

WORLD ANTI-DOPING AGENCY
Health, Medical & Research Committee Meeting Minutes
August 26-27 2021, by videoconference

Participants:

Health, Medical & Research Committee (HMRC)

Prof. Lars Engebretsen, Chair
Prof. Takao Akama
Dr. Reema Alhosani
Prof. Xavier Bigard
Dr. Lenka Dienstbach-Wech
Prof. Lena Ekström
Dr. Matt Fedoruk
Prof. Andrew McLachlan
Prof. Margo Mountjoy
Prof. Yannis Pitsiladis
Prof. Christian Strasburger

Ex-Officio Members

Prof. Odile Cohen-Haguenaer
Prof. David Gerrard
Dr. Audrey Kinahan
Dr. Terence Wan

WADA Personnel

Dr Osquel Barroso
Dr. Marcia MacDonald
Dr. Irene Mazzoni
Dr. Olivier Rabin
Dr. Alan Vernec

Guests

Prof. Mike McNamee, Chair of WADA Ethics Committee (for item 13)
Ms. Frederique Horwood, Legal Department (for item 13)

Observers

Prof. Fabio Pigozzi, Fédération Internationale de Médecine du Sport



Apologies

Prof. Wayne Derman, HMRC member.

Prof. Christiane Ayotte (INRS, Montreal, Canada), observer, representing the World Association of Anti-Doping Scientists (WAADS) and Director of the Montreal anti-doping laboratory.

Dr. Timothy Armstrong, observer, World Health Organization.

1. Welcome

- Prof. Lars Engebretsen, Chair of the Health, Medical and Research Committee (HMRC), welcomed the members, indicating that Prof. Wayne Derman, (Director of the Institute of Sport and Exercise Medicine, and Co-Director of the IOC Research Centre of South Africa and member of the International Paralympic Committee Medical Commission), would be absent since he was working at the Tokyo Paralympic Committee, and that Prof. Xavier Bigard (Medical Director of the Union Cyclist International (UCI) would join on day 2 for logistic reasons. Prof Engebretsen then introduced himself, indicating that he is a sports physician and a Professor in Orthopedics and an orthopedic surgeon in Norway and Head of Science and Research at International Olympic Committee (IOC) since 2007.
- Subsequently, Dr Olivier Rabin, Senior Director, WADA Science and Medicine, welcomed the Committee members, thanking them for their help and expertise, hoping that next year the meeting will be in person.
- Afterwards, all the other Committee members introduced themselves:
 - Prof. Margo Mountjoy, clinician and PhD in sports medicine, member of the IOC Medical Commission, Fédération Internationale de Natation (FINA) and World Rugby Anti-Doping Advisory Committee, former international artistic swimmer and former member of the WADA Therapeutic Use Exemption (TUE) Expert Group,
 - Prof. Andrew McLachlan, academic professor, pharmacist with main expertise in pharmacology, from Sydney, Australia,
 - Prof. Christian Strasburger, clinical endocrinologist, Chief of Clinical Endocrinology at the Department of Medicine of Charité-Universität, Berlin, and initially got involved with anti-doping as the developer of the growth hormone isoforms test,
 - Dr Reema Alhosani, sports physician and PhD in sports medicine, President of United Arab Emirates National Anti-Doping Committee, Chair of the UNESCO's Fund for the Elimination of Doping in Sport,
 - Dr Matt Fedoruk, PhD in pathology and laboratory medicine, Chief Science Officer at USADA, member of the International Paralympic Committee (IPC) Anti-Doping Committee, co-Chair of the Scientific Advisory Board for the Partnership for Clean Competition (PCC) and member of several WADA working and expert groups including Athlete Biological Passport (ABP) and Contaminants,
 - Prof. Takao Akama, professor at the Faculty of Sports Science at Waseda University, Japan and Medical Director to the Tokyo 2020 Olympic and Paralympic Organizing Committee, and former team doctor of the Japan Olympic Team.

Prof. Yannis Pitsiladis, PhD in sports and exercise science and medicine, Member of the Medical and Scientific Commission of the IOC, professor of Sports and Exercise Science at University of Brighton, UK and former member of the List Expert Group,
Dr. Lenka Dienstbach-Wech, Surgeon in Frankfurt, Germany, Chair of the World Rowing Federation (FISA) Athletes Commission and former rowing champion,
Prof. Lena Ekström, PhD, chemist and toxicologist, researcher at the Division of Pharmacology at the Karolinska Institute in Sweden.

- Next, the Ex-officio members introduced themselves: Prof. David Gerrard, Chairman of the WADA TUE Expert Group, specialized in internal and sports medicine at the University of Otago, former Olympic swimmer, and working in anti-doping for 30 years,
Dr. Audrey Kinahan, Chair of the WADA List Expert Advisory Group (LiEAG) and pharmacist, PhD in pharmacy and assessor of the Irish and European Medicines Regulation authorities,
Dr. Terence Wan, Chairman of the WADA Laboratory Expert Advisory Group (LabEAG), chemist, Chief Advisor, Doping Control of the Hong Kong Jockey Club,
Prof. Odile Cohen-Haguener, Chair of the Gene and Cell Doping Expert Advisory Group (GCDEAG), onco-geneticist, Professor in Oncology, Hôpital Saint-Louis and Faculty of Medicine, Paris, France.
- Next, the observer introduced himself: Prof. Fabio Pigozzi, President of the Federation International de Medecin du Sport (FIMS) and professor in internal medicine.
- Finally, the remaining members of WADA personnel from the Science & Medicine Department, introduced themselves: Dr Alan Vernec, Chief Medical Officer, sports physician; Dr Marcia MacDonald, Associate Director Research, biochemist and PhD in molecular biology; Dr Osquel Barroso, Senior Associate Director, Laboratories chemist and PhD in immunology and Dr Irene Mazzoni, Associate Director List, chemist and PhD in neuroscience.

2. Conflict of Interest

- Prof Engebretsen requested whether there were any conflict of interests and asked that any members that declared conflict of interest during the grant review should identify themselves in due time and disconnect from the meeting during the pertinent discussions and decisions.
- Prof Engebretsen remarked that the HMRC was a scientific and medical committee and opinions should be limited to those domains.

3. Review of 2022 Prohibited List, report from the List Expert Advisory Group (LiEAG) and recommendation to the WADA Executive Committee

2022 Draft Prohibited List

- The Draft of the 2022 Prohibited List, prepared by the LiEAG, was presented by Dr. Audrey Kinahan, Chair of the LiEAG. The draft List was circulated to about 3,000 stakeholders from May to July. The changes proposed were as detailed below:
 - a) *S0: Non approved substances*
 - i. BPC-157 will now be prohibited under S0 following a recent re-evaluation and added as an example. BPC-157 is a 15 amino-acid portion of the Body

Protective Compound found in gastric juice. The effects were not well known. The LiEAG evaluated it on a few occasions in the past under S2: Peptide hormones, growth factors, related substances and mimetics because it appeared to affect some growth factors. However, based on the scant information it was considered of interest but not prohibited. It was at one point on clinical trials but discontinued. Recently, this non – approved substance had become heavily marketed in sports as a having multiple positive effects and was available as intravenous and oral forms on the internet. In view of this, the LiEAG re-evaluated BPC-157 under S0: non-approved substances and concluded it was prohibited. Since it was considered non-prohibited in the past, it was necessary to disseminate its new status and was proposed to be added as an example.

b) *S1: Anabolic agents*

- i. Tibolone was transferred from S1.2 to S1.1 because its mechanism of action is more appropriate to the S1.1 subclass. In this regard, it had clinical effects as a synthetic oral androgen largely due to its conversion to the potent androgen delta-4 tibolone metabolite. The status remained the same.
- ii. Osilodrostat, a newly approved medicine, was added to S1.2 due to its off-target increase in circulating testosterone.

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

- i. The long-acting GH analogues lonapegsomatropin, somapacitan and somatrogen were added as examples. They were designed for once-a-week dosage, aimed in particular at children. Because of these inclusions, subclass S2.2.3 became too long and cumbersome, so it was split into S2.2.3: GH analogues and fragments, and S2.2.4: growth hormone releasing hormones.

d) *S3: Beta-2-agonists*

- i. A mathematical pharmacokinetic model was developed by the Service of Pharmacology at Université de Lausanne to evaluate all data of published and unpublished urinary excretion studies following salbutamol administration. This analysis showed that a very small percentage of individuals could surpass the salbutamol Decision Limit when the drug was inhaled at permitted levels of 800 µg altogether. In addition, good medical practice was moving away from high dosage of salbutamol such as 1600 µg daily. For example, most licensed beta-2-agonists recommended dose was 200 µg 4 times per day for a total of 800 µg for the treatment of asthma and bronchoconstriction. In view of this, it was proposed to lower the daily dosing time intervals for salbutamol to 600 µg over 8 hours starting from the time any dose is taken (previously 800 micrograms over 12 hours), in order to reduce the risk of a potential Adverse Analytical Finding after high doses were taken at once. The total permitted daily dose remained at 1600 µg over 24 hours. A Therapeutic Use Exemption (TUE) should be sought for doses in excess of these limits. A retroactive TUE was also an option, for example

after an asthma crisis when the athlete administered higher salbutamol doses altogether. This change needed to be disseminated well among athletes and health support personnel.

e) *S6: Stimulants*

- i. Several designer phenidates as well as hydrafinil were added as examples, as they were widely available and consumed as alternatives of methylphenidate or modafinil, respectively.
- ii. The term “imidazole derivatives” was changed to imidazoline derivatives to distinguish between generic imidazole derivatives and sympathomimetic imidazolines.
- iii. It was clarified that the urinary threshold of 5 µg/mL cathine referred to both isomers of norpseudoephedrine.

f) *S9: Glucocorticoids*

- i. Flucortolone was updated to its International Non-proprietary Name (INN), flucortolone.
- ii. All injectable routes of administration will now be prohibited in-competition period, as proposed in the draft 2021 Prohibited List and approved by the WADA’s Executive Committee on 14-15 September 2020. It was also clarified that the permitted routes referred to therapeutic approved doses. In addition, more examples of prohibited routes were added, in particular for oral administration. WADA had plans to extensively communicate those changes on different fronts, but was put on hold until the end of the 2020 Tokyo Olympic and Paralympic Games not to create confusion. The dissemination included TUE Guidelines for physicians, press releases, webinars for different audiences, fact sheets and the scientific article published in the *British Journal of Sport Medicine*, to name a few.

g) *P1: Beta-blockers*

- i. Underwater Sports (CMAS) subdisciplines were regrouped to facilitate the use of ADAMS. This change did not affect the current subdisciplines where beta-blockers were prohibited.
- ii. As additional information, Federation International du Ski (FIS) had similar issues with harmonizing the subdisciplines prohibited with the design of ADAMS, but were working to find a solution.

h) *Monitoring Program*

- i. The monitoring of bemitil and glucocorticoids would be discontinued as the required data were obtained.
- The HMRC discussed the proposed changes. It was noted that the work done on glucocorticoids was an example to follow as it was thorough and backed by science and a peer-reviewed paper. It was necessary to communicate the changes effectively, especially to physicians who were the ones who prescribed and administered these substances. Additional efforts should be done to explain the possibility of requesting a retroactive TUE.

- In addition, it was necessary to communicate extensively the change in the dosage of salbutamol, as the new dosage regimen could be potentially confusing. Some physicians may not agree that there was a proper recommended dose of salbutamol, as this was a rescue medication and athletes in a crisis may surpass at large the permitted dose. At the same time, the chances to surpass the Decision Limit were small, and if it happened, the athlete could do a controlled excretion study, which may reveal unusual metabolism of salbutamol. Dr Kinahan added that the research group in Lausanne was preparing a paper for publication and had presented the results already in scientific meetings. The new proposed dosage would be subjected to the pharmacokinetic model to see how much it decreased chances of surpassing the salbutamol Decision Limit.
- The HMRC was unsure if the prohibition of beta-blockers was based on solid science. Besides, there seemed to be inconsistencies within and between the sports that prohibited them.
- Finally, there were concerns whether osilodrostat was a very potent inhibitor of cortisol with serious side effects and probably unlikely to be abused in sports.
- The HMRC approved unanimously the proposed changes to the draft 2022 List and Monitoring Program and would recommend it to the WADA Executive Committee (ExCo) at the 14 September meeting. Prof Engebretsen congratulated the LiEAG for doing an excellent job on complex subjects and under challenging circumstances.

Future considerations

- Dr Kinahan also informed the HMRC that the LiEAG proposed to do an in-depth review on the status of cannabis in 2022 following the aftermath of a high-profile case and subsequent specific requests from a few stakeholders and external organizations.
- Dr Kinahan clarified that the review of cannabinoids was done routinely every year as part of the annual review of the stakeholders' comments.
- Dr Kinahan presented some facts on how class S8: cannabinoids, evolved in the List along the years.
 - Before 2004 when the IOC compiled the Prohibited List, the International Federations decided how they wanted to manage cannabis in their sport. The urinary metabolite threshold concentration was set at 15 ng/mL of carboxy-THC.
 - Since WADA took responsibilities of the List in 2004, cannabinoids (e.g., hashish and marijuana) were prohibited in competition only and in all sports and the threshold remained unchanged.
 - In the 2010 List it was clarified that synthetic cannabinoids were included and the 2011 List incorporated cannabimimetics.
 - In May 2013, the threshold of carboxy-THC was largely increased to 150 ng/mL with a decision limit at 180 ng/mL, to avoid detecting use out-of-competition. This concentration was quite high and would only detect chronic users and/or individuals consuming very close to the doping control.
 - In 2018 cannabidiol (CBD) was listed as an exception.
 - Since 2021, the Code defined the Substance of Abuse and established of the in-competition period from 11:59 p.m. the day before. In this regard, THC was designated

as a substance of abuse, meaning that the sanction could be limited to 3 months if the athlete can prove that the use was unrelated to sport, rather than months or years as before 2021.

- Prior to the increase in the Decision Limit in 2014, there were about 300 Adverse Analytical Findings (AAF) of THC per year and afterwards the numbers decreased, reaching 130 cases in 2019. The impact of the Substance of Abuse designation is yet to be determined.
- Out of 3,000 or so stakeholders receiving the List for consultation, 4 requested the removal of S8 from the List, 8 requested to review and determine the inclusion of cannabinoids in the List, and several others made comments encouraging changing urine for another matrix where the drug was eliminated faster.
- Cannabinoids were strongly debated outside sports as well. Use of THC had been legalised in some parts of the world, as well as some cannabis-based medicines were authorised in some countries. However, in large sections of the world, cannabis possession remained a criminal offence. There was even disagreement within sections of the same governments based on political or emotive issues. International conventions still maintained cannabis as an illegal and schedule 1 controlled substance and there was no indication that such status would change anytime soon. In addition, cannabinoids production and sales were big profit and aggressive marketing extended to a range of cannabinoids.
- The LiEAG proposed to do an in-depth review of the status of cannabinoids, similar to the one done about a decade ago, based on Article 4.3 of the Code (criteria for inclusion), and including any new pertinent scientific and medical information.
- The LiEAG was composed of a critical mass of experts in stimulants and substances of abuse, toxicologists, and scientific representative of the United Nations Office of Drugs and Crime (UNODC) and physicians.
- Finally, the LiEAG suggested to conduct a neutral survey after the review was done, aiming to hear comments from all stakeholders.
- The HMRC thanked Dr Kinahan and discussed the proposal. While they agreed with reviewing in-depth the status of S8 in the List, they believed the survey may not engage all stakeholders as wished by the LiEAG, and therefore, it would create a bias. It was expected that there would be some strong and emotional debates within the sports and governments. The LiEAG should see in particular what new information and what changes occurred since the time the review article on cannabis (Huestis et al, 2011) was published 10 years ago.
- Other subject for future considerations included the writing of Dr Kinahan's feedback letter to the stakeholders who made comments on the draft 2022 List.

Impact of the changes in the 2021 List

- Dr Kinahan summarized the impact that the changes introduced for the 2021 List had in anti-doping.
- The feedback on the redesigned 2021 List aiming at improving usability and being more athlete-friendly was very well received by the stakeholders.

- It was too early to say how Article 4.2.3 on Substances of Abuse will impact anti-doping. It was expected that this change would affect mostly results management. As presented in last year's HMRC meeting, the guidelines on interpretation of cocaine cases to facilitate the results management tasks, was published in early January 2021. These guidelines were derived from the analysis by the LiEAG of all published data on cocaine excretion studies. Stakeholders requested to identify more substances as substances of abuse but the LiEAG would do a one-by-one evaluation.
- Asthmatic athletes and physicians welcomed allowing inhaled vilanterol at the recommended therapeutic doses, which also enabled more treatment options including once daily dosage.
- The inclusion of examples of imidazole derivatives was welcomed as they are found primarily as decongestants and usually purchased without prescription.
- The prohibition of injectable glucocorticoids, to come into effect in 2022, had very positive feedback in general. Stakeholders welcomed the extensive explanatory note and the British Journal of Sports Medicine paper. The stakeholders also requested a strong educational and communication support.
- The report of the LiEAG concluded and the HMRC thanked Dr Kinahan.

4. Review and recommendation for the 2021 WADA Call for Scientific Research Projects

- Prof. Strasburger and Dr Fedoruk presented the conclusions and recommendations of the Scientific Project Review Working Group (SPRWG) to the HMRC. The SPRWG was formed by two HMRC members and three external scientific experts. Four members from WADA's Science & Medicine Department assisted when needed. The SPRWG met virtually on 20 and 25 August and reviewed the grants based on the independent external reviewers' evaluations (three per application) as well as the SPRWG own assessment. SPRWG members with conflict on interest on particular projects disconnected during those discussions.
- Investigators from 26 different countries and 5 continents submitted 65 research projects to WADA in 2021.
 - Theme A - 17 projects were submitted in the category "Detection of Prohibited Substances/Methods: Methodologies in Analytical Chemistry"
 - Theme B - 8 projects were submitted in the category "Detection of Prohibited Substances/Methods: Affinity-Binding and Biochemical Methodologies"
 - Theme C - 22 projects were submitted in the category "Pharmacological Studies on Doping Substances/Methods"
 - Theme D - 10 projects were submitted in the category "The Athlete's Biological Passport"
 - Theme E - 8 projects were submitted in the category "Detection of Doping Substances/Methods: Molecular Biology, Omics and Miscellaneous Methodologies"
- The HMRC considered the recommendations from the SPRWG and discussed in more detail several applications. As a result, 24 projects were selected and recommended for funding.
 - Nine projects addressed improving detection of anabolic steroids.

- Five projects aimed to improve detection of peptide/protein hormones and metabolic modulators.
- Four projects proposed to distinguish permitted from prohibited use of substances.
- One project was designed for autologous blood transfusion detection, another to improve the ABP, and another to support dried blood spot implementation.
- One project would synthesize reference material and two others aimed to detect gene doping.
- The HMRC discussed the proposals. Some conditions were imposed on some grants, for example:
 - Completion of previously funded grants.
 - Change the matrix used from plasma to serum.
 - Provide preliminary data.
 - Increase dosage to maximal permitted and extend time of sample collection.
 - Increase the number of tested antibodies, and then select the best 10 %.
 - Increase the number of volunteers and perform several analytical checks to ensure proper chemical entities.
 - Diversify genetic background of participants.
 - Add more targets.
- The budget of one grant was slightly increased as the HMRC requested a comparison with a different analytical method.
- The budget of one grant was reduced as part of the proposal was not approved.
- Two grants were considered to have some limitations, but they would be valuable to evaluate two new technologies. Nevertheless, several strict requirements were imposed such as justification of some experimental conditions, possible window of detection in blood and estimated concentrations. For one of the projects that budget was greatly reduced, as only part of it was supported.
- The HMRC concluded the discussions on the projects and would submit the recommendations for funding of the 24 selected projects during the ExCo meeting on 14 September 2021.

5. Outcomes of research:

- Dr Marcia MacDonald presented a summary of the outcomes of projects completed within the last 12 months, and their impact in anti-doping. Some studies delivered solid results while others were not as completely successful.
- Thirty-three studies were finished: 20 from the annual call for proposals, 8 from the targeted/reactive program and 5 from the DBS consortium:
 - a) Results from several studies affected the Prohibited List, e.g. data analysis on salbutamol threshold and decision limit, which led to the 2022 changes in salbutamol dosage; discrimination of permitted (e.g. cyanocobalamin) and prohibited use of cobalt; attempt to distinguish oral and inhaled administration of terbutaline; dietary and physiologic factors affecting excretion of salbutamol.
 - b) Others were useful for the Athlete Biological Passport (ABP), e.g. use of plasma volume markers to eliminate influence of plasma volume expansion.

- c) Three projects tested the usefulness of supercritical fluid chromatography, to find it could be valuable as an additional technique in anti-doping.
 - d) Several improved the analytical capabilities to detect prohibited substances, including increased sensitivity of EPO detection or identification of new markers of blood doping.
 - e) Several studies advanced the detection of prohibited substances with dried blood spots (DBS), such as comparison of sampling sites, stability of DBS during transport and storage including stability of steroid esters, measurement of hematocrit.
 - f) Other studies were useful for results management, e.g. distinguishing doping from food contamination.
 - g) Some studies were not always successful, e.g. distinction of different routes of administration of terbutaline; identification of metabolites of some anabolic steroids (notably the sulfate fraction) that did not improve their window of detection; impossibility of large-scale production of useful steroid sulfate metabolites.
- There were 39 publications in the last 12 months from WADA funded project, some where from grants completed several years before and it was very likely that there were other papers where WADA was not acknowledged.
 - The HMRC considered the impact of the WADA funded project to be very satisfactory and thanked Dr MacDonald for the presentation.

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

- Prof. David Gerrard, Chair of the TUE Expert Advisory Group (TUEEAG) gave an update on the group's activities during 2021.
 - 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 that detected warning signs. In 2020 there was a 30 percent decrease in the reporting of TUE in ADAMS, most likely due to the ongoing SARS-CoV-2 pandemic.
 - b) TUE by class: Glucocorticoids had the highest number of TUE requested, mainly for chronic inflammation, injuries and asthma, followed closely by stimulants, the majority of which were related to the treatment of Attention Deficit Hyperactivity Disorder (ADHD). It remained to be seen how the new rules on injectable glucocorticoids would affect the number of TUEs. Hormone and metabolic modulators were 3rd, mainly for insulin, followed by diuretics and masking agents, beta-2-agonists and peptides hormones.
 - c) TUE Reviews and Appeals: Several TUE reviews were done in the past 12 months by WADA. Among them the instances where decisions of NADOs or IFs to grant TUEs were upheld included the use of testosterone for a post-cancer treatment. In one case the decision of the International Federation rejecting a TUE for a solution containing cocaine was reversed by WADA TUEEAG as it was considered justified treatment to treat nose bleeding following an accident. Examples of reversed decisions included mostly for the

use of anabolic steroids. In one case the TUE was reduced to 1 year for the treatment of hypogonadism with testosterone, as the case may not be responsive to this drug; three other reversals included a TUE granted to use anabolic steroids and diuretics, another for erythropoietin and diuretics, because the diagnosis and supportive information were insufficient, as well as a TUE for treatment of hypogonadism caused by previous abuse of anabolic steroids.

- d) TUE Physician Guidelines (TPG): The TUEEAG also worked on the annual update of the Physician Guidelines, assigned to different members of the EAG.
- e) New initiatives: Prof Gerrard also outlined some new initiatives including
 - a. The TUE Program Development project, which was a multi-department effort, with the objectives of raising awareness of the List and TUE process among athletes and support personnel, strengthening the ADO TUE administrative process and developing capabilities by training TUE administrators and TUEC physicians
 - b. Webinars: there was a significant increase in the number of webinars to National Olympic Committees doctors, sport medicine groups and ADOs.
- f) The HMRC discussed the presentation. There were questions on whether there had been TUE requests for the treatment of COVID-19, but that was not the case, as the only prohibited substances used were glucocorticoids, but in patients hospitalized in the intensive care unit.
- g) The HMRC thanked Prof Gerrard and congratulated the TUEEAG for their work. Prof Engebretsen noted that Prof Gerrard had been Chair of the TUEEAG for 15 years and this was the end of his tenure, and therefore, he wanted to thank Prof Gerrard for his excellent work and dedication and for his collaborative disposition. Prof Gerrard said he was privileged to work for WADA along with former Presidents Dick Pound and John Fahey, scientific and medical experts like Arne Ljungqvist, athletes like Beckie Scott and many others and thanked the Medical team for their disposition, work and help.

7. Report from the Laboratory Expert Advisory Group

- Dr. Terence Wan, Chair of the Laboratory Expert Advisory Group (LabEAG), gave an update on their activities during 2021:
 - a) The LabEAG was composed of 12 members: 4 representatives from WADA-accredited labs (3 Directors, 1 Scientific Deputy Director) and 8 independent experts from ADOs, accreditation bodies, and related analytical fields (forensics, food safety, clinical, horse racing). Two of the independent experts were new.
 - b) The key activities of the LabEAG consisted in directing the process of accreditation, re-accreditation and ABP-approval 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)], revising the laboratory standards, evaluating laboratory results from the WADA External Quality Assessment Scheme (EQAS) and provide feedback to laboratories to improve performance and harmonization, reviewing selected WADA-funded research projects and providing recommendations for implementation and providing recommendations regarding laboratory compliance and performance to WADA decision bodies.

- c) Since the previous HMRC meeting (August 2020), the LabEAG held 3 scheduled virtual meetings: 23-25 November 2020, 17-19 March 2021 and 21-23 June 2021, and 2 *ad hoc* virtual meetings: 18 September 2020 and 28 October 2020.
- d) There were currently 30 WADA-accredited laboratories, including 3 under suspension.
- e) There were 2 probationary laboratories: a) Laboratório de Análises de Dopagem (LAD) (Lisbon, Portugal) which underwent its Final Accreditation Test in September 2020 and an on-site assessment by WADA. The technical and administrative requirements were fulfilled but the issue of the Lisbon laboratory's independence from their Sport Authorities was currently being clarified. b) the Laboratorio de Control al Dopaje Coldeportes Nacional (Bogotá, Colombia) which requested delay in re-accreditation process due to the continuing work to establish their independence from the Ministry of Sport as well as the delayed renovation of the laboratory's facility impacted by the COVID-19 pandemic. The last update provided by the laboratory was in July 2021.
- f) There were 3 WADA-approved laboratories for blood testing in support of the ABP with pending situations: Egyptian Doping Control Laboratory (Cairo, Egypt), which was also seeking full accreditation; National Anti-Doping Laboratory (Moscow, Russia), currently provisionally suspended pending the outcome of the Russian Anti-Doping Agency non-compliance case and Lancet Laboratory (Nairobi, Kenya), where a successor was appointed to replace the retired Laboratory Director.
- g) There were 2 candidate anti-doping laboratories: a) Egyptian Doping Control Laboratory, Cairo, Egypt, for which the WADA on-site assessment and the Cairo laboratory's Pre-Probationary Test were planned for September 2021; b) Athletes' Anti-Doping Laboratory, Almaty, Kazakhstan, where preparations for the WADA on-site assessment and pre-probationary test for entry into the probationary phase of accreditation were on-going.
- h) There was 1 candidate ABP laboratory: Genetix Clinical Laboratory (Panama City, Panama). Its application was approved by WADA Executive Committee on November 2019 and WADA on-site assessment was planned for September 2021. King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia) withdrew its application and may re-apply in the future.
- i) There were 3 laboratories suspended: a) the National Dope Testing Laboratory (New Delhi, India), suspended since August 2019, it underwent remote assessment in June 2021 and the LabEAG would review soon the responses to the assessment findings. b) Doping Control Laboratory of Athens, Greece, suspended since 1 October 2019 and extensions provided due to the lack of progress related to institutional/governmental support and the COVID-19 pandemic. The decision to revoke its WADA accreditation

was recommended by the Disciplinary Panel and confirmed by the WADA Executive Committee on 19 August 2021 and would be effective within 30 days. c) National Doping Control Centre, Bangkok, Thailand, suspended since 18 November 2019, underwent a remote assessment by WADA in May 2021. The LabEAG recommended the reinstatement of the Bangkok laboratory, which has just been confirmed by the Chair of the Executive Committee on 26 August 2021.

- j) The new WADA ISL2021 that came into force on 1 January 2021 was a major task. It was revised to be in line with the provisions of the new ISO/IEC 17025: 2017 and the World Anti-Doping Code (WADC) 2021 and was approved by the WADA ExCo on 15 September 2020.
- k) Thirteen Technical Documents (TDs) were updated to ensure consistency with the WADC 2021 and the ISL2021 and came into force in April-May 2021. Four TDs were currently under revision (TD2022DL, TD2022IRMS, TD2022EPO, TD2022MRPL) and were in the consultation phase until 31 August 2021.
- l) 22 Technical Letters were updated for consistency with WADC, ISL and TDs and were implemented by the laboratories by June 2021. Two new TLs (TL23, TL24) were published.
- m) 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 rounds distributed -3rd round scheduled for November-December), 2-3 rounds for the Educational EQAS to harmonize the identification and reporting of substances and improve analytical procedures (1st round scheduled September, 2nd around end 2021) and monthly rounds of EQAS for ABP blood samples in collaboration with CSCQ (EQAS provider in Switzerland). There were some delays in shipments due to the COVID-19 pandemic
- n) Multiple documents were prepared by WADA Science Department, Laboratory section, to address the management and technical requirements of ISO/IEC 17043:2010, "Conformity assessment – General requirements for proficiency testing" as applied in the EQAS program; these documents were reviewed by the LabEAG and a decision would be taken by WADA Management for either proceeding with an ISO/IEC 17043 accreditation by an Accreditation Body or a self-declaration by WADA of compliance with the ISO/IEC 17043. The process for implementation of compliance with ISO/IEC 17043 was currently underway
- o) A tender for an EQAS Sample Provider was organized in late 2020 and 2 EQAS providers were selected and secured for 2022-2027: IMIM (Institut Hospital del Mar d'Investigacions Mèdiques), Barcelona, Spain (WADA's present EQAS Sample Provider) and WFSR (Wageningen Food Safety Research), University and Research Centre in Wageningen, Netherlands; the latter is ISO/IEC 17043- and ISO/IEC 17025- accredited. The providers agreed to split the different EQAS rounds. Having two (2) WADA EQAS Sample Providers would result in a more robust EQAS system.

- p) Since September 2020, laboratory assessments were done for Lisbon (hybrid: combination of on-site and virtual), Helsinki (hybrid), Athens (virtual), Tokyo (hybrid assessment: second technical visit to the Tokyo Olympic Laboratory) and New Delhi (virtual).
- q) The LabEAG also reviewed reports of 7 selected research projects related to new laboratory methodologies and possible implementation in anti-doping laboratories, and improved detection of prohibited substances. Recommendations were communicated to the relevant research groups and the information was disseminated to all laboratories when appropriate.
- r) The HMRC discussed the activities of the LabEAG and thanked Dr. Wan for the update and congratulated the LabEAG for their work.

8. Report from the Gene and Cell Doping Expert Advisory Group

- Prof. Odile Cohen-Haguener, Chair of the Gene and Cell Doping Expert Advisory Group (GCDEAG), provided a summary of the activities of the EG during the last 12 months.
 - a) The EG was composed of experts in the domain, working in different areas such as gene therapy, gene transfer, drug regulation of gene expression, sports muscle physiology and disease including cancer and blood diseases.
 - b) The role of the GCDEAG consisted in monitoring advances in genetics and their potential impact and application to sport, in accordance with their expertise in gene therapy, gene editing and stem cell biology, and advise on detection strategy and methods. There was regularly the testimony from external experts at the meeting. The GCDEAG also advised WADA on the implementation of new assays in testing laboratories, in particular during 2020 and 2021 and assisted the HMRC with the evaluation of grant applications and the review of progress reports of WADA-funded studies.
 - c) The GCDAEG was satisfied with the definition of Gene and Cell Doping in the Prohibited List so there were no revisions recommended for 2022.
 - d) Regarding the detection of gene and cell doping, there were 2 approaches possible:
 - a. Direct detection of
 - nucleic acids with strong focus on DNA-based strategies or
 - editing machinery such as CRISPR-Cas/ Prime.
 - b. Indirect detection:
 - immune response to vector or exogenous protein product (e.g., designer nucleases)
 - longitudinal changes in biomarkers (e.g. cells, proteins, or metabolites, RNA levels) similar to the ABP
 - changes in sequences due to gene editing
 - altered posttranslational modifications pattern e.g. following injection of a doping gene in muscle.
 - e) There were 2 types of administration possible:

- a. Ex-vivo, where cells are extracted from the athlete, modified and reintroduced. Since this procedure would be personalized, it would probably not be much used in doping.
 - b. In-vivo, where the gene of interest was introduced into a vector and this vector would be introduced in the target tissue by injection.
 - f) In order to improve gene doping detection, the GDCEAG proposed to do a 2-step scheme, starting with an indirect detection of the immune response to the vectors, followed by direct detection with nucleic acid sequence methods able to detect changes in sequence or unknown sequences.
 - g) Among the direct detection methods, deep next generation sequencing (NGS) could be targeted and would detect vector sequences very accurately, while whole genome sequencing (WGS) would be able to detect changes in sequence including unknown and/or due to gene editing.
 - h) Another direct detection method was CARMEN/SHERLOCK which was very specific and targeted multiplexed nucleic acids sequences, applying CRISPR technology. It was necessary to know the sequence one was looking for.
 - i) Finally, cell-free DNA (cfDNA) based direct detection could be useful as well, based on the fact that following strenuous exercise, free DNA increased in blood stream.
 - j) It was paramount that all methods developed to detect gene and cell doping were tested in samples from clinical and pre-clinical studies that involved gene transfer. In this regard, members of the GCDEAG offered to donate clinical samples providing that the informed consent allowed miscellaneous studies. In addition, detection should be expanded e.g. to genes, vectors, regulatory sequences to widen the range of transgenes and sequences detected
 - k) From the WADA funded projects, the PCR-based detection assay by Dr Anna Baoutina would be implemented in Tokyo. There was a project on deep NGS but was discontinued by the researchers because of personal reasons.
 - l) WADA also funded indirect detection strategies. One of them by Dr Giuseppe Ronzitti was targeting the immune response to AAV vectors because AAV-based gene therapy induced titers much higher than the naturally occurring ones. Others targeted molecular markers, with mixed outcomes.
 - m) It was the opinion of the GCDEAG that the program engaged to detect gene and cell doping through yearly calls since 2006 had an inappropriate balance between the level of funding, and scientific accuracy and the overall outcome was disappointing. The GCDEAG advised to do more targeted research aiming at selecting the best teams in order to provide WADA with an accurate arsenal of tests in a timely manner.
- The HMRC discussed the presentation and recommendations. Prof Yannis Pitsiladis asked whether a consortium of research groups working in the detection of gene and cell doping would be advantageous, including the creation of a biobank to share samples. Dr Rabin noted there were pros and cons because the experimental conditions may be very dissimilar. Nevertheless, WADA was keeping samples of high interest. Prof. Cohen-Haguenaer suggested that in order to decrease costs, WADA should approach specialized centers in deep sequencing.

- The HMRC was satisfied with the approach proposed and thanked Prof. Cohen-Haguenaer and the GCDEAG.

9. Update on muscle memory project:

- Dr. Olivier Rabin updated the HMRC on the possibility of funding muscle memory projects. He recapitulated that last year there was a proposal to extend the knowledge on muscle memory, and that the HMRC was very interested, but the project was not funded because it was considered that the design was not optimal. However, WADA remained interested in the subject and probably would open a special call for grants whenever sufficient funds were available.

10. Update on investigation of EPO variant

- Dr Osquel Barroso informed the HMRC on the findings of the EPO variant NM_000799.4:c.577del present in a small percentage (0.5-1 %) of the east Asian population.
- The variant comprised a single nucleotide deletion in the last exon (5) of the EPO gene, producing a frameshift with a consequent loss of the normal stop codon, a change of last amino acid of the reference protein (Arg193Asp) and addition of 26 amino acids, resulting in a 3-kDa longer protein. There were no additional N-glycosylation sites and the clinical significance was unknown.
- For the moment it was rarely detected in a few Chinese athletes. All cases detected were heterozygous.
- SDS/SAR-PAGE Analysis in blood showed that the variant displayed a double band, as opposed to a single band of the wild type endogenous EPO. In addition, the variant displayed a pattern similar to recombinant epoetin alfa and the only difference was that the variant would not change with successive sampling of the athlete. In urine, the pattern was less clear, perhaps due to degradation.
- To address this variant, the LabEAG and experts were drafting an Annex for the TD2022EPO. In it, a clear roadmap of possible scenarios in blood and urine and the actions to be taken, will be presented.
- The HMRC thanked Dr Barroso for the presentation and explanations.

11. Presentation and discussion on the application of monitoring devices in the anti-doping context

- Prof. Mike McNamee, Chair of the Ethics Committee and Ms Frederique Horwood, Lead Counsel, Privacy and Data Governance, WADA Legal Department, and Prof Yannis Pitsiladis presented in this section of the meeting.
- Dr Rabin introduced the subject noting that advances in technology allowed athletes, sports teams, and physicians to monitor functional movements, workloads, and biometric markers (e.g. heart rate, body temperature, etc.) with the purpose of maximizing performance and minimizing injury. Several companies approached WADA to find out if these devices were allowed by WADA so this subject was brought to the attention of the HMRC.

- Prof. McNamee presented first, indicating that WADA had to look for harms and benefits. It could be very useful for safety (e.g. detect overtraining, overheating) or could help in rapid detection of doping depending on the technology. It was also a means to generate profits and with it, pressure on the athletes to use it.
- Prof McNamee believed that there were some salient points to consider. For example, how to ensure confidentiality, the means to do a secure transfer of the data collected (e.g. avoid hacking and leakage), ownership of the data (e.g. some regions had frameworks but most did not). It carried a degree of unfairness, as richer countries or sports would have the possibility of using them and gain an advantage. If the information was hacked, it could be used for betting, manipulation against the athlete or blackmail.
- Subsequently Ms Horwood presented some considerations from a legal perspective. There were some universal principles to determine if: a) the data could be collected, b) which data could be collected and c) what could be done with it.
 - a) There should be a balance between the benefit to the individual and the interest of the organization and in terms of doping, between the benefit for anti-doping and the individual. For now, there was no solid evidence that the monitoring devices were useful. The degree of invasiveness of the device should also be considered. It should also be justified that the use did not infringe human or constitutional rights to private life.
 - b) whatever can be collected should be accurate. For example, there were attempts to use some of these devices to determine road accidents but deemed to be not accurate and could not replace an eyewitness.
 - c) the use of the data should be limited to what was needed. There could be possible secondary uses outside of doping that could infringe rights. The extra use could be limited with the technology itself. Nowadays the protection of the data was weak.
- Finally, Prof Pitsiladis gave a presentation to illustrate how these devices could benefit the athlete. The study, entitled "Beat the heat" was supported by funds from the IOC and the data was collected during the 2020 Tokyo Olympic Games. As example, risk sports like hockey, triathlon, rugby were assessed and select athletes used wearable devices to measure numerous physiological and biomechanical parameters e.g. skin temperature, gait, heart rate, core temperature, air and land temperature. The overall success of this proof of concept project has re-opened the debate about the advantages and disadvantages of using technology (e.g., technology and data, both personalised and environmental) to protect athletes at risk of harm (e.g., exertional heat stroke by removing them from competition in extreme environments). In events like Formula 1, the race car had sensors for almost every aspect of the car functionality but not for the pilot. The devices could also be used to acclimatize to cold and hot weather.
- Prof Pitsiladis mentioned that in a previous project they used patches and would take about a month to analyse the data, but with the new technology the data analysis was immediate. It remained to be seen whether similar devices could be used in anti doping.
- Due to lack of time, unfortunately the discussion had to be cut.



- The HMRC thanked Ms. Horwood and Profs McNamee and Pitsiladis for the introduction to this subject.

12. Closing Remarks

- Prof. Engebretsen thanked the HMRC members and WADA staff for a very productive and intense meeting and for all their contributions.
- Some of the subjects, such as the draft 2022 Prohibited List and the research recommendations would be presented to the WADA Executive Committee meeting on 14 September for consideration and eventual approval.

13. Next meetings

- The next HMRC meeting was estimated to be scheduled for **25-26 August 2022** and would hopefully be in-person in Montreal.
- The meeting was adjourned.