

# MINUTES

Health, Medical & Research Committee Meeting

30-31 August 2022– Montreal, Canada

Hybrid: In-person & by videoconference (9:00 – 17:00 EDT)

## **Participants:**

Prof. Lars Engebretsen, Chair

Prof. Takao Akama

Dr. Reema Alhosani

Prof. Xavier Bigard

Prof. Wayne Derman

Dr. Lenka Dienstbach-Wech

Prof. Lena Ekström (by videoconference)

Dr. Matthew Fedoruk

Prof. Andrew McLachlan

Prof. Yannis Pitsiladis

Prof. Christian Strasburger

Prof. Milica Vukasinovic-Vesic (by videoconference)

## **Ex-Officio Members:**

Prof. Odile Cohen-Haguenaer

Dr. Audrey Kinahan

Dr. Terence Wan

Dr. Susan White (day 2) (overlap with TUE Expert Advisory Group meeting)

## **WADA staff:**

Dr Osquel Barroso (by videoconference) for “Report from the Laboratory Expert Advisory Group”

Dr Léonie Egli (by videoconference) for “DBS update”

Dr. Marcia MacDonald

Dr. Irene Mazzoni

Mr. Olivier Niggli for introduction of “Review and recommendation for the 2021 WADA Call for Scientific Research Projects”

Dr. Olivier Rabin

Dr. Alan Verneq (day 2) (overlap with TUE Expert Advisory Group meeting)

Mr. Ross Wenzel (by videoconference) for “GC TUE process during Washout Period”

### **Observers**

Prof. Fabio Pigozzi, Fédération Internationale de Médecine du Sport

### **Apologies**

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.

## Abbreviations

AAF: Adverse Analytical Finding  
ABP: Athlete Biological Passport  
ADHD: Attention-Deficit/Hyperactivity Disorder  
ADO: Anti-Doping Organizations  
DBS: Dried Blood Spot  
DCF: Doping Control Form  
DL: Decision Limit  
EAG : Expert Advisory Group  
ExCo: Executive Committee  
FAQ: Frequently Asked Questions  
GC: Glucocorticoids  
GCDEAG : Gene and Cell Doping Expert Advisory Group  
GCWG: Glucocorticoid Working Group  
HMRC: Health, Medical and Research Committee  
IC: In-Competition  
IPC: International Paralympic Committee  
IS : International Standard  
LabEAG : Laboratory Expert Advisory Group  
LiEAG: List Expert Advisory Group  
MP: Monitoring Program  
MRL: Minimum Reporting Level  
NADO: National Anti-Doping Organization  
OOC: Out-of-Competition  
PE: Performance enhancing  
SARM: Selective Androgen Receptor Modulator  
SoA: Substance of abuse  
TD: Technical Document  
TUE: Therapeutic Use Exemption  
TUEEAG: Therapeutic Use Exemption Expert Advisory Group  
UCI: Union Cycliste Internationale  
WP: Washout periods  
WG: Working group

## Day 1

### Welcome

- Prof. Lars Engebretsen, Chair of the HMRC, welcomed the members, introducing Dr Milica Vukasinovic-Vesic as a new member replacing Dr Margo Mountjoy whose term came to an end 31 December 2022. Dr Prof. Vukasinovic-Vesic is a sports physician and university professor and has been the Director of Anti-Doping Serbia for the last 5 years. 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.
- Afterwards, all the other Committee members introduced themselves:
  - Prof. Takao Akama, professor at the Faculty of Sport Sciences 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.
  - 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,
  - Prof. Xavier Bigard, sports physician, researcher specialized in skeletal muscle and Medical Director of the Union Cycliste Internationale (UCI)
  - 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 IPC Medical Commission,
  - Dr. Lenka Dienstbach-Wech, Surgeon in Frankfurt, Germany, Chair of the World Rowing Federation (FISA) Athletes Commission and former international rowing champion,
  - Prof. Lena Ekström, PhD, chemist and toxicologist, Head of the Division of Pharmacology at the Karolinska Institute in Sweden
  - Dr Matt Fedoruk, PhD in pathology and laboratory medicine, Chief Science Officer at USADA, member of the IPC Anti-Doping Committee, co-Chair of the Scientific Advisory Board for the Partnership for Clean Competition and member of several WADA working and expert groups including ABP and Contaminants,
  - Prof. Andrew McLachlan, academic professor at the University of Sydney, Australia, pharmacist with main expertise in pharmacology, and member of Anti-Doping Australia for over a decade,
  - 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 Advisory Group,
  - Prof. Christian Strasburger, clinical endocrinologist, Chief of Clinical Endocrinology at the Department of Medicine of Charité-Universität, Berlin
- Next, the Ex-officio members introduced themselves:
  - Prof. Odile Cohen-Haguenaer, Chair of the Gene and Cell Doping Expert Advisory Group (GCDEAG), Professor in Oncology, Hôpital Saint-Louis and Faculty of Medicine, Paris, France,
  - Dr. Audrey Kinahan, Chair of the WADA (LiEAG) and pharmacist, PhD in pharmacy and assessor of the Irish and European Medicines Regulation authorities,

- Dr. Terence Wan, Member and Chairman of the WADA Laboratory Expert Advisory Group (LabEAG) since respectively 2012 and 2017, chemist, Chief Advisor, Doping Control of the Hong Kong Jockey Club,
- Dr Susan White (introduced on day 2) Chair of the TUEEAG, physician, Chair of the Australian Sports Drug Medical Advisory Committee.
- Next, the observer introduced himself:
  - Prof. Fabio Pigozzi, President of the Federation Internationale de Médecine du Sport (FIMS) and professor at the Italian National Sports University.
- Finally, the members of WADA personnel from the Science & Medicine Department present in the meeting introduced themselves: Dr Olivier Rabin, Senior Executive Director in charge of the Science & Medicine Department for 20 years; Dr Alan Vernec (day 2), Chief Medical Officer, sports physician; Dr Marcia MacDonald, Associate Director Research, biochemist and PhD in genetics; and Dr Irene Mazzoni, Associate Director List, chemist and PhD in neuroscience.
- Dr Rabin mentioned the unexpected passing away of Mr Fred Donzé, Chief Operating Officer, a journalist by profession, who had been a key member of WADA for many years. Mr Donzé left a wife and child behind, he was a much liked colleague and will be deeply missed.

## Disclosure of conflict of interest

- There could be some potential conflict of interest when the review of the research grants from the Annual Call are discussed. It was established that in that case the person would not be able to participate in the discussions and should step out of the room until the end of the discussion of that proposal. Profs Pigozzi and Pitsiladis submitted a grant and they would therefore not participate in the discussions of that project.

## Presentation of the draft 2023 Prohibited List

- The Draft of the 2023 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 to the HMRC were as detailed below:

### S1: Anabolic agents

- New examples were added:
  - Ractopamine: growth promoter
  - Adrenosterone (11-oxoandrostenedione (11-OXO): weak androgen
  - Epistane (17 $\alpha$ -methylpithiostanol): prodrug of desoxymethyltestosterone found in dietary supplements
  - S-23 and YK-11: examples of SARMs

### S4: Hormone and metabolic modulators

- S4.3 was updated to include antibodies of precursors of myostatin and as example, apitegromab was added.

- Next year the LiEAG may again discuss the possibility of removing clomiphene from the List for females weighing up the potential performance benefits against the common use in female fertility treatment and long urinary excretion period.

#### S5: Diuretics and masking agents

- The introductory language of the section was revised to harmonize with other sections of the List.
- Torasemide was added as an example of a diuretic and was already named in a WADA Technical Document (TD MRPL) and a WADA Technical Letter (TL24).
- It was clarified that a TUE is not required for topical ophthalmic administration of a carbonic anhydrase inhibitor (e.g. dorzolamide, brinzolamine) or for local administration of felypressin in dental anesthesia in conjunction with a threshold substance

#### M1: Manipulation of blood and blood components

- Donation by athletes of plasma or plasma components by plasmapheresis was proposed to be no longer prohibited. Dr Kinahan clarified that in many countries the definition of athlete was broad, so the prohibition of plasmapheresis was affecting the regular supply of plasma. In addition, the Hematological ABPWG was consulted and confirmed that the effects on the passport were very transient and the blood passport stabilized fast, so the procedure could not be used as a confounding factor to mask doping practices. Finally, WADA Legal was consulted as well and re-affirmed that the effects of plasmapheresis on plasma volume were transient and could not be used as an excuse for doping. Several HMRC members expressed concern that it could be used to manipulate the biological passport. Since the proposal to withdraw plasmapheresis from the List was not circulated to stakeholders with the Draft, the HMRC believed there were too many concerns raised and decided not to accept this change. They recommended the LiEAG to gather more details on the pros and cons of allowing plasmapheresis. Dr Kinahan asked the HMRC to compile and send the concerns to the LiEAG for discussion next year. ACTION POINT.
- Voxelotor: this new product was added as an example, as it alters the ability of hemoglobin to release oxygen in the body, and a consequence, enhancing arterial oxygen saturation. As a side effect, it increases serum erythropoietin, which has been shown to result in higher hemoglobin concentration in healthy individuals. WADA contacted the company to request additional information on the clinical trials but received limited support. The company was acquired recently by Pfizer, so WADA will insist. ACTION POINT

#### S6: Stimulants:

- Several synonyms of dimethylamylamine (DMMA) were added as alternative common names 2 DMMA derivatives already listed.
- The new drug Solriamfetol was included in S6b due to its activity as a dopamine and norepinephrine reuptake inhibitor resulting in stimulant effects.
- Tetryzoline was added as an imidazoline derivative under Exceptions and was clarified that otic administration of imidazoline derivatives is not prohibited.

#### S7: Narcotics

- Tramadol: the LiEAG recommended the prohibition of tramadol in competition as it fulfills the 3 criteria defined in the Code:
  - Potential performance enhancement: WADA funded 3 studies to test the effects of tramadol on performance. The first study showed tramadol improved performance in a time trial, a second study showed no effect and a third, recently finished study using highly trained cyclists showed

significant improvements in a 25-mile time trial completion times. In this regard the study demonstrated greater power output and lower perception of effort. This well-designed study imitating road cycling conditions showed that a participant could improve from a 2/3 position to a position in the 1/3. Another study not funded by WADA showed performance enhancement in a time trial for cyclists not negatively affected by the drug.

- Potential risk for health: tramadol is a centrally acting opioid analgesic. It is a non -selective pure agonist at mu,  $\delta$  and  $\kappa$  opioid receptors and inhibits as well neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol abuse and addiction is an internationally known problem. In this regard, a few stakeholders requested tramadol to be considered a Substance of Abuse. The LiEAG will discuss this possibility in 2023.
- Violation of spirit of sport: tramadol has been on the WADA Monitoring Program since 2012, showing a significant use in sports, mainly in cycling, rugby and football.
- The LiEAG recommended to postpone the prohibition of tramadol until 1 January 2024 to thoroughly communicate the rule changes and to allow sufficient time for information and education. In addition, the delay would allow athletes and medical personnel to better prepare for the change, sports authorities to develop educational tools and laboratories to update their procedures. In this regard, a comprehensive excretion study is required to set an MRL, taking into account that tramadol is a pro-drug, converted by hepatic CYP2D6 to the active metabolite O-desmethyltramadol, which is more potent than tramadol itself. CYP2D6 activity is impacted by genetic polymorphisms.
- The HMRC agreed that tramadol fulfilled the Code criteria and should be prohibited. It was noted the Union Cycliste Internationale (UCI) prohibited the use of tramadol in competition for health reasons, including loss of balance, vertigo and dependence. Before the prohibition 4.5-6% of riders were using tramadol and currently it had decreased to 0.25 %. UCI tests the riders using DBS after the 1<sup>st</sup> day of a multistage race, targeting the parent compound and 2 metabolites qualitatively. Overall, the HMRC believed that tramadol merited to be prohibited in the 2023 List, but agreed that it would be advisable to delay the prohibition until 2024 for the reasons explained above.

#### S9: Glucocorticoids:

- It was clarified that the otic route was permitted.
- In addition, Dr Kinahan informed that there were ongoing additional excretion studies with different GC and routes of administration to define new MRLs and WPs for other commonly used GC.

#### P1: Beta-blockers:

- Two sports federations were added to P1 upon their requests:
  - World Mini-Golf Federation (WMF), added in competition
  - World Underwater Federation (CMAS) requested beta-blockers to be prohibited not only IC but also OOC in all subdisciplines of freediving, spearfishing and target shooting.

#### Monitoring Program:

- Dermorphin and analogs were added to detect patterns of use in sport in-competition; they are known to be abused in horses
- Based on intelligence information, GnRH analogs will be tested in females under 18 years to detect patterns of abuse in sport,

- Hypoxen (polyhydroxyphenylene thiosulfonate sodium) was added as it was declared in Doping Control Forms during the 2020 Tokyo Olympic Games, primarily by Russian athletes over a range of sports. It was developed in Russia in the 1980s with the clear intention of boosting anti-oxidative capacity to give a performance advantage in strenuous sports.

#### S8: Cannabinoids

- Dr Kinahan updated the HMRC on the review that the LiEAG did during the course of 2022 on the status of cannabis, which was agreed upon during the HMRC meeting in August 2021.
- Dr Kinahan explained that the status of cannabis evolved since WADA took responsibility of the List in 2004. In the 2004 List until 2013, the THC threshold was 15 ng/mL to distinguish active consumption from passive exposure. In 2013 it was raised to 150 ng/mL to avoid detection of OOC consumption, which resulted in a considerably decrease (50 %) in AAFs. Cannabidiol (CBD) was no longer prohibited in 2019 and in 2021 the revised Code introduced the concept of SoA where a sanction could be reduced to 3 months if the athlete proved that the consumption was OOC and unrelated to sport.
- The majority (approximately 62%) of AAF in the last 3 years were from Europe and about 6 % from USA and none in Canada.
- In most countries, cannabis remained illegal but in some places the law was not enforced; in some places it was legalized. The potency of cannabis was now much higher than in the 1970s. Not only the contents increased but also the availability, which included not only smoked but also edible, oils, etc
- In January 2022, the LiEAG agreed to do a detailed *de novo* review of tetrahydrocannabinol (THC) under Code article 4.3 where a substance must meet two of the three criteria for consideration for inclusion on the List.
  - Potential health risks: a “Health subgroup” of the LiEAG did a full literature review and met with external ad-hoc experts.
  - Potential to enhance performance: a “PE subgroup” of the LiEAG did a scientific literature search using keywords, as well as searched for socio-scientific information including anecdotal reports and met with external ad-hoc experts.
  - Spirit of sport: Consulted the WADA Ethics Expert Advisory Group to provide an opinion/judgement.
  - In addition, Dr Kinahan presented the problem to the WADA Athlete Committee and received their feedback.
- Regarding the health risks, the Health group mainly consulted the latest review on cannabis done by the World Health Organization (WHO) in 2016 and identified the risk for the athlete’s health of non-medical consumption of cannabis. The definition of health was that of the WHO Constitution: “.. a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” and in this case it refers to the health of the athlete. The risks are:
  - Neurological:
    - Cerebral structure modification, mainly in early and frequent onset of use
    - Increased risk of psychosis, anxiety
    - Problems in coordination, reaction times, concentration
    - Cardiovascular



- Other health risks (testicular and lung cancer, reproduction...)
- Negative societal impact (impairment of driving, increase suicide ideation, increase admissions to ER).
- Specific risks in the context of sport:
  - A significant proportion of the athletic population is young and thus more at risk
  - Some aspects of THC risks might be exacerbated in the context of sport:
    - Cardiovascular risks
    - Respiratory impact
    - Negative impact on coordination or concentration
    - Impairment of reaction time, coordination and decision making.
  - Athletes have traditionally short careers, so it is a duty of their entourage and health care providers to ensure that their health is protected during and beyond their sport career.
- The Health group discussed the findings with an Ad hoc group of four international experts in cannabis (forensic toxicology, behavioral science, addiction, neurology). The conclusion from the meeting was that:
  - There are detrimental effects of THC on health. It is important to acquire more knowledge on the cannabinoid system and its complexity.
  - The Health group covered all angles except that dependence should be added to the list of adverse health effects. However, studies on myocarditis and cardiac risks were at an early stage.
  - The susceptibility to develop negative health problems will depend on the dose, frequency, age at onset of use, genetic predisposition, etc. There are many risks to evaluate, and they will likely be additive and with interindividual differences.
  - Therefore, the criteria on potential or detrimental risk for health is fulfilled based on current knowledge.
  - Regarding the Spirit of Sport, the WADA Ethics Expert Advisory Group was consulted. The values of Spirit of Sport were slightly changed in the 2021 Code. The Ethics EAG found that there were five values that had specific relevance for the judgement of the status of cannabis:
    - Health: consumption of cannabis had demonstrable health diminishing effects. This point had already been considered by the Health Group.
    - Excellence in performance: may be thought to be undermined by consumption of cannabis during the in-competition window at levels that produce an AAF. This point was addressed by the PE group.
    - Character and education: as a role model (irrespective of one wishes) one ought not to model behaviours that are widely criminalized worldwide.
    - Respect for rules and laws: Cannabis use, in most parts of the world, is illegal.
    - Respect for self and other participants: the safety and welfare of other participants and team-mates may be compromised by impaired judgement of in-competition cannabis use.

- In addition, the threshold for reporting THC use was high enough to exclude most samples of OOC users so it did not interfere with athletes' private life.
- The Ethics EAG concluded that in consideration of the values encompassed by the Spirit of Sport, as detailed above, the use of THC IC violates the Spirit of Sport.
- The assessment of the potential enhancement of performance was the most challenging. The PE group compiled and discussed the evidence and then discussed their conclusion with the Ad Hoc experts. The findings were:
  - There were no controlled PE studies available and no systematic reviews. Evidence was mostly in general reviews and self-report evidence.
  - There was no solid evidence of physical PE effects on primary endpoints e.g. muscle strength, endurance, but only soft evidence on self-reported psychological effects, e.g. reduced stress, anxiety and pain, increased focus, being "in the zone", improved mental health, help forget unpleasant experiences, decreased perception of danger (e.g. competitor bolder, increasing risk for opponents) and reduced boredom (e.g. ultramarathons).
  - Even if the psychological effects were genuine, the studies available were not of high quality.
  - Based on the scientific literature, THC seemed to be ergolytic rather than ergogenic in terms of physiologic PE, but users could titrate the dose. Occasional THC users could feel different effects than chronic.
  - Based on scientific literature, THC could potentially have psychological benefits, inducing euphoria, decreasing anxiety and stress, increasing motivation and decreasing fatigue.
- Regarding PE, it was concluded that:
  - There was no evidence of physical PE effects and the issue of psychological effects impacting performance was not clear.
  - There were gaps in the literature that would need to be addressed with solid scientific studies to be able to evaluate with sufficient scientific rigor the PE effects.
  - Overall, knowledge of PE aspect has not improved much since the 2011 review even if certain perceptions on cannabis (decriminalization, therapeutic) slightly changed.
  - It was possible that THC may be PE in a narrow group of sports and disciplines.
  - Even if the evidence was weak, the potential for psychological PE could not be discounted
- Finally, Dr Kinahan consulted the Athlete Committee with five questions on PE prepared by the PE group. The answers were varied and reflected different positions and diversities among countries regarding cannabis use:
  - Overall, it was felt that cannabis especially in countries where it was readily available, was used for: relaxation e.g. coming down from a high-adrenaline state post-competition; dealing with mental health issues e.g. a coping mechanism; alleviating pre- and post-competition stress, helping with sleeping; focus/concentration ("getting into the zone").
  - On PE, opinions ranged from no physical PE effects to it may have PE effects in certain sports or certain disciplines within a sport.
  - Cannabis may have psychological benefits in terms of "courage", and in terms of concentration and focus or "getting into the zone".
  - The risk for health from cannabis use was considered no more than the risk of other substances to which athletes are exposed but sport specific health risks could exist (e.g. as drowning, risk of

injury in team sports. In addition, there was general agreement that could be a health impact on the developing brain, more likely to affect younger athletes. Overall, it was recognized that there were potentially health risks for the athlete and other competitors.

- The Athlete Committee recommended that the sanctions associated with the use of cannabis and/or SoA could be re-evaluated as part of the next Code review.
- In conclusion, from the exhaustive literature and data search and the 10 meetings carried out with different expert groups, the LiEAG concluded that currently THC fulfills 2 out of the 3 Code criteria and recommends it should remain prohibited.
- The HMRC discussed the issue, recognizing that the LiEAG had done an exhaustive investigation and a systematic approach. The HMRC acknowledged that the findings reflected the controversial nature of cannabis use and it was advisable not to change the status. These conclusions will be presented to the WADA Executive Committee.
- The HMRC encouraged and recommended the LiEAG to publish the process and the findings and congratulated the LiEAG for the work done. Dr Kinahan said that it was the intention of the LiEAG to publish a scientific article.
- The HMRC approved the proposed draft 2023 List, Explanatory Note and Monitoring Program as recommended by the LiEAG except for the exclusion of plasmapheresis. These versions would be recommended to WADA Executive Committee for approval at their 23 September meeting.

## Review and recommendation for the 2022 WADA Call for Scientific Research Projects

- Mr. Olivier Niggli, WADA Director General, joined momentarily the HMRC meeting to welcome the participants and acknowledge the importance of this scientific committee. Mr Niggli mentioned that the budget for research would be substantially increased for the next three years, as it became evident how important research was to advance the detection of doping. In addition, WADA would seek partnerships with the private sector as well as collaborations with other funding agencies. Mr Niggli thanked the HMRC for their key work and left the meeting.
- Prof. Strasburger, Dr Fedoruk and Prof. Bigard presented the conclusions and recommendations of the Scientific Project Review Working Group (SPRWG) to the HMRC. The SPRWG was formed by three HMRC members and three external scientific experts. Four members from WADA's Science & Medicine Department assisted when needed. The grants were initially reviewed by three independent external experts who submitted their evaluations and recommendations. The SPRWG met virtually on 22 and 24 August and reviewed the grants based on the independent external reviewers' evaluations as well as the SPRWG's own assessment. SPRWG members with conflict of interest on particular projects disconnected during those discussions. The SPRWG ranked the proposals roughly by priority and presented the outcome to the HMRC.

Investigators from 5 continents submitted 45 eligible research projects to WADA in 2022.

- Theme A - 12 projects were submitted in the category "Detection of Prohibited Substances/Methods: Methodologies in Analytical Chemistry"
- Theme B - 7 projects were submitted in the category "Detection of Prohibited Substances/Methods: Affinity-Binding and Biochemical Methodologies"

- Theme C - 13 projects were submitted in the category “Pharmacological Studies on Doping Substances/Methods”
- Theme D - 7 projects were submitted in the category “The Athlete Biological Passport”
- Theme E - 6 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, 18 projects were selected and recommended for funding.
  - Four projects addressed improving detection of anabolic agents, including one that would investigate muscle memory after use of anabolic agents.
  - Five projects aimed to improve detection of peptide/protein hormones and metabolic modulators.
  - Three projects proposed to perform pharmacokinetics studies to distinguish permitted from prohibited use of substances.
  - One addressed defining MRL for DBS implementation.
  - Four addressed different aspects of the ABP
  - One project aimed to evaluate a novel gene doping detection approach.
- The HMRC discussed the SPRWG recommendations. Some conditions were imposed on some grants, for example:
  - Completion of report of previously funded grant.
  - Increase frequency of sample collections and change the matrix used from plasma to serum.
  - Increase the number of volunteers
  - Explain the choice of drug instead of another that is more effective.
  - Clarify the choice of samples and sport chosen.
  - Add collection of additional matrices and routes of administration.
  - Generate preliminary data and proof of principle
  - Remove some objectives not considered priority.
  - Monitor additional markers or metabolites
  - The budget of 7 grants was reduced based on the different conditions described above.
- The HMRC concluded the discussions on the projects and would submit the recommendations for funding of the 18 selected projects during the WADA Executive Committee meeting on 23 September 2022. Prof Engebretsen thanked the SPRWG for their thorough review and work.

## Research impact: highlights of research outcomes 2021-2022 and planning more detailed research impact assessment

- Prof. Engebretsen highlighted the importance of showing where the research money had impacted antidoping. In this regard, Dr MacDonald presented some example outcomes of the research projects completed in the previous 12 months:

- There were 13 projects from the annual call, 8 from the targeted/reactive group, 2 from WADA / Partnership for Clean Competition (PCC) joint grants and 2 from the DBS consortium.
- From the projects impacting the List it was worth highlighting:
  - The study by Alexis Mauger, where it was shown that highly trained cyclists enhanced their performance administering prescription doses of tramadol. This result was important for the recommendation of the LiEAG to add tramadol to the 2024 List.
  - A study by Thevis and Pereira, where it was shown that regular amounts of fruits containing higenamine cannot be the source of an AAF. These results are useful for results management. A follow up study from 2022 will investigate higher and repeated consumption.
- From projects affecting laboratory performance the most salient were:
  - A project by de la Torre that assists in the interpretation of laboratory results for DHEA, 7-keto-DHEA and arimistane. From its outcome, the LabEAG recommended to include the monitoring of a new metabolite of arimistane.
  - A qualitative method was developed as Initial Testing Procedure by Thevis for insulin-mimetic peptides in plasma.
- Examples of improved detection and ABP advancement included:
  - A study by Saugy addressed the blood steroid profile, which is a powerful complementary approach to the existing urinary steroid profile either for targeting confirmatory GC/C/IRMS analysis or as a single evidence of testosterone doping. In this study a UHPLC-MS/MS method was validated for quantitative analysis of eleven free and eight conjugated steroids in DBS. A high correlation was observed between DBS and serum concentrations for most compounds.
- An example of studies affecting ABP management would be:
  - The potential use of machine learning to improve specificity of adaptive model for steroidal passport, decreasing the number of negative samples that are flagged as atypical. An extension of this project by Touzani was recommended earlier.
- Two examples were given for the production of Certified Reference Materials:
  - For a mix of 41 small peptides and metabolites by Goebel, and
  - Certified Reference Material for carbon isotope ratios of human urinary steroids by Armishaw.
- Regarding new matrices:
  - A study by Mercolini showed that dried urine spots could increase the stability of certain peptides.
  - A pilot study by van Eenoo demonstrated that steroid profiling in oral fluid longitudinal monitoring proved to be superior for certain routes of administration.
- There are also projects that were unsuccessful but from which one could learn the pitfalls for future similar studies.
  - As study by Malm on markers of autologous blood transfusion showed initially promising results but the team later informed that the markers were not reproducible and requested to modify a conditionally approved project proposal to focus on new marker discovery, but this new project was referred to a future intake of proposals.

- Another study on markers of erythropoiesis stimulating agents and hypoxia had mixed results and had been sent to an independent reviewer. However, the sample collection was very good and it was being used for proteomics analysis.

In addition, Dr MacDonald informed the HMRC that the Science and Medicine Department was under increasing scrutiny to report the research impact. For 2021, the key scientific performance indicators were:

- Number of projects approved: 31
- Number of publications in 2021 with WADA funding or staff: 51; there was an increase from previous years, perhaps because the Covid pandemic liberated time to write.
- Number of targeted/reactive/special project applications: 7 approved, 2 not approved
- Diversity of institutions submitting 74 applications
  - number of submissions with applicant co-applicant from a WADA laboratory: 43
  - number of unique lead institutions: 49
  - number of unique institutions including co-applicants: 71
  - number of WADA laboratories applying: 18
  - number of ADOs: 3; in general not too involved, more dedicated to social science.
- Regional distribution of approved funding: 72% Europe, 16% Americas, 13% Asia/Oceania
- 43 publications resulting from WADA-funded research and WADA Science staff between August 2021 and July 2022
  - From projects approved between 2008 and 2020
  - 3 from targeted ABP research projects with WADA Science staff
  - 11 in Drug Testing and Analysis

More subjective indicators include:

- Funding for “innovation projects”, which is difficult to define
- Number of projects translated in new anti-doping tools/solutions in the last 5-year period, also difficult to evaluate e.g.
  - When to count? e.g. when applied to anti-doping testing and analysis? after approval of relevant regulatory document? when results reported in ADAMS?
  - What to count? if it leads to a change in a TD or lab practices?
  - How to assess? e.g. long-term outcomes of all WADA-funded projects?

External recent examples of anti-doping research impact assessment include:

- A history of 7 WADA-funded projects on supercritical fluid chromatography
- Women’s footprint in Anti-Doping Sciences
- iNADO Scientific Research Report summarizing funding areas and institutions but not impact.

Possible approaches to address impact include:

- Narrative reviews of some well-known examples
- Analysis of project reports and related literature
- Cross-referencing bibliographies of WADA documents with WADA-funded projects
- Analysis of testing figures for changes in AAFs linked to analytical methods



- Highlights from WADA-accredited laboratories that received WADA funding, which would add more work for the laboratories
- Surveys of WADA-accredited laboratories and ADOs for perceptions of scientific advances that have had the biggest impact on anti-doping
- Bibliometrics

To note, the resources within the Science and Medicine Department to do this impact evaluation are limited.

- The HMRC believed that the outcome of all these years of research was quite impressive and that it was difficult to measure the impact, especially at the level of daily anti-doping operations.
- There were questions on why the total number of applications for the Annual call was significantly decreased from previous years. The overall limited funds for the program could be a factor, especially since research was more expensive lately, with significant increases in the price of equipment, reagents and salaries. In addition, the pandemic obliged some laboratories to lay off personnel. But the positive note was that the budget will increase starting next year.
- Concerns were raised by Prof Pitsiladis about the process of recommending research projects for funding. Specifically, the stated role of the scientific project review working group (SPRWG) versus the external peer reviewers.
- Dr Fedoruk believed that the collaboration between WADA and the Partnership for Clean Competition (PCC) should be strengthened to avoid overlaps and improve outcomes. It is important to target research but requires lengthy time and human resources. PCC system is more flexible and reactive and American laboratories favoured it above WADA. Dr Rabin agreed that WADA's Annual call for grant extended over a long period of time (about 10 months) from the moment the call is opened, grants sent to the 3 external reviewers, the review by the SPRWG, the HMRC and WADA Executive Committee.

## Research Perspectives

- Drs Rabin and MacDonald presented the research perspectives for the next 5 years.
- Dr Rabin believed that the 20 years of WADA research program contributed very positively to anti-doping science. Moving forward he thought that there were two ways to continue, one through more creative and innovative research, which demanded more money, or with more partnerships.
- The annual research budget will substantially increase in the next years, tripling by 2026.
- In addition to the 18 projects from the Annual Call recommended earlier for funding, the Gene and Cell Doping Panel asked for special requests for applications on gene doping detection for: (1) targeted sequencing-based method and other sequencing approaches; (2) multiplexed CRISPR-based detection method, as well as to follow-on targeted funding for methods for immune detection of AAV vectors.
- The HMRC had also requested targeted research on long-term effects of steroids on muscle memory but may be partially addressed by a project approved for the 2022 Annual Call.
- There were also other recommendations from the Expert Advisory Groups (List, Laboratory, ABP). The HMRC should request as well if they feel the need.
- Overall, it is expected that the number of targeted research will increase based on needs, or to bridge gaps, requests from Intelligence & Investigations, etc. Other ways to improve research programs and facilitate turnover of projects would be to do multiple/continuous calls per year, reduce time between submission and

first payment, more helpful feedback for unsuccessful teams, rapid development projects for targeted funding and project database and other tools to optimize monitoring.

- Prof. Pitsiladis suggested to create a consortium to establish a biobank to gather all samples from WADA studies and share them. These samples were very valuable and costly to collect and right now they were not being taken advantage of. Dr Rabin had reservations that samples could be valuable for different projects and due to cost of maintenance of biobanks but Prof. Pitsiladis believed it was worth exploring.
- Dr Fedoruk suggested to revisit the priorities frequently and add more details on why the projects are needed (e.g. improve sample collection, results management, decrease costs, distinguish contamination).
- In some occasions, constructive feedback was provided for a possible resubmission and if requested, the investigators were provided with the anonymized external reviews.

## 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 2022:
  - The LabEAG was composed of 12 members: 4 representatives from WADA-accredited laboratories (3 Directors, 1 Scientific Deputy Director) and 8 independent experts from ADOs, accreditation bodies, and related analytical fields (forensics, food safety, environmental, horse racing). Three of the independent experts were new.
  - 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 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.
  - Since the previous HMRC meeting (August 2021), the LabEAG held 2 virtual meetings and 1 in-person meeting: 22-24 November 2021, 21-23 March 2022 and 7-9 June 2022. Additional meetings will be held on 13 September (virtual) and 28-30 November 2022 (in-person).
  - There were currently 29 WADA-accredited laboratories and none under suspension. There were 2 probationary laboratories: a) Laboratório de Análises de Dopagem (LAD) (Lisbon, Portugal) which had addressed the issue of laboratory's independence from their Sport Authorities. The laboratory's documentation for WADA's re-accreditation would be presented for approval to WADA's Executive Committee on 23 September 2022. b) the Laboratorio de Control al Dopaje Coldeportes Nacional (Bogotá, Colombia) which requested delay in re-accreditation process due to relocation to establish their independence from the Ministry of Sport as well as lack of resources and incomplete method validation.

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; Lancet Laboratory (Nairobi, Kenya); and Genetix Clinical Laboratory (Panama City, Panama), newly approved on 4 August.
  - There were 3 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 done in 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; and c) Shanghai Anti-Doping Laboratory, Shanghai, China where WADA was assessing their progress and will organize the Pre-Probationary Test and on-site assessment when the laboratory confirms its readiness to proceed. It was important not only to have the required number of samples per year but also to count on government support. Many laboratories suffered during the pandemic and the process of accreditation and re-accreditation is very difficult. In addition, new and more sophisticated techniques were being implemented for analysis, which added to costs.

- There was 1 applicant laboratory: Doping Control Laboratory of Athens (Greece), where the decision to grant Candidate laboratory status will be presented for approval to the WADA ExCo at its meeting on 23 September 2022.
- The issue of laboratory impartiality and independence from the national sport authorities was very important, as established in Article 4.4.2.4 of the International Standard for Laboratories (ISL) 2021. Only Madrid (Spain) laboratory was not compliant at the moment and was given until October 2022 to address the issue.
- Several TDs were scheduled for revision. In 2022: TD IDCR and TD LDOC. Thereafter: TD MRPL, TD NA, TD DL, TD IRMS, TD GH, TD EPO, and TD EAAS. A new TD will be drafted: TD HBT.
- One Technical Note was being prepared on Chromatographic-Mass Spectrometric Confirmatory Procedures, and another planned to be drafted on Measurement Uncertainty and Use of QC-Charts.
- The EQAS included 3 rounds of 5 blind urine samples annually for the Regular EQAS (2 already completed, the other scheduled for late September-early October).
- In the double-blind EQAS, 5 urine samples would be presented annually as athlete's samples and distributed to laboratories by Testing Authorities on behalf of WADA (1 round completed, 2<sup>nd</sup> and 3<sup>rd</sup> rounds scheduled for September and November-December respectively). Six and 2 double-blind samples were introduced for the Beijing Olympic and Paralympic Games, respectively. Laboratories can be suspended if they do not perform well in these EQAS. The double blind EQAS are complicated to prepare since it cannot use spiked samples and has to be collected from excretion studies to imitate exactly an athlete's sample.
- The purpose of the 2-3 rounds per year of the Educational EQAS is to harmonize the identification and reporting of substances and improve analytical procedures. One was conducted on HIF-activators in October 2021, and a second one comprising hGH isoform QC blood samples and for the endocrine ABP – hGH biomarkers and steroids in blood, performed in early 2022. Another is planned for September-October this year. There are also monthly rounds of EQAS for ABP blood samples in collaboration with CSCQ (EQAS provider in Switzerland).
- Multiple EQAS Management System (MS) documents were prepared by WADA Science Department, Laboratories Division, in line with the management and technical requirements of the ISO/IEC 17043: 2010 standard, "Conformity assessment —General requirements for proficiency testing". The EQAS MS documents were reviewed by the Lab EAG as WADA is planning to pursue the process of self-declaration of compliance with the ISO/IEC 17043 standard. Evaluation of WADA EQAS MS will be conducted by two independent international experts.
- There had been some problems with the 2<sup>nd</sup> EQAS sample provider, who faced challenges in preparing the 2<sup>nd</sup> round of 2022 EQAS and with subcontracting the clinical administration studies. Therefore, IMIM, who has provided WADA with EQAS samples since 2003, agreed to take over, and in turn the 2<sup>nd</sup> EQAS sample provider will take care of the 3<sup>rd</sup> round.
- Since September 2021, laboratory assessments were done for Panama City (Panama), on-site assessment of the ABP-candidate; Cairo (Egypt), on-site assessment and conducting pre-

probationary test; Beijing (China), 1 remote and 2 on-site assessments for Olympic Games; New Delhi (India), post-suspension on-site assessment; and Rio de Janeiro (Brazil), on-site regular assessment.

- The LabEAG also reviewed reports of 5 selected research projects related to improved laboratory methodologies (establishing the sources of cobalt, new peptide hormones, reference material of a mixture of small peptides, and distinction of endogenous and exogenous steroids). Recommendations were communicated to the relevant research groups and the information was disseminated to all laboratories when appropriate.
- The HMRC discussed the activities of the LabEAG and thanked Dr. Wan for the update and congratulated the LabEAG for their work.

## Report from the Gene and Cell Doping Expert Advisory Group

- Prof. Odile Cohen Haguenaer, Chair of the Gene and Cell Doping Expert Advisory Group (GCDEAG), gave an update on their activities during 2022:
  - The GCDEAG was composed of experts in the domain, working in different areas such as gene therapy, gene transfer, drug regulation of gene expression, gene editing, sports muscle physiology and disease including cancer and blood diseases.
  - The terms of reference 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, stem cell biology and related analytical methods, including inviting outside consultants for the meetings;
    - Advise WADA on the implementation of new assays aiming at improving detection of gene doping;
    - Assist the HMRC to review progress reports of WADA-funded studies and evaluate grant applications.
  - The GCDAEG was satisfied with the definition of Gene and Cell Doping in the Prohibited List so there were no revisions recommended for 2023. It was not necessary to include examples because the technology was constantly changing. However, it would be possible to compile an internal listing.
  - There are 2 main types of administration of gene doping possible:
    - Ex-vivo, where cells are extracted from the athlete, modified and reintroduced. It would be easily detected if it is engineered.
    - In-vivo, where the gene of interest is introduced into a vector and this vector would be introduced in the target tissue by injection.
  - The window of detection will depend on the type of administration, e.g. modifications permanently integrated will be detected longer than free circulating foreign nucleic acids; on the type of technology e.g. gene editing machinery (CRISPR-Cas/Prime) has a very short detection window.
  - For the direct detection of foreign transgenic cassettes, it may be necessary to know which genes, regulatory sequences or vectors to target, while for the indirect detection the immune response to the vector or exogenous protein product is targeted.
  - The GCDEAG recommended strategy to improve detection includes:

- Direct detection:
  - Deep NGS, but no project is funded recently; aim for targeted project.
  - CARMEN/SHERLOCK based direct detection
  - Cell-free DNA (cfDNA) based direct detection
  - Self-amplifying RNA (saRNA):
- Two step detection scheme:
  - Indirect detection first by testing immune response to vectors, which induces titers much higher than naturally occurring viral infections;
  - Followed by direct detection.
- It is paramount to evaluate all methods with samples from clinical and pre-clinical studies that involve gene transfer and to expand the range of transgenes and sequences targeted and immune response to vectors or exogenous protein products (e.g., designer nucleases).
- WADA funded several projects in the area:
  - Direct detection
    - PCR-based detection: multi-phase project, PCR-based Gene Doping Test.
    - Deep sequencing-based detection
      - Where targeted research is urgently required with a key concern on accuracy, sensitivity and reproducibility. The GCDEAG will provide a registry of known sequences which should not be ignored.
    - 2021 Thevis et al: detection of CRISPR-Cas machinery
  - Indirect detection
    - Immune response to AAV vectors: developing detection of a multiplex ELISA assay:
    - The GCDEAG recommended to further fund for validation.
- The HMRC discussed the information. It was imperative that WADA continued funding these projects because the use of gene doping could be imminent. It was also recommended to encourage ADOs to submit samples for gene doping analysis, as well as other anti-doping laboratories to implement the current PCR-based test.

## Report from the TUE Expert Advisory Group

### *Impact of all injectables GC prohibition in competition*

- Dr Susan White gave an update on the impact of the change in rules prohibiting all glucocorticoids (GC) injections.
  - As introduction, Dr White pointed out that for several years there had been evidence that GC injections via permitted routes were reaching performance-enhancing systemic levels of GC during competition. In this regard, a GCWG was convened by WADA and from their work they established bioequivalent doses of different GC compared to cortisol and defined doses and routes of different GC that were potentially performance enhancing. This led to the prohibition of all injectable GC and the review of some of the MRL, some of which increased (e.g. betamethasone), some remained at

30 ng/mL and triamcinolone acetonide decreased. Washout periods for the main GC were established as well

- Local injections of GC are commonly used mainly for musculoskeletal injuries, but the injection of a GC for these injuries on the day of competition has little clinical benefit. Nevertheless, some physicians still use local GC injections for musculoskeletal injuries close to competition and is very much dependent on the country and medical practice culture. Most local injections are intra-articular.
  - Regarding timing for IC use the decision to inject is usually not known more than 2-3 days in advance so there is little time to apply for a TUE and for a TUE Committee to consider an application in advance. Advanced TUE are mostly for chronic problems. Therefore, most TUE applications will always be retroactive under Article 4.1.b (inadequate time) of the ISTUE. If the use is during the WP, the GC are not prohibited and a TUE is needed if a GC is reported as an AAF. In this case the TUE criteria 4.1.e (use OOC but detected IC) is used.
  - In order to help physicians, a Decision Tree was designed to assist when the GC is used IC (TUE required), OOC but in WP (prepare medical file for a post-AAF retroactive TUE) or OOC and outside the WP (highly unlikely a retroactive TUE needed but prepare medical file).
  - Prior to the implementation of the new rule, the TUE Committees feared that there would be massive rise in TUE requests, increasing the workload considerably. In addition, physicians and athletes feared that injections given during the WP would result in an AAF and wanted reassurance that a retroactive TUE would be accepted. It is possible that a retroactive TUE is rejected but only in cases where it is badly justified. In view of this, WADA and the NADOs embarked in a massive campaign to educate doctors and update medical information and checklists, advising that TUE were not required during the WP unless the athlete tested positive. However, some NADOs offered to provide proactive TUE, like Spain and Italy.
  - In the first 6 months of 2022, there has not been an apparent massive increase in the number of TUE, as there was about half the requests as pre-pandemic. From those only 30 % were for local injections and most from the Spanish NADO that gives pro-active TUE. Overall, 90 % of the TUE were from NADOs.
  - Although, the information is partial for 7 months, it appears that the number of GC AAF decreased compared to pre-pandemic values. From WADA Results Management System, there were 35 GC AAFs, with 9 TUE associated AAF: (5 oral/intramuscular, 3 local injections = intrabursal, intratendinous, intra-articular), 7 retroactive TUEs and 2 prospective. Twenty of the 35 cases were still open. Only 1 AAF was OOC and all were for triamcinolone acetonide, which takes longer to excrete.
  - In conclusion, there is so far no evidence that injections are being used close to the competition for doping and it appears that physicians are avoiding using injectable GC close to the competition, which is overall good medical practice.
- The HMRC discussed the presentation. Dr Vernec said that the introduction of clear WP was very useful as well, and that unless in exceptional cases, GC should be avoided close to the competition. Dr. Dienstbach-Wech mentioned that for rowing in Germany it was recommended to avoid injectables GC and if not possible, to avoid triamcinolone acetonide.
  - Overall, the HMRC was satisfied with the outcomes of the GC injectables prohibition based on current knowledge.

### *GC TUE process during Washout Period*

- Mr Ross Wenzel, WADA General Counsel, Legal Department, joined the meeting for this point to review the advantages and disadvantages of asking for a TUE during the WP.
  - Pros:
    - Could potentially limit the abuse of TUE requests where GCs are taken with PE implications (although misuse cannot be excluded even if the TUE application is submitted before the AAF);
    - Could speed up the TUE process which might limit the risk of an athlete being prevented from continuing to compete at a Major Event. However, if athletes follow the advice and have the medical file readily available, the gain in time should be minimal.
  - Cons:
    - TUEs are not required when the use of a substance is not prohibited, which is the case for GC during the WP OOC; requiring TUEs for non-prohibited substances would be a significant shift in the TUE system.
    - There was a major roadblock with data privacy/protection concerns (and associated liability for ADOs):
      - asking for TUE applications (including sensitive medical/personal information) for a substance that is not prohibited would risk being considered neither necessary nor proportionate (in particular as only a fraction of cases of injections during washout would result in AAFs and the potential benefits are marginal).
    - Mr Wenzel concluded that, for the time being, the advantages did not outweigh the disadvantages of the privacy concerns and shift in TUE system.
- Mr Wenzel noted that Dr White's presentation showed the unlikelihood of an AAF during the WP. He added that certain ADOs could be able to deal with a quick turnover of a TUE application during an event, but that should be voluntary.
- The HMRC discussed the issue. It was noted that despite the flexibility, some physicians and athletes would like to be reassured that the TUE would be accepted in case of an AAF. Dr White said that if it is proven that the injection is necessary, that there are no alternatives and the standard dose is used and the dossier accompanied by imaging, then there should not be a problem to obtain the retroactive TUE.
- The HMRC believed the system was appropriate and that more education would help understand it.

### *Update on the TUEEAG activities.*

- Dr Susan White gave an update on the activities of the TUEEAG
  - The TUEEAG is composed exclusively by physicians, the majority of which are actively involved in TUE and athlete care. They held a virtual meeting in April and an in-person meeting on 29-30 August in Montreal.
  - Number of new TUE registered in ADAMS: there were 1556 TUEs granted. There had been a 32 % increase for the 1<sup>st</sup> half of 2021, which was perhaps due to less restrictions linked to the pandemic, resulting in more sports events. Of those approved, 75 % were prospective and 25 % retroactive, while 206 were rejected or incomplete. Most are approved by the NADOs.
  - The sports with the highest number of granted TUEs were football, cycling, athletics and basketball.

- TUE by class: GC had the highest number of TUE requested, followed closely by stimulants. Hormone and metabolic modulators were 3<sup>rd</sup>, mainly for insulin.
- TUE Reviews and Appeals: WADA Medical team use a prioritization screening algorithm that flags doubtful TUEs for review. Several TUE reviews were done since 2021:
  - In 2021, 8 reviews finished:
    - Testosterone (3) – 2 rejected, 1 supported the NADO decision
    - Methylphenidate (2) –inadequate information –both rejected
    - Tamoxifen– no diagnosis - rejected
    - Beta- blocker– diagnosis of cardiovascular problem not proven and performance enhancement was a concern - rejected
  - 2022: 6 reviews finished, 2 in progress
    - Testosterone (2) - rejected
    - Spironolactone – overturned NADO decision and approved
    - GH –overturned rejection by NADO
    - Lisdexamphetamine- no medical evidence of ADHD – rejected
    - Multiple anabolic agents including hCG, sustanon and clomiphene– in process
- Reviews under ISTUE 4.3: as a matter of fairness these are reviews that do not meet ISTUE 4.2a criteria or meet all 4.2 criteria but do not strictly meet any of the retroactive criteria. In the last 7 months there were 18 requests reviewed by WADA, 77% were approved and 23% denied. They are mainly linked to non-specified ADHD medications, followed by diuretics in older athletes with hypertension and letrozole/clomiphene in older women with infertility issues or breast cancer.
- In addition, the TUEEAG updates the TUE Physician Guidelines Annually. In particular, last year they were revised where appropriate to reflect the changes in the GC rules.
- The EAG also worked on educational initiatives to raise awareness about TUE among athletes and building capabilities for TUE administrators and TUE Committee members.
- In addition, the ISTUE will be revised in 2023 based on comments and suggestions received from stakeholders and to make it compatible with the new TUE module in ADAMS.
- Finally, the 5<sup>th</sup> WADA TUE Symposium will be held in Incheon, South Korea, between 31 May and 2 June 2023. It is directed to TUE Committee physicians and managers and the aim is to harmonize practices and decisions and educating less experienced TUE Committees.

## Dried Blood Spots: state of development and perspectives

- Dr Léonie Egli, Manager, DBS Program, gave an update on the state of DBS analysis:
  - The Program started in 2013 at WADA and until now there had been 10 funded projects that evaluated methods in DBS for a range of prohibited substances. The promising DBS results by WADA-accredited laboratories motivated ADOs to conduct pilot studies of DBS collection.
  - In 2019 WADA initiated a collaborative project to fill knowledge gaps and implement DBS samples in anti-doping, in particular, to develop DBS testing for routine implementation as soon as possible and



no later than at the 2022 Beijing Olympic and Paralympic Winter Games and if possible, to test some aspects during the 2020 Tokyo Olympic and Paralympic Summer Games. It was expected to generate guidelines for routine collection, transport, analysis and storage of DBS compliant with the World Anti-Doping Code and relevant IS.

- In order to do so, several high-priority short-term research projects were funded, e.g preference of fingertip or upper arm for sample collection, or stability during transport and long-term storage.
- There is a TD on DBS testing and implementation written, which became effective since September 2021. Even if DBS testing is not mandatory for ADOs and laboratories, so far 12 testing authorities have reported a total of over 1700 DBS samples into ADAMS, with 3 laboratories reporting results. In addition, DBS testing was used for the first time in a major event at the Beijing Olympic and Paralympic Games
- The targets of the DBS analysis are to complement urine/blood samples for substances not easily detected or unstable (e.g. detection of steroid esters) and as alternative matrix for increasing the number of tests. It is envisaged and minimum menu of selected non-threshold substances without MRL for all laboratories testing DBS, that will allow for mass screenings, testing in remote areas, testing of younger athletes, etc. All substances in the menu should be detected with the same sample preparation and substances previously identified as AAFs will be prioritized. The number of substances will increase with time.
- Future perspectives include the development of pre-analytical and analytical requirements for quantitative analyses, special analyses of certain substances like EPO and GH which remain challenging given the small volume and the Final DBS Project report including recommendations for the continued research and development of DBS implementation.
- Currently there are 3 long-term DBS research activities underway: detection of GC, hCG, and biomarkers for the detection of autologous blood transfusion and rHuEPO misuse. However, there are remaining funds to support new research projects, e.g. advancing quantitation, further developing DBS collection procedures, advancing specific laboratory test methods and verifying conditions for long-term storage.
- All partners liked the model of collaboration, sharing of information and resources. Dr MacDonald noted that the fact that Ms Egli was a dedicated project manager was key to the success of the project, and thanked her for the excellent effort. Dr Rabin said that there were many isolated groups working on DBS which WADA had brought together. Dr Bigard added that UCI was using DBS for tramadol analysis and cyclists were very compliant.
- The HMRC thanked Dr Egli for the presentation and work.

## Prevalence of Doping update

- Dr MacDonald presented an update on prevalence of doping, including some slides provided by the Chair of the Prevalence WG (PWG), Prof Andrea Petroczi
  - The PWG builds on early exploratory work to assess the prevalence of doping. The Group first aimed to determine if strategies, reliable methods and tools could be developed to assess prevalence, and then worked to develop tools that can ultimately be used by stakeholder ADOs.
  - It started operating in 2017 reviewing the literature and developing the Doping Prevalence Index (DPI) concept. They produced a survey in 2019 that was refined in 2020-2021. The DPI combines

- the prevalence estimation via the survey, plus prevalence based on the ABP plus the doping control tests. It will work with color codes, identifying issues that require urgent action, others that need attention, and others that are not a problem.
- From 2017 until 2022, the survey was used in 10 studies, including by 2 NADOs and 5 sport event organizations, surveying more than 7,000 athletes. Another 4 surveys are ongoing or planned.
  - In an example, the Spanish Commission for the Fight Against Doping in Sport conducted the survey on-line but with a low response rate. Probably on-site surveys would be more successful as the athletes can be incentivised to participate.
  - For the remainder of the term the PWG will develop guidelines for implementation, complete outstanding research papers, carry on 2 more implementation trials and write a final report. WADA's activities include targeted research, further development of the survey tool application to facilitate more independent use by ADOs, empirical testing of the doping prevalence index and program support for ADOs.
- The HMRC discussed the presentation. Dr Rabin noticed that the prevalence would be an interval of values, depending on the sport, but at least it would guide NADOs where to put their resources. It was not easy to do the surveys and, in some cases, literacy could be an issue. Nevertheless, athletes are not identifiable and should feel protected.

## Transgender athletes and WADA's position

- Dr Alan Verneq presented WADA's position of transgender issues:
- As a general background, the main concern is regarding the levels of testosterone, as the muscle retains the advantage of exposure once puberty starts in males. The advantage is not equal depending on the sport.
  - However, WADA does not take a position on eligibility, ethics or fairness because the Prohibited List applies to all athletes. The same can be said in terms of TUE, with a few exceptions, e.g. in woman to man, testosterone is accepted as it would be considered like treating a hypogonadal male. WADA has transgender guidelines and Frequently Asked Questions but aimed mainly for Doping Control Officers.
  - In summary:
    - Inclusivity and respect are paramount, but WADA regulates the Prohibited List and TUEs.
    - It is possible that the ABP may expose trans-athletes.
    - Some women, including menopause, ovariectomized, orchidectomized transgender, apply for small doses of testosterone but that is not acceptable.
    - WADA does not have an eligibility position: when an athlete is declared man or woman, then the rules apply.
- The HMRC discussed briefly the subject. In general, each Federation was dealing with the issue with their own rules and the 10 nmol/L testosterone threshold for male to female athletes was under review.



## Miscellaneous

- The HMRC requested that WADA provides the Minutes of the List EAG to the Committee. ACTION POINT

## Calendar for meeting 2023

- August: TBD based on Executive Committee and HMRC meetings

## Closing of meeting

Prof Engebretsen thanked the members of the HMRC for their dedication and work  
The meeting was adjourned.