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WORLD ANTI-DOPING AGENCY
Health, Medical & Research Committee (HMRC) Meeting Minutes
August 28-29 2018

Participants:

Prof. 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. Audrey Kinahan	Attending
Dr. Margo Mountjoy	Attending
Dr. Aya Nakitanda	Attending
Prof. Maria Orbetzova	Attending
Dr. José Antonio Pascual	Attending
Dr. Orlando Reyes	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. 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).

1. Welcome and Review of the Agenda

- Dr. Uğur Erdener, Chairman of the Health, Medical and Research Committee (HMRC) welcomed the Committee, in particular the newly appointed members: 1- Dr Aya Nakitanda, physician and former Olympic swimmer, currently member of Uganda Swimming Federation Medical Committee; and 2- 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.

- 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 an Executive Committee and Foundation Board Member of WADA;

  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, UCI and UIPM;

  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 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, 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 12 years;

  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, member of the IOC Medical Commission and FINA Sports Medicine Committee, and former international synchronized swimmer.

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

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

  Prof. Christian Strasburger, endocrinologist, Chief of Clinical Endocrinology at the Department of Medicine of Charite-Universität, Berlin, and developer of the growth hormone isoform assay;

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

  Prof. Ye Tian, researcher and former member of CHINADA.

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

- Finally, the observers introduced themselves: Prof. Christiane Ayotte representing WAADS and Director of the Montreal anti-doping laboratory and Prof. Fabio Pigozzi, physician in internal medicine, representing 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 isoform test. It was decided that for the general discussion, these members could remain in the room but for specific discussions on projects where they had potential conflict of interest and the final decision they would be asked to leave the meeting room.

3. Review of 2019 Prohibited List, report from the List Expert Group (LiEG) and recommendation to the WADA Executive Committee

- The Draft of the 2019 Prohibited List, prepared by the LiEG, was presented by Dr. Audrey Kinahan, Chair of the LiEG. The draft List was circulated to about 2,600 stakeholders in April, aiming to make little changes on the draft, if any, in August. For the 1st time, the consultation was divided in two, one part specifically addressing the proposed changes and a second part for themes for future consideration. The changes proposed were as detailed below:
    a) S1: Anabolic steroids: changes were done in collaboration with the Laboratory Expert Group (LabEG). Some substances were reclassified to better reflect their biological activity or their possible endogenous origin. Only examples of endogenous metabolites and isomers that were known to be currently available in nutritional supplements remained in S1.1b. There was a new example of endogenous anabolic steroids and a SARM was renamed by its international non-proprietary name (INN). For future consideration, the LiEG would explore the possibility of eliminating the distinction between endogenous and exogenous anabolic steroids.
    b) S2: Peptide hormones, growth factors, related substances and mimetics: more examples of Hypoxia-inducible factor (HIF) activating agents and growth hormone secretagogues were added. For accuracy, the title of S2.2 was changed to "Peptide Hormones and their Releasing Factors". Finally, some examples were renamed by their INNs.
    c) S3: Beta-2-agonists: tretoquinol (trimetoquinol) was added as an example. It is commonly available in some countries in Asia.
    d) S4: Hormone and metabolic modulators: 2-Androstenone was transferred from S1.1b to S4 to better reflect its biological activity and some of its analogues and isomers were added as examples. In addition, the title of S4.4 was changed to: "Agents preventing Activin receptor IIB activation" to reflect the multiple ways in which this receptor could promote ergogenicity and many more examples of this subclass were added.
    e) M3: Gene doping: with the help of the Gene and Cell Doping Panel chaired by Prof. Friedmann, the title was changed to reflect that cells were already included in this class. In addition, the term "post-transcriptional" was added to more completely define the processes that can be modified by gene editing.
    f) S6: Stimulants: two analogues of methylhexaneamine were added as examples and some amphetamine derivatives were renamed by their INNs.
    g) P1: Beta-blockers: levobunolol was removed as an example because it was redundant with bunolol.
    h) Monitoring Program: No changes were introduced.
    i) The draft 2019 List was put into consideration and approved by the HMRC. This draft would be presented to WADA Executive Committee for approval on September 20, 2018.
- Dr Kinahan informed the HMRC of future projects to be discussed by the LiEG in 2019, some of which were ongoing discussions.
    a) Inhaled beta-2-agonists:
        - Ongoing WADA-funded projects were attempting to develop thresholds to distinguish administration by inhalation, considered not performance

enhancing at therapeutic doses, from other routes of administration. These included vilanterol and procaterol. In addition, there would be a meta-analysis of data obtained from salbutamol excretion studies to ensure that the threshold reflected therapeutic use. Besides, the wording of the salbutamol pharmacokinetic study would be reviewed.

b) Stimulants:
- The LiEG would explore the possibility of prohibiting stimulants, or at least some of them, at all times because some athletes may be using them out-of-competition for doping while training. In addition, the LiEG would work with the LabEG to try to establish values for cocaine used in- or out-of-competition.

c) Plasmapheresis:
- This method was currently prohibited for the donor but the LiEG would work with the Athlete Biological Passport (ABP) group to determine how plasmapheresis could affect the blood profiles.

d) Aromatase inhibitors:
- The LiEG would explore whether this subclass could be prohibited in males only. The use by transgender athletes could pose an additional problem.

e) Glucocorticoids:
- A newly formed Working Group (WG) was exploring whether it was possible to define thresholds based on performance enhancement and, if not, to improve the reporting thresholds for glucocorticoids (see details Section i).

f) Thyroid hormones:
- The position article written by Dr. Martin Bidlingmaier, member of the LiEG, had been submitted to a journal and was going through revision.

g) Tramadol:
- Union Cycliste International (UCI) would prohibit tramadol as a health issue. In the meantime, WADA was continuing the monitoring of its use and the results of an ongoing study on performance enhancement.

h) Miscellaneous subjects: The HMRC discussed additional points related to the List:
- The LiEG should try to define "potential to enhance performance" in the Gene and Cell Doping class, more in particular regarding the manipulation and use of cells/stem cells. ACTION POINT
- The HMRC also requested the LiEG to review the wording of S8: Cannabinoids, in particular when referring to synthetic forms. ACTION POINT

i) Glucocorticoids (GC) Working Group (GWG):
- Dr. Olivier Rabin updated the HMRC on the progress addressing the recommendations done in 2017 by the extended Working Group (WG) on Glucocorticoids. In this regard, a new subgroup was formed to study the possibility of establishing reporting thresholds based on performance enhancement. The WG is composed of 2 experts in pharmacokinetics, 2 anti-doping laboratory experts, 1 pharmacist, 1 expert in glucocorticoid performance enhancement and 2 members of WADA Science and Medicine. The group met in May and believed that it would be very difficult to establish (a) threshold(s) based on performance enhancement due to the different potency and pharmacokinetics of the various glucocorticoids as well as the limited data on performance enhancement. Nevertheless, there were ways to improve the current situation, including the individual thresholds based on the different parent compounds and their metabolites. Eventually, the Laboratory EG,

TUEEG and Results Management would get involved in the process. A follow-up meeting was scheduled for December 2018.

j) Low level Adverse Analytical Findings:

- The laboratory limits of detection had improved significantly compared to the time of the inception of WADA and very low concentrations of drugs could be detected. In some cases, it was argued that those low levels were due to contamination. This contamination could be present in meat or in supplements, although it was also possible intentional spiking in the case of supplements. There were a couple of cases of contamination of pharmaceutical products, which need to be 99 % pure, leaving a 1% possibility of containing prohibited substances. There was a debate on whether to accept that contamination existed and to establish a floor level below which substances were not reported. In addition, substances that were prohibited only in competition may be detected even if administered out-of-competition close to the sport event or if the excretion was long. At the moment, the issue was also being addressed by the Code Review Team. The HMRC acknowledged the problem and believed that there could be some cases of contamination but that the low levels could also be due to the end tail of the excretion. In addition, long-term metabolites of anabolic steroids, which had greatly helped to catch dopers in retroactive testing, as well as GH-releasing peptides or PPARδ agonists, were always excreted at low levels. Furthermore, substances consumed out-of-competition could still be active in-competition. It would be difficult to establish a unique floor due to different potencies and pharmacokinetics. Finally, it could encourage athletes to increase the intake of supplements, as prohibited substances would be unreported below a certain level. Therefore, the HMRC recommended not generalizing the idea of contamination for the relevant substances and classes of substances on the List, to keep in mind that some supplements were purposely spiked, some thresholds would be not possible to establish if the drug was illegal or a drug in development and that establishing thresholds would mean the need of quantitation. Overall, the HMRC believed that there should be some flexibility to analyse the data and circumstances advances by the athlete.
- The draft 2019 Prohibited List, Explanatory Notes and Monitoring Program were finalized by the HMRC for recommendation to the WADA Executive Committee.
- 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

- Profs. Handelsman, Ekstrom and 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 WADA's Science Department, had met on August 27 and had 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 10 different individuals.
- Investigators from 27 different countries and 4 continents submitted 83 research projects to WADA in 2018.
    - Theme A - 16 projects submitted in the category "Detection of Prohibited Substances/Methods: Methodologies in Analytical Chemistry"

  - Theme B - 12 projects submitted in the category “Detection of Prohibited Substances/Methods: Affinity-Binding and Biochemical Methodologies”
  - Theme C - 19 projects submitted in the category “Pharmacological Studies on Doping Substances/Methods”
  - Theme D - 20 projects submitted in the category “The Athlete’s Biological Passport"
  - Theme E - 14 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, 18 projects were selected and recommended for funding. Four (4) of those would be supported by the Special Research Funds.
  - For 13 projects, budgetary revisions were recommended.
  - Three projects were considered to be important but successful outcomes were considered to be uncertain. Therefore, pilot projects of one-year duration were recommended with greatly reduced budgets.
  - For one project, it was requested that the metabolomics study be put on hold and to concentrate on the excretion studies. Samples should be kept for eventual metabolomics analysis depending on the results of the study.
  - Only half of one study was approved because the second study was considered redundant.
  - For 2 studies, the HMRC requested that only the human studies and not the in vitro were done, as the latter were less relevant for anti-doping.
  - For 2 studies it was requested to concentrate initial efforts on the synthetic substances to prove the proposed detection method would work and to put on hold the endogenous ones, that will require more complex methods of analysis.
  - For one project, there was a request to attempt to develop a universal antibody for some growth hormone secretagogues rather than several antibodies specific for each substance.
  - In one project, there was a request to compare the proposed new analytical method to existing ones.
  - In another study, there was a request to use blood and urine as matrix, but not saliva.
  - For one project, there was a request of a back-up plan in case the targeted sport event would not be possible to attain.
  - For another study, it was requested that enough reference material was produced to distribute to all anti-doping laboratories.
  - All the other projects were funded as submitted.
- The HMRC would recommend the funding of the 18 projects during the Executive Committee meeting on 24 September 2017.
- In addition, the HMRC discussed a project that was conditionally approved in 2015 but was subjected to a successful completion of previously ongoing projects by the principal investigator. The HMRC concluded that the results from the previous grants were positive and decided to approve the follow up project.
- Finally, in 2017, one grant had the funding decreased because it was expected that one substance could be obtained from the manufacturer, avoiding chemical synthesis. However, this proved to be unsuccessful because the drug had been discontinued. Therefore, the HMRC approved reinstating the original budget for the grant to cover for the costs of synthesis.

5. Special call for grants:

- Update on markers of erythropoietin stimulating agents:
  - The HMRC was informed that the Special Grant on Markers of Erythropoiesis Stimulating Agents, approved late in 2017, had started a few months ago after finalizing contract negotiations and ethics approval.
- Special call for grants on Artificial Intelligence (AI) Application in Anti-Doping:
  - Dr Rabin informed the HMRC that anti-doping activities generated massive amounts of data that were left largely unexplored. Montreal was considered a hub in AI and WADA had already engaged in a pilot project on the feasibility of using this data to define e.g. doping trend or suspicious profiles. One of the hurdles that would be encountered was data protection.
  - In view of this, and in conjunction with the Fonds de Recherche du Quebec (FRQ), which depends from the Province of Quebec government, WADA 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 idea was to develop algorithms and have a tool to analyse the data.
  - The maximum grant per project would be CAD$500,000.
  - The Call for Grants was posted on 24 May 2018 and the deadline was 5 October 2018.
  - The grant review would include independent peer reviewing and review by FRQ and WADA scientific committees.
  - The selected grants would be presented to the Executive Committee for approval later in the year.
  - A maximum amount of USD 1,000,000 was set aside.

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 2018. Prof. Gerrard commented that despite the fact that the TUE system came into question after the 2016 cyberattack following the Rio Olympic Games, recent unpublished data demonstrate that only 1.2 % of able-bodied athletes and 3.4% of disabled athletes at the Rio Olympics/Paralympics had active TUEs, and only 1 % of the medals were won by athletes with TUEs. These data indicate that TUEs were clearly not a means to dope. In addition Dr Gerrard informed the HMRC of:
  a) TUEEG and Medical Team composition: The Expert Group was the only WADA Committee composed exclusively of physicians.
  b) ADAMS: There continued to be an increase of 64 % in the use of ADAMS by the stakeholders during the previous year. Some International Federations (IF) and National Anti-Doping Organizations (NADO) still did not comply.
  c) 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. Most of the TUE came from NADOs.
  d) TUE Physician Guidelines: The TUEEG also worked on the annual update of the Medical Guidelines several of which were finalized in recent months e.g for

ADHD, adrenal insufficiency, anaphylaxis, male hypogonadism, beta-blockers for heart conditions. Others were being updated, e.g. asthma, growth hormone deficiency, musculoskeletal conditions, renal transplants and infertility. The TUEEG was also developing a TUE Checklist that athletes should bring to their physicians to facilitate the process of TUE applications.

e) 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 NADOs or IFs that had approved the use of testosterone or stimulants or metabolic modulators or intravenous infusions in the treatment of a number of conditions across different sports. In addition, cases where the TUEEG supported the NADO decisions were presented as well.
f) The HMRC discussed the presentation and agreed that the TUE process was sound and its integrity was unquestionable.
g) The HMRC thanked Dr Gerrard and the TUEEG for their work.

8. Report from the Laboratory Expert Group

- Dr. Terence Wan, Chair of the Laboratory Expert Group (LabEG), gave an update on their activities during 2018:
    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, assessing laboratory 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 of the WADA External Quality Assessment Scheme (EQAS) rounds, reviewing technical issues pertaining to the operation of WADA accredited laboratories, reviewing selected WADA-funded research projects and providing recommendations for application, revising as needed the ISL, TDs, TLs and LGs and providing recommendations regarding laboratory performance to WADA decision bodies.
    3. There were 32 WADA-accredited laboratories, including those under suspension: Lisbon (Portugal), Bogota (Colombia), Bucharest (Romania) and Stockholm (Sweden, provisional partial suspension) and 1 probationary laboratory (Bloemfontein). Three laboratories were reinstated: Los Angeles (USA), Mexico City (Mexico) and Paris (France).
    4. There were 6 WADA-approved laboratories for blood testing in support of the Athlete Biological Passport (ABP): SADC (Bloemfontein, South Africa); National Anti-Doping Laboratory (Moscow, Russia), Labtests Limited (Auckland, New Zealand), Egyptian Doping Control Laboratory (Cairo, Egypt), National Doping Control Laboratory (Bogota, Colombia) and Lancet Laboratory (Nairobi, Kenya).
    5. There was 1 Candidate Laboratory: Santiago laboratory (Chile): which must submit an updated and satisfactory business plan by 31 December 2018 to maintain its candidate status.
    6. There were several interviews with newly appointed Laboratory Directors who pointed out several challenges, like lack of funds, insufficient staff and instrumentation, lack of qualified personnel and lack of support from authorities.
    7. WADA ISL was currently under revision: the ISL Working Group (WG) met in September 2017 to draft the new version. The 1st consultation by circulation with only laboratories took place in March-April. After the review of comments and modifications, the 2nd

consultation with all WADA stakeholders was taking place July-September. Following their review of the comments, the WG would meet in October for the final draft, which would then be sent to the LabEG for approval and subsequently submitted to WADA Executive Committee in 14 November 2018. The proposed date for the ISL to come into force would be 1 March 2019.

8. The main modifications to the ISL included updates to the Introduction regarding description of different laboratory standards, inclusion of new metrological and method validation terms, important modifications and updates on the process and requirements for accreditation, a new section merging urine and blood analysis, modifications to the EQAS program and the addition of new procedural rules for the Disciplinary Committee of the ISL.
9. Six revised Technical Documents were published between September 2017 and August 2018: TD2017LDOC (Laboratory Documentation), TD2018MRPL (Minimum Required Performance Levels for Detection and Identification of Non-threshold Substances), TD2018CG/LH (Reporting and Management of Urinary Human Chorionic Gonadotrophin (hCG) and Luteinizing Hormone (LH) Findings in Male Athletes), TD2018DL (Decision Limits for the Confirmatory Quantification of Threshold Substances), TD2018BAR (Blood Analytical Requirements for the Athlete Biological Passport) and TD2018EAAS (Endogenous Anabolic Androgenic Steroids Measurement and Reporting).
10. Five TLs (Oxymorphone, Ostarine, Trimetazidine, Differences in "A" and "B" sample urine characteristics, Hydromorphone) and 2 LGs (Conducting and Reporting Subcontracted Analysis, TUE Enquiries by Accredited Laboratories) were published as well.
11. The EQAS in urine included 3 rounds of 5 blind samples annually for the Regular EQAS, 5 samples for the double-blind EQAS, which were identically presented as an athlete's samples, 2-3 rounds for the Educational EQAS and monthly rounds of EQAS for blood samples.
12. There were 11 site visits to the laboratories since the last HMRC meeting, including Seoul (2), Cairo, Paris, Lisbon, Bloemfontein, Nairobi, Salt Lake City, Bogota, London and Athens. The reasons were varied: e.g. preparation for upcoming major events, prior to entry into process of accreditation or final evaluation of accreditation for general anti-doping or ABP testing, non-compliant performance in EQAS or routine operations, ISL/TD infringements, LabEG evaluation and decision and as part of WADA's continuous laboratory monitoring activities.
13. The LabEG also reviewed reports of 7 selected research projects related to new laboratory methodologies and possible implementation in anti-doping laboratories, improvements of detection methods, detection of new markers for the ABP, synthesis of metabolites and excretion studies to define beta-2-agonist thresholds. Recommendations were communicated to the relevant laboratories and the information was disseminated when appropriate.
14. On-site assessment was very time consuming and 2 new scientists were being recruited to help in the process. In addition, Guidelines for site-visit were developed to harmonize and streamline the process.
15. 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. Theodore Friedmann, Chair of the Gene and Cell Doping Panel (GCDP) opened the discussion by noting that gene transfer of viruses carrying expression genes had evolved very quickly and had now reached clinical application, the preparation of material was simpler and the arrival of gene editing increased the level of possibilities of misusing these techniques in

sport. Dr Friedmann subsequently summarized the discussions that took place during the GCDP meeting:

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.
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. Previous invited guests 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.
4. Salient points discussed in the last meeting included reviewing the results of a study on genetic signatures of EPO administration that had been ongoing for several years. The discovery phase was concluded and the next step required validation of the putative markers. The GCDP evaluation helped in the HMRC decision to support the follow-up study as discussed in Item 4.
5. Other points of discussion included the assessment of the emerging problems of do-it-yourself gene manipulation promoted and sold on the internet. It was very easy to buy a vector, do a construct at home and auto-inject it. In this regard, the position of the US Federal Drug Administration (FDA) was weak, as it declared the sale for self-administration to be illegal but consumers were not violating the law if they did it for themselves.
6. The GCDP also heard a presentation by Dr Jerry Mendell, from the Ohio State University, on the progress in muscle gene therapy. There were 2 important clinical advances in muscular dystrophies. 1) Clinical trial of muscle-specific AAV-delivered myostatin inhibitor follistatin in Becker muscular dystrophy. 2) Use of anti-sense oligonucleotide (Spinraza) to prevent development of spinomuscular atrophy. None of these methods were likely to enhance muscle function in normal individuals.
7. At the request of the LiEG, the GCDP also reviewed the status of Nusinersen (Spiranza) and as noted above, concluded it was not prohibited. On the contrary, anti-myostatin antibody (REGN1033) and anti-activin antibody (REGN2477) were considered prohibited under S4. In addition, the GCDP helped the LiEG to restructure section S4.4 of the List which was now called *Agents preventing Activin IIB receptor activation*.
8. Finally, the GCDP heard a presentation on the role of sequence analysis in the ABP, by Dr Marcia MacDonald, WADA APB Deputy Director, with special attention to gene editing. Technical issues included frequency and specificity of editing changes, nature of target tissue, deep sequencing of targeted gene panel (EPO, EPO-receptor, VEGF, myostatin, IGF-1, follistatin, PPARδ, etc.) or whole genome or exome sequencing.

- The HMRC agreed that gene doping new developments should be closely followed to avoid potential abuse as well as harm and thanked Dr Friedmann and the GCDP.

10. Doping Prevalence: Presentation by Prof. Andrea Petroczi

- The HMRC also received the visit of Prof. Andrea Petroczi, Chair of WADA Prevalence Working Group (PWG) and Professor at Kingston University of London. Prof. Petroczi is a psychologist with a Ph. D. in Social Sciences whose research bridged social and hard sciences and focused on

behavioural choices on drug use including doping. Prof. Petroczi formed part of the original WADA PWG a few years ago and was chosen Chair once the group was re-established about 1 year ago.

- Prof. Petroczi informed the HMRC of the aims of the PWG:
    a) Initially, review several different approaches to determine prevalence and establish the most appropriate for prevalence of doping in sports. The PWG was currently looking at methodologies and alternatives.
    b) Eventually they would develop (an) accurate prevalence measure(s) for doping that would allow for the evaluation of programs as well as provide easy tools for anti-doping stakeholders to determine the extent of doping in a country or sport.
    c) To date, the WG reviewed the existing literature and explored unpublished data. The purpose was to target elite athletes but the published literature included diverse populations so it would not be possible to do a meta-analysis. In addition, many of these studies addressed doping rather than prevalence. Furthermore, when the definition of doping was left to the athletes, the variability further increased. There was also confusion on the substances that were prohibited. The PWG would try to improve the quality of the data available.
    d) The survey would have to take into account the sensitivity of talking about doping, so there was a need to protect the athlete beyond anonymity. The survey was designed by statisticians and psychologists would only intervene if needed e.g. to try to improve the language.
    e) A pilot survey was already implemented during the Commonwealth Games. Some countries refused to participate and the reason was not clear. One could envision that doping athletes would be worried of participating in the survey and that clean athletes would not want to spend the time. The immediate plan was to analyse the data and introduce improvements.
- The HMRC thanked Prof Petroczi and discussed the presentation. The wording used was important, as general terms for drugs may be confusing especially when some athletes could also be experimenting with borderline performing enhancing drugs. It was also acknowledged that some athletes may feel that the survey was an imposition; however, it was necessary to involve the engaged athletes to get their input. It seemed logical that one prevalence figure would not mean much in isolation, but changes along time would be more important to see how the anti-doping message was outreaching. There were also risks that a NADO or IF could bias a questionnaire to avoid finding out high figures of prevalence in their sport or country. The survey would also need to be multicultural and multisport. The HMRC was pleased with the progress and looked forward to more results in the future.

11. Update on the Athlete Biological Passport (ABP)

- Dr Marcia MacDonald, WADA ABP Deputy Director, updated the HMRC on the ABP program.
- The Athlete Passport Management Unit (APMU) referred to the people responsible for the management of passports (passport review process, monitoring sample validity, providing target-testing recommendations). Currently, a Technical Document on APMU Requirements and Procedures was being developed, and it had already undergone consultation and was up for consideration at the Executive Committee in September 2018. The TD aimed to ensure that ABPs were managed with an appropriate and consistent level of analysis and rigor by all ADOs. The APMU would need to be associated with a WADA-accredited laboratory or a NADO.
- The HMRC also learnt of the increase in the number of ADOs running the ABP program, currently at 117.
- In addition, the haematological module would become mandatory 1 January 2019 for all sports with a minimum level of analysis of erythropoietin stimulating agents (ESA) of 30% or greater.

- Finally, there was an update on the research projects undertaken to improve the ABP, including the recently approved study aiming to identify biomarkers to discriminate altitude from ESA and a study aiming to correct for plasma volume shifts. In addition, the sample collection for the longitudinal IGF-1 detection pilot project was completed.
- The HMRC was satisfied with the progress made in and the course of action and thanked Dr MacDonald.

12. Open access to WADA data

- The HMRC was informed that WADA frequently received comments that it should give more access to results from its sponsored-research studies, following recent trends of making scientific work openly available. In this regard, Dr MacDonald presented a summary of the advantages and disadvantages of Open Data access for the WADA-sponsored projects to generate a discussion.
- The advantages included transparency, reproducibility, quick exposure of results, avoidance of duplication of work, sharing of samples and better data interpretation.
- The disadvantages included competition between investigators for ideas, patents and limited funding, unfair criticism, confidentiality of participants and generated data, cost and sense of ownership.
- The HMRC discussed the possibilities. Consent and anonymization of data could present hurdles. Although it was admitted that it was useful to share knowledge, it was also true that the traditional peer review process was important and there were concerns that Open Access may degrade the quality of the research available. It was not possible for WADA to impose on the research groups to publish their findings because the researchers were the owners of the data. In addition, the investigators were in the best position to decide if the results of a study were valuable and adequate for publication, or more research was needed.
- Overall, the HMRC believed that the information presented was a good base for future discussions but for the moment it was premature to implement.

13. Information on the International Testing Agency

- Dr. Uğur Erdener updated the HMRC on the newly formed International Testing Agency (ITA).
- Three years ago, the IOC proposed an independent global anti-doping testing and sanctioning system. Later on, this possibility was discussed by IOC and WADA, it was agreed to go ahead with the idea, a Working Group was formed and from it, the basis of the ITA were established.
- The Foundation Board was now formed by Dr Valérie Fourneyron (France) as Independent Chair, Prof. Uğur Erdener (Turkey) as IOC representative, Mr Francesco Ricci Bitti (Italy) as International Federations representative, Ms Kirsty Coventry (Zimbabwe) as IOC Athlete Commission representative and Prof. Dr Peijie Chen (China) as Independent Member.
- The ITA became operational in June 2018 and was located in Lausanne, Switzerland. It would take several years to inform and negotiate with the International Federations (IF) and it was estimated that by 2023 all agreements with the IF would be finalized.
- The main activity of the ITA is all aspects of testing (e.g. setting up tests, arrange contracts), which is currently in the hands of each event organizer, and there will an educating aspect as well.
- The ITA was not meant to replace WADA's activities and responsibilities and there would not be any duplications of tasks, as WADA remained the regulatory body. In addition, the establishment of the ITA did not change an IF or Major Events Organizations responsibility under the World Anti-Doping Code, as they would continue to be responsible for compliance with the Code, which was monitored by the WADA.

- There was a need to work in close cooperation and establish a very good collaboration between ITA and WADA.
- The presentation generated great interest by the HMRC and they expected to hear an update in next year's meeting.

13. Closing Remarks

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

14. Next meeting

- The next Project Review Panel and HMR Committee meetings were scheduled for **August 2019 (most likely 25-28 August).**

- The meeting was adjourned.

ACTION POINTS HMR COMMITTEE MEETING- August 28-29 2018

Subject	Action Point	Responsible	Due date
Gene and cell doping	Attempt to define instances of performance enhancement esp. for stem cells	GCDP	2019
Cannabinoids	Reviews wording of synthetic	LiEG	2019