the sensitivity could be improved. The results would be ready soon.
- There was also a search of new biomarkers mainly through "omics" and a special call for grants on "Markers of erythropoietin stimulating agents and hypoxia" had been issued (see Section 5).
- There had been an administrative restructuring within WADA and a new Deputy Director for the ABP was recently hired.

11. Markers to detect urine manipulation

- WADA was approached by the company RUMA (Germany), manufacturer of urinary markers to detect urine manipulation, because they believed that their technology could be useful to prevent certain forms of tampering and substitution.
- The markers were composed of a panel of polyethylene glycols (PEG)of different molecular weights detectable by liquid chromatography (LC) that have to be ingested at least 30 min before the sample collection.
- The PEGs were stable, not metabolized in the body, innocuous and had been approved by the Food and Drug Administration in USA and European health authorities. Preliminary results showed that they would not interfere with routine doping control analysis.
- The method would not be useful to detect urine dilution or addition of proteases.
- The HMRC discussed benefits and drawbacks of the method. The Committee believed that it was very difficult to tamper when the sample was collected in the presence of the doping control officer. Therefore, the markers would be redundant. Although for some athletes it could be embarrassing to collect the sample in front of a stranger, in general seemed to be an issue for a small percentage of the population. In addition, it would not solve all tampering instances (e.g. proteases, dilution) but would detect substitution.
- There could also be a lack of acceptance on the part of the athlete to swallow a pill perceived to be an unknown substance. In addition, if one removed the doping control officer as an observer it would make it easier to tamper undetected with urine samples. There were also fears that the athletes would blame the markers as a reason for an Adverse Analytical Finding.
- Making this method mandatory would also raise some serious questions (e.g. risk in case of pregnancy)
- The costs were estimated to be low.
- Overall, the HMRC did not see a clear advantage for using this technology as an aide for doping control sample collection and unanimously rejected further consideration for this methodology in the anti-doping context.

12. Procedure to include a prohibited substance in the testing menu

- One of the HMRC members requested to know the procedure to introduce a substance in the Technical Document on Sport Specific Analysis (TDSSA).
- It was explained that the TDSSA was developed because for some sports the need to test for certain substances was smaller based on risk assessment.
- The standard menu, meant all the substances that were not defined in the specific testing menu (e.g. GH, EPO, IRMS, GHRP) and was updated regularly.

13. Closing Remarks

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

14. Next meeting

- The next Project Review Panel and HMR Committee meetings were scheduled for **August 2018 (most likely 28-29 August).**

- The meeting was adjourned.

ACTION POINTS HMR COMMITTEE MEETING- August 30-31 2016

Subject	Action Point	Responsible	Due date
Platelet Rich Plasma	Revise updated literature	LiEG	2018
Unique List	Present generalities to ExCo	WADA management	Next meeting 2017