

MINUTES

Health, Medical & Research Committee Meeting 31 August – 1 September 2023– Montreal, Canada

Participants:

Prof. Lars Engebretsen, Chair
Prof. Takao Akama
Dr. Reema Alhosani
Prof. Xavier Bigard
Prof. Wayne Derman
Dr. Lenka Dienstbach-Wech
Dr. Matthew Fedoruk (day 1 afternoon + day 2)
Prof. Andrew McLachlan
Prof. Yannis Pitsiladis
Dr. Malav Shroff
Prof. Christian Strasburger
Prof. Milica Vukasinovic-Vesic

Ex-Officio Members:

Prof. Odile Cohen-Haguenauer
Dr. Audrey Kinahan
Dr. Terence Wan
Dr. Susan White (day 1)

WADA staff:

Dr. Irene Mazzoni
Dr Luciana Meirotti (day 2)
Prof. Olivier Rabin
Miss Claire Traversa (day 2)
Dr. Alan Vernec
Mr Marc-Andre Matton (day 2, for Artificial Intelligence presentation)
Mr James Sclater (day 2, for Prevalence presentation)

Observers

Prof. Fabio Pigozzi, Fédération Internationale de Médecine du Sport

Dr. Timothy Armstrong, World Health Organization (by videoconference on day 1)

WADA staff observers:

Dr Osquel Barroso (day 1)

Dr Anne Danion (day 1)

Dr Simon Fortier

Abbreviations

AAF: Adverse Analytical Finding
ABP: Athlete Biological Passport
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
GCDEAG : Gene and Cell Doping Expert Advisory 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
SoA: Substance of abuse
TD: Technical Document
TUE: Therapeutic Use Exemption
TUEEAG: Therapeutic Use Exemption Expert Advisory Group
WP: Washout periods
WG: Working group

Day 1

Welcome

- Prof. Lars Engebretsen, Chair of the HMRC, opened the meeting and welcomed the members. 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 Anti-Doping Agency (JADA) Chair, Japan and Medical Director to the Tokyo 2020 Olympic and Paralympic Organizing Committee, and former Chief Medical Officer and Team Doctor of the Japan Olympic Team.
 - Dr Reema Alhosani, sports physician and PhD in sports medicine, President of the United Arab Emirates (UAE) National Anti-Doping Agency (NADO), Deputy Chairperson of the Medical Committee of the UAE Football Association, former Board member of UAE swimming federation,
 - 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 Chair of the IPC Medical Commission,
 - Dr. Lenka Dienstbach-Wech, surgeon in Frankfurt, Germany, a World Rowing Council member, and a member of the IOC Medical Committee as well as a former rowing World Champion, who represented Germany at three Olympic Games
 - Prof. Andrew McLachlan, academic professor at the University of Sydney, Australia, pharmacist with main expertise in pharmacology, and member of Anti-Doping Australia for twenty years,
 - Prof. Yannis Pitsiladis, PhD in sports and exercise science and medicine, Professor and Head of Department of Sport, Physical Education and Health at Hong Kong Baptist University and member of the Medical and Scientific Commission of the IOC,
 - Prof. Christian Strasburger, clinical endocrinologist, Chief of Clinical Endocrinology at the Department of Medicine of Charité-Universität, Berlin; Deputy Chairman of the National Anti-Doping Agency, Germany and co-founder of the company that developed the Growth Hormone (GH) isoform kit;
 - Dr Prof. Vukasinovic-Vesic is a sports physician and professor at the University of Belgrade, and was the Director of Anti-Doping Serbia for the last 5 years.
 - Dr. Malav Shroff, former Olympic sailor, current president of the Asian Sailing Federation and board member of World Olympians Association;
 - Dr Matt Fedoruk, Chief Science Officer at USADA, was not present during the members introduction, as he joined the meeting after midday, once the meeting of the Strategic Testing Expert Advisory Group he was chairing was over.
- 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 with vast experience in medicine's regulation, especially clinical trials.,
 - 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, Chair of the TUEEAG, physician, Chair of the Australian Sports Drug Medical Advisory Committee.
- Next, the observers introduced themselves:
- Prof. Fabio Pigozzi, Director of the Federation Internationale de Médecine du Sport (FIMS), President of the Italian NADO and professor at the Italian National Sports University.
 - Dr. Timothy Armstrong, Director Department of Governing Bodies of the World Health Organization and serving as link with WADA.
- Finally, the members of WADA personnel and observers from the Science & Medicine Department present on day 1 introduced themselves: Prof Olivier Rabin, Senior Executive Director in charge of the Science & Medicine Department for 20 years; Dr Alan Vernec, Chief Medical Officer, sports physician; Dr Irene Mazzoni, Associate Director List, chemist and neuroscientist; Dr Osquel Barroso, Senior Associate Director, Laboratories Division, chemist and immunologist; Dr Anne Danion, Senior Manager, Prohibited List, chemical engineer and Dr Simon Fortier, Manager, Research, specialized in molecular biology and genetic engineering.

Disclosure of conflict of interest

- Prof. Engebretsen noted that there could be some conflict of interest when the review of the Annual Call for grants were discussed. 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 evaluation of those proposals. Prof. Strasburger declared being a board member of the company CMZ manufacturing the hGH kits. No other conflict of interest declared.

Presentation of the draft 2024 Prohibited List

- The Draft of the 2024 Prohibited List, prepared by the LiEAG, was presented by Dr. Audrey Kinahan, Chair of the LiEAG. The draft List was circulated to about 1100 stakeholders from May to July. There were 253 comments received, some of them duplicated from different institutions working closely (e.g Council of Europe and member states).

- The changes proposed to the HMRC were as detailed below:

S0: Non Approved substances

- 2,4-Dinitrophenol (DNP) and troponin activators such as Reldesemtiv and Tirasemtiv were added as examples.

S1: Anabolic agents

- Examples of nandrolone (19-nortestosterone) analogues were added:
 - trestolone (7 α -methyl-19-nortestosterone, MENT)
 - dimethandrolone (7 α ,11 β -Dimethyl-19-nortestosterone)
 - 11 β -methyl-19 nortestosterone

S2: Peptide Hormones, Growth Factors, Related Substances, and Mimetics

- It was clarified that all testosterone-stimulating peptides are prohibited. This comprises of GnRH and its analogues, which now includes the new example histrelin, as well as kisspeptin, and its analogues which act to stimulate GnRH secretion. Kisspeptin is readily available and easily purchased
- Other examples added included:
 - In S2.2.2 : Tetracosactide (ACTH 1-24)
 - In S2.2.4: Capromorelin and ibutamoren (MK-677)
 - In S2.3: The INN name for recombinant human IGF-1, mecasermin.

S4: Hormone and metabolic modulators

- Rev-Erb- α agonists were added and exemplified with SR9011 as well as the relocation of SR9009.

S5: Diuretics and masking agents

- Editorial changes were made to section S5 to improve clarity. Conivaptan and mozavaptan were added as nontraditional diuretics and further examples of vaptan drugs

M1: Manipulation of blood and blood components

- Donation by athletes of plasma or plasma components by plasmapheresis will no longer be prohibited. Dr Kinahan stressed that hematological experts agreed that plasmapheresis could not be used as an excuse or a confounding factor for justifying an altered hematological passport. The proposal was welcome by the stakeholders because in many countries the definition of athlete was broad, so the prohibition of plasmapheresis was affecting the regular supply of plasma.

S6: Stimulants:

- 2-phenylpropan-1-amine (BMPEA, β -methylphenethylamine) was added as an example of a specified stimulant due to its presence in dietary supplements.
- Tramazoline was added as an imidazoline derivative under Exceptions d.

S7: Narcotics

- Tramadol:
 - The prohibition of tramadol in-competition, approved by the Executive Committee in September 2023 with a 1-year delay, will come into effect on 1 January 2024.
 - The clinical study to establish the Minimum Reporting Level and a possible washout period was well advanced and the full set of results should be ready in late October, or early November.

S8: Cannabinoids

- As proposed by the HMRC in 2022, the LiEAG wrote a paper describing the process of review of the status of tetrahydrocannabinol in 2022. The paper was recently published in the journal Addiction.

S9: Glucocorticoids:

- There were no changes in the List with regards to glucocorticoids. However, the minimum washout period following rectal administration of glucocorticoids are now included in the Glucocorticoid

Washout Table that is posted in the 2024 Explanatory Note, the List FAQ the Glucocorticoid and TUE Guidance document and other WADA website resources associated with glucocorticoids. This washout period is equivalent to oral administration.

- Dr Kinahan explained that the intention was to continue adding information to the table, for example, other glucocorticoids, and this required funding more administration studies.
- It was acknowledged that triamcinolone acetonide injections, which are used quite frequently, has an extended washout period. In this regard, Dr White mentioned that it was advised that if a glucocorticoid was used within the washout period, there was a high chance of returning an Adverse Analytical Finding (AAF). Therefore, it was strongly recommended to have appropriate documentation to justify the procedure and there was a checklist to this end. This would be needed in case of requesting a retroactive Therapeutic Use Exemption (TUE) if and AAF occurs.

Monitoring Program:

- Salmeterol and vilanterol below Minimum Reporting Level (MRL) were removed as the results indicated an extremely low prevalence.
- Tapentadol and dihydrocodeine were added to monitor patterns of use In Competition following the prohibition of tramadol.
- As part of the evaluation of weight management drugs, semaglutide was included to see prevalence of use in sports. Use of this drug has become widespread in the general population and may be attractive for weight control in certain sports.

The HMRC discussed the changes proposed by the LiEAG. There were only some concerns of possible misuse of plasmapheresis so it was clarified in the List that the procedure shall take place in a registered collection center.

The HMRC approved the proposed draft 2024 List, Explanatory Note and Monitoring Program as recommended by the LiEAG with the inclusion of the clarification on plasmapheresis. These versions would be recommended to WADA Executive Committee for approval at their 22 September meeting.

Perspectives of the Prohibited List revisions for 2024 and beyond

- Dr. Kinahan informed the HMRC of subjects that would be addressed in the near future by the LiEAG. These included:
 - In the Emerging Therapeutic area, it was of interest to gather information on drugs under development for sickle cell disease as well as sarcopenia.
 - There were plans to discuss the role of substances used for weight management, for example GLP - 1 agonists, diuretics, not only in weight category sports but also for other instances like, for ex. high power to weight ratio.
 - With regards to the minor cannabinoids, the aim would be to investigate in-depth one by one, focusing on the psychoactive properties of each substance, while investigating the possible harm for health and biological effects. The aim would be to determine if any of those minor cannabinoids would fulfil criteria for exemption from the List.
- The development and commercialization of novel psychoactive substances will be monitored using databases such as that of the United Nations Office of Drug and Crime (UNODC), as well as open searches in the internet (e.g. supplements sites, chats, stimulants under clinical development, etc)

- The Guidelines for Substances of Abuse will be updated: the cocaine section will be expanded and the heroin one will be created.
- Based on the results of a recent WADA-funded project, the dosage of formoterol may be reviewed.
- The investigation on the possible performance enhancing effects of ecdysterone and the distinction between the presence in food and doping dosage will continue to be investigated and discussed.
- The results from studies using less classical glucocorticoids and routes of administration will be discussed to expand the table of MRLs and washout periods.

Report from the TUE Expert Advisory Group (TUEEAG)

- 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 at NADOs or International Federations and in athlete care.
 - Number of new TUE registered in ADAMS: there were 3523 TUEs granted as of 15 February 2023. There had been a gradual increase in numbers, reverting back to pre-pandemic numbers with around 3000 new TUE per year. Of those approved, 74 % were prospective and 26 % retroactive. There were 4293 active TUE in ADAMS due to a duration of approval of greater than 12 months. About 80 % were approved by the NADOs because IFs recognize the NADO TUEs and do not grant new TUEs very often.
 - TUE by class: glucocorticoids (GC) had the highest number of TUE requested, followed closely by stimulants. Hormone and metabolic modulators were 3rd, mainly for insulin. The distribution was similar to previous years.
 - The overall number of TUE for GC did not increase with the prohibition of all injections in 2022. Prior to 2022, oral GC TUEs made up the largest number of approved TUEs. After the introduction of the new GC rules oral GC TUEs decreased but still make up the largest proportion (51 %) while local injection constitutes 31%.
 - Almost half of the GC TUEs are retroactive. From the prospective, the vast majority are from the Spanish and Italian NADOs and for administrations during the washout periods. So far there were no AAF attributed to the use during washout periods.
 - TUE Reviews and Appeals: All TUEs entered into ADAMS are monitored and screened by the WADA medical staff. The clinical screening uses a prioritization algorithm based on sport and substance that flags doubtful TUEs for review.
 - IFs and Major Events Organizers may also review NADO TUEs and refuse or may directly reject a TUE application.
 - Each review is done by a 3-person panel formed by a member of TUE EAG who acts as Chair, a clinical expert and a 3rd member (clinical expert or member of TUE EAG). Reviews are very time consuming and takes 4 to 6 weeks. The final draft is reviewed by WADA Legal Department
 - Several TUE reviews were done since 2021:
 - In 2022, 14 reviews on appeal were completed:
 - In 4, the rejections by NADO and IF were overturned
 - For the other 10, the approvals by NADO or IF were overturned.
 - Re-applications are closely watched.

- The WADA decisions are always accepted by the NADO or IF; never a case went to the Court of Arbitration for Sport.
- Many of the inappropriate decisions can be corrected with good education.
- WADA provides the reasons why a request was rejected or overturned
- 2022: 6 full reviews finished, 2 in progress
 - Testosterone (2) - rejected
 - Spironolactone – overturned NADO decision and approved
 - GH –overturned rejection by NADO
 - Lisdexamfetamine- 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, or the diagnosis is inappropriate.
- In addition, the TUEEAG updates the TUE Physician Guidelines Annually.
- Finally, the 5th WADA TUE Symposium was held in Incheon, South Korea, between 31 May and 2 June 2023 and it was a great success.
- It was directed at TUE Committee physicians and managers and the aim was to harmonize practices and decisions and educating less experienced TUE Committees. There were 250 participants, including top experts, as well as medico-legal sessions. There were also consultation booths for people who do not feel comfortable speaking in publicly or required more private or in-depth discussions.
- Dr Jamie Kissick who passed away recently, was remembered. In addition, Profs David Gerrard and Andrew Pipe, long-time serving TUEEAG Chairs and members of TUE Committees, were recognized and honoured.
- In addition, the ISTUE was under review, and the TUE EAG was engaged in several educational initiatives.
- Current challenges include repeated requests regarding TUEs for testosterone in women, 4.3 reviews and retroactive clauses and the time and expertise required for TUE Reviews

The HMRC thanked Dr White for her presentation.

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), gave an update on their activities during 2023:
 - The GCDEAG is 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 diseases 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. This year, Dr Anna Baoutina, who developed a gene doping detecting assay, was invited.

- 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 current definition of Gene and Cell Doping in the Prohibited List but they decided to review it for the 2024 List and perhaps add a line on the “potentiation” of cells. The GCDEAG will work closely with the LiEAG.
- 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 shorter 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 is monitored.
- The GCDEAG recommended strategy to improve detection, which includes:
 - Direct detection:
 - Deep NGS,
 - CARMEN/SHERLOCK based direct detection
 - Cell-free DNA (cfDNA) but applicability is still to be evaluated
 - Self-amplifying RNA (saRNA):
 - Two steps 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.
- The GCDEAG reviewed several final reports:
 - Immune response to AAV vectors: Giuseppe Ronzitti
 - Tested 52 healthy donors and studied the subclasses that could be altered following injection of AAV8 vectors, identifying a potential biomarker.
 - It was concluded that the proposal was successful in this small cohort and now needs to be tested in a larger pool
 - Other projects funded were indirect detection by Prof. Anna Baoutina, deep sequencing-based detection, by Prof. Hidde Haisma, which was promising but the research team discontinued the project and a project by Prof Mario Thevis for detection of CRISPR-Cas machinery.
- However, the GCDEAG believed that the successful projects left many questions unanswered so there was a special call for grants in January 2023, directed to projects using sequencing and multiplex-CRISPR-based method to detect gene doping.

- There were 13 expressions of interest (EOI) and 5 of them were selected for full application.
- Future challenges will include:
 - Do a survey to measure the proper outcome of funded projects, making sure that they translate into established assays in anti-doping laboratories at reasonable costs
 - Follow the evolving field of novel technologies, e.g.
 - gene editing of stem cells, which is extremely complicated and need very specialized methodology
 - RNA-based delivery: similar to the Covid-19 vaccine
- The HMRC thanked Prof. Cohen-Hagenauer for the presentation.
- To conclude the subject, Prof. Strasburger, mentioned that in addition to the grants from the annual call, there was a special call for applications on techniques for gene doping detection. The format of the call for these grants was different, in that researchers presented Expression of Interests (EOI) as a short grant description. Subsequently the EOI were evaluated by the GCDEAG who selected 5 grants to send a full application. The GCDEAG reviewed these full grants and submitted their evaluation and recommendations. Subsequently, these grants were evaluated by the Scientific Project Review Working Group (SPRWG), formed by three HMRC members and three external scientific experts. Four members from WADA's Science & Medicine Department assisted when needed.
- From the 5 grants, one did not follow recommendations provided after the EOI and was not approved. In total, 3 grants were approved, which combined 3 different direct and indirect detections and would provide an arsenal of techniques that are also going to be complementary to ongoing projects.
- The HMRC were satisfied with the recommendations and will present them to the Executive Committee for approval.

Report from the Laboratory Expert Advisory Group

- Dr. Terence Wan, Chair of the Laboratory Expert Advisory Group (LabEAG), gave an update on their activities since September 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, metrology, food safety, environmental, horse racing). Two of the WADA-accredited laboratory directors were new in 2023.
 - The key activities of the LabEAG consisted of directing the process of accreditation, re-accreditation and ABP-approval of anti-doping laboratories; assessing laboratory compliance and performance in accordance with the International Standard for Laboratories (ISL), Technical Documents (TD), Technical Letters (TL) and Laboratory Guidelines (LG); evaluating results from the WADA External Quality Assessment Scheme (EQAS) and providing feedback to laboratories to improve performance and harmonization; reviewing selected WADA-funded research projects and providing recommendations for implementation; drafting, reviewing and revising the WADA Laboratory standards; and providing recommendations regarding laboratory compliance and accreditation status to WADA decision bodies for final decision.

- Since the previous HMRC meeting (August 2022), the LabEAG held 2 virtual meetings and 2 in-person meetings: 13 September 2022, 28-30 November 2022, 10-12 March 2023 and 19-21 June 2023. Additional meetings will be held on 4 October (virtual) and 20-22 November 2023 (in-person).
- There were currently 30 WADA-accredited laboratories and none under suspension. An Analytical Testing Restriction (ATR) for the GC/C/IRMS method was currently imposed to 2 laboratories. There were 2 probationary laboratories: a) Athletes' Anti-Doping Laboratory (Almaty, Kazakhstan) on probation since May 2023; a 2nd on-site assessment will be performed by WADA during the probationary phase. b) Egyptian Doping Control Laboratory (Cairo, Egypt), whose entry into the probationary phase was delayed due to the appointment of a new Director in May 2023; a 2nd on-site assessment will be performed by WADA during the probationary phase.
- There were 3 WADA-approved laboratories for blood testing in support of the ABP: a) Egyptian Doping Control Laboratory (Cairo, Egypt), which is also approved as Probationary laboratory; Lancet Laboratory (Nairobi, Kenya); and Genetix Clinical Laboratory (Panama City, Panama).
- There were 2 candidate anti-doping laboratories: a) Shanghai Anti-Doping Laboratory, Shanghai, China where WADA was assessing their progress and will schedule an on-site assessment and Pre-Probationary Test for entry into the probationary phase of accreditation. The laboratory had also initiated the ABP approval procedure as it continues its preparations for WADA accreditation. b) Doping Control Laboratory of Athens (Greece), preparing for the WADA on-site assessment and Pre-Probationary Test for entry into the probationary phase of accreditation.
- There were several changes in Directorship of WADA laboratories, 4 in the accredited laboratories, 1 in a probationary laboratory and 1 in a candidate laboratory.
- Article 4.4.2.4 of the International Standard for Laboratories (ISL) 2021 establishes that the Laboratory shall be administratively and operationally independent from any organization that could exert undue pressure on the Laboratory and affect the impartial execution of its tasks and operations. As of today, all WADA-accredited Laboratories were considered compliant with ISL 4.4.2.4.
- WADA ISL 2021, Article 4.4.2.8, Maintain Professional Liability Insurance Coverage establishes that Laboratories shall provide documentation to WADA including evidence that professional liability risk insurance coverage is maintained of no less than two (2) million USD annually. At the Laboratories' request, WADA was assisting in obtaining the insurance coverage. Currently 14 Labs were participating in the WADA Laboratory Group Insurance while all others make their own arrangements.
- The ISL will undergo a review process starting on the last quarter of 2023 and the first draft is expected to be produced during January to April 2024.
- TD2023IDCR, TD2023DBS, TD2023APMU and TD2023LDOC revisions were approved; TD EPO and TD MRPL were being revised; a new TD – TD HBT was being drafted and several other TDs were scheduled for revision (TD NA, TD DL, TD IRMS, TD GH and TD EAAS).
- One Technical Note on Chromatographic-Mass Spectrometric Confirmatory Procedures was approved, and one on Measurement Uncertainty and another on Quality Control and use of QC-Charts were being drafted.
- The EQAS included 3 rounds of 5 blind urine samples annually for the Regular EQAS (2 already completed, the other scheduled for September).
- In the double-blind EQAS, 5 urine samples are presented annually as athletes' genuine samples and distributed to laboratories by Anti-Doping Organizations or Delegated Third Parties on behalf of WADA (1 round completed, 2nd round started in June and 3rd round is scheduled for October).

- 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 performed in late 2022 for the endocrine ABP – hGH biomarkers in serum while another on glucocorticoids was done in April 2023. There are also monthly rounds of EQAS for ABP blood samples in collaboration with CSCQ (EQAS provider in Switzerland).
- There were problems with one of the EQAS sample provider, who faced challenges in preparing the samples according the WADA's specifications, so the contract was terminated in February 2023.
- WADA EQAS Management System (MS) was audited by 2 independent international experts. The outcomes were very positive. Three recommendations for improvement were received. EQAS MS documents were revised to be in line with the requirements of the new ISO/IEC 17043: 2023 standard. WADA plans to pursue a self-declaration of compliance with ISO/IEC 17043: 2023 after completing the audit of the EQAS sample provider.
- Since September 2022, laboratory assessments were done for Bloemfontein (South Africa), on-site assessment triggered by the EQAS performance; Almaty (Kazakhstan), on-site assessment and pre-probationary test; Cologne (Germany): virtual regular assessment; and Paris (France): 1st on-site assessment for Major Event (Olympic Games 2024). A 2nd and 3rd assessment are planned for Paris for February and May-June 2024.
- Dr Wan ended his talk by informing the HRMC that after 12 years of serving on the LabEAG he would be leaving this group at the end of the year. Dr Wan thanked everyone who he had the pleasure of working with at WADA, at the HMRC as well as other expert advisory groups, with particular gratitude to all members of the LabEAG for their time, dedication and expertise; and the entire team of the Laboratories Division of the WADA Science & Medicine Department for their support, commitment and hard work.
- Profs. Engebretsen and Rabin expressed their extreme gratitude for Dr Wan's contribution to anti-doping and in particular for raising the bar as the Chair of the LabEAG.
- The HMRC discussed the activities of the LabEAG. It was noted that it was desirable that new laboratories were outside Europe where the vast majority of accredited laboratories are located. An issue some of the new laboratories may face was the lack of enough samples.
- The HMRC thanked Dr. Wan for the update and congratulated the LabEAG for their work.

2021-2022 Research projects outcomes and impact assessment

- Prof. Engebretsen highlighted the importance of showing where the research money had impacted antidoping. In this regard, Prof. Rabin mentioned that it was important that the feedback from the HMRC be incorporated in the call for grants to improve the research projects. Dr Meirotti presented research outcomes and impact assessment.
- Some example outcomes of the research projects completed in the previous 12 months included:
 - There were 18 projects from the annual call, 5 from the targeted/reactive group, 2 from WADA / Partnership for Clean Competition (PCC) joint grants and 1 from the DBS consortium.
 - From the projects impacting the List it was worth highlighting:
 - A study by Buisson on the effects of hydrocortisone topical versus oral administration on endogenous production of cortisone, hydrocortisone or metabolite concentrations.

- The study by Mauger, where it was shown that highly trained cyclists enhanced their performance administering prescription doses of tramadol. This result was key to add tramadol to the 2024 List.
- A project by Diel to test the anabolic activity, potency and mechanisms of action of the higenamine in-vitro.
- A study by R. de la Torre and Ventura on metabolism and excretion of oral tramadol to establish an MRL to distinguish in-and out-of-competition use of tramadol in sports. If needed, a washout period will be added.
- A project by Hostrup to determine potential performance enhancing effects of formoterol and terbutaline at maximal allowed doses
- From projects expanding the laboratory testing menu, one found:
 - A study by Reichel on the detection of follistatin in urine and blood
 - A project by Thevis on the development of an IRMS-based method for the detection of 11-ketotestosterone and 11-ketodihydrotestosterone
- From projects affecting laboratory performance the most salient were:
 - A project by Thevis on a novel approach to distinguish endogenous phenethylamine from a potential misuse using levels of differentiate major metabolites combined by logistic regression analysis; further research fusing IRMS will be needed to compliment the findings.
- An example of studies advancing gene doping detection was:
 - A study by Ronzitti to detect AAV-mediated gene doping targeting anti-AAV antibodies. The method now needs validation as the next step.
- An example of studies affecting ABP management would be:
 - A project by Nordborg to detect rhEPO microdosing and small-volume autologous blood transfusion identifying a number of biomarkers.
 - A study by Faiss on the impact of acute and chronic training as confounding factors for the ABP results interpretation.
- Three examples were given of studies on doping detection using DBS:
 - One study by Marchand evaluating DNA mixtures as a detection method for homologous transfusion.
 - Another by Mercolini following the stability of doping-relevant peptides in DBS
 - A third by Eichner to verify a novel erythropoiesis stimulating agents analytical method in a second laboratory.
- There are also projects that were unsuccessful but from which one could learn the pitfalls for future similar studies.
 - A study attempting to increase the sensitivity of GC-QTOF screening by using chemical ionization showed lower sensitivity but could be useful as confirmation procedure

WADA was increasingly asked to report the impact research has in anti-doping. The plan was to lead by example by taking bold steps to proactively tackle emerging issues. Demonstration of high research impact will serve to advocate for more funding. In addition, the impacts will be announced and highlighted by Communication Tweets, news, website. Key scientific research performance indicators for 2022/23 included:

- Number of projects approved in 2022/2023: 20; 75 % in Europe, 10 % in America, and 15 % in Asia

- Number of applications received in 2023: 76
 - 54 for the Annual Call
 - 7 targeted projects
 - 15 full applications for the Special Calls (26 Expression of interest received)
- Diversity of institutions submitting
 - number of submissions with applicant co-applicant from a WADA laboratory: 49
 - number of unique lead institutions: 50
 - number of unique institutions including co-applicants: 89
 - number of WADA laboratories applying: 17
 - number of ADOs: 4
- Regional distribution of submissions: 64% Europe, 8% Americas, 24% Asia, 4% Oceania
- 42 publications resulting from WADA-funded research and WADA Science staff between August 2022 and July 2023 although it was believed that the number was underestimated as some may be short communication presented internally or in scientific meetings.
 - From projects approved between 2011 and 2021
 - 12 articles in Drug Testing and Analysis

Possible approaches to address impact include:

- Narrative reviews of some well-known examples (e.g DBS)
- 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
- 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. Evidently the majority of studies came from Europe, but it was not possible to distribute the funding regionally as quality and impact of grant applications in anti-doping remain the primary considerations for grant evaluation.
- A few of the projects that had excellent results may be difficult to implement. It was also noted that the overhead costs provided was considered low and that was a reason why some universities did not apply for WADA projects.

History and perspectives of the evaluation process of scientific research projects

- Prof Rabin presented the history of the evaluation project and a proposal for future years.

- Since 2001, WADA has launched the Annual Call for proposals and more than 500 projects were funded.
- The Annual Call timeline implies:
 - The call is opened in December and closes in March
 - Review process includes 3 steps that takes about 8 months:
 - Review by 3 independent experts from April to June
 - Review by the Scientific Program Review Working Group (SPRWG) in July and August
 - Review and recommendations by the HMRC during its annual meeting in August
 - The recommended grants are reviewed and approved by the Executive Committee during their September meeting.
 - Additional time is needed for:
 - Contract negotiations
 - Ethics approval
 - Teams adjusting requirements of HMRC (if needed)
- Overall, the long period of release of funds was detrimental to the attractiveness of the scientific program and the need for a more dynamic program to address doping issues in a rapid fashion.
- Therefore, a new year-round approval system for scientific research projects is proposed where researchers can apply all year around, involving a shorter review process and quicker feedback:
 - Researchers will submit short Expressions of Interest (EOI) that would be reviewed by 2 independent experts and WADA management,
 - There will be a virtual session to choose the EOIs to be called for full submission,
 - There will be a live virtual session where 3 independent reviewers and WADA Science and Medicine will discuss the projects
 - Finally, the HMRC will be consulted for the selected projects before presenting to the Executive Committee meetings for final approval
- There will be a robust review process, with the same quality and integrity standards than the current. The aim is to have 2-3 months elapsed between the full application submission and release of decisions.
- Researchers can apply at any time of the year but there will be 3 rounds aligned with the number and dates of Executive Committee annual meetings.
- The change will have implications as there will be an increase in the workload for staff in the Science & Medicine department, as well as for the external experts from the anti-doping community who participate as reviewers, working group members, and HMRC members.
- In the short-term, it will be necessary to train staff and improve the current application tool (WADA Grants) and in the longer term there will be an investment in a more efficient grant management / funding tools.
- The HMRC discussed the proposal. Prof. Engebretsen informed the HMRC that it would mean more time investment on their part. Prof Strasburger, who Chaired the SPRWG discussions for several years, noticed that he was pleased with speeding up the process, but the lack of funding should also be considered as one of the limiting factors for the lack of applications. He noted that the SPRWG would no longer be part of the process and, although it implied considerable work, he felt that the contribution of this WG to integrate different expertise and have a global view of the projects and process was tremendous. It was an extra layer of scrutiny and the discussion was the richest and worthwhile to elevate the level of the review

process. Prof. Strasburger reminded that not all external reviewers were experts in anti-doping and although he agreed with speeding up the process, he was convinced that there had to be an integrating step like the SPRWG. Prof McLaughlan, also part of the SPRWG, supported this view and stressed the importance of the discussion in addition to the individual reviews. Prof Rabin said that the number of steps will remain it is the organization of the review process that will be modified and also that directors of the anti-doping laboratories will be part of the reviewers. Besides, as of 2024, a very experienced laboratory director will join the HMRC. Several members mentioned that they were clinicians with little experience in research, while other believed that the time allocated for the reviews by the HMRC should be more than 2 weeks.

- In the end, Prof. Rabin thanked for the feedback and said that the suggestions would be taken into consideration.

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

- Profs. Strasburger (Chair of the SPRWG), McLachlan and Bigard presented the conclusions and recommendations of the 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 23 August and in hybrid mode on 30 August and reviewed the grants based on the independent external reviewers' evaluations as well as the SPRWG's own assessment, which took into account the scientific merit/rigour, the recommendations from external expert reviewers to fund, conditionally fund or not fund, the translation into anti-doping/ List implementation and WADA priority areas. The outcome of their task was to rank fundable research grants by order of merit and priority and present to the HMRC.
- SPRWG members with conflict of interest on particular projects disconnected or stepped out during those discussions. The SPRWG ranked the proposals and presented the outcome to the HMRC.

Investigators from 4 continents submitted 54 research projects to WADA in 2023 through the Annual Call program.

- Theme A - 21 projects were submitted in the category "Detection of Prohibited Substances/Methods: Methodologies in Analytical Chemistry"
- Theme B - 5 projects were submitted in the category "Detection of Prohibited Substances/Methods: Affinity-Binding and Biochemical Methodologies"
- Theme C - 11 projects were submitted in the category "Pharmacological Studies on Doping Substances/Methods"
- Theme D - 12 projects were submitted in the category "The Athlete Biological Passport"
- Theme E - 5 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, 23 projects were selected and recommended for funding.
 - Five projects addressed improving detection of non-peptide prohibited substances.

- Five projects aimed to improve detection of peptide/protein hormones and metabolic modulators.
- Four projects proposed to perform pharmacokinetics studies to investigate the metabolism of prohibited substances or distinguish permitted from prohibited use.
- One aimed to produce standards for non-threshold analytes at the MRL/MRPL levels
- One addressed detecting prohibited substances by DBS.
- Five addressed different aspects of the ABP
- One addressed muscle memory
- One project aimed to evaluate a novel gene doping detection approach.
- Some conditions were imposed on some grants, for example:
 - For 2 grants, add analysis of an extra biomarker.
 - Confirm statistical power considering e.g. confounding factors, routes of administration, gender.
 - Add more samples before and following treatment.
 - Remove a matrix not used in anti-doping
 - Compare proposed model with current.
 - Clarify some points of the project plan.
 - Reduce budget for a proof of principle.
 - Collaborate with an anti-doping laboratory.
- One project would potentially be co-funded with Partnership for Clean Competition (USA)
- The HMRC concluded the discussions on the projects and would submit the recommendations for funding of the selected projects during the WADA Executive Committee meeting on 22 September 2023.
- Subsequently, Prof. McLachlan informed the HMRC that there was also a special call for grants for DBS., where 10 full applications were selected out of 13 EOI on the subjects of Hypoxia-Inducible Factor (HIF) activating agents in DBS samples (4 full applications) and Detection of small peptides in DBS samples (6 full applications).
- From the 10 grants, the SPRWG reviewed the evaluations of the external independent reviewers and selected 2 for each subject, with some modifications for 3 of the proposals such as:
 - Add 1 timepoint after 1 year.
 - Add another similar drug to gather more data.
 - Do not fund part of the proposal as it was already done in other studies.
- Prof Engebretsen thanked the SPRWG for their thorough review and work.

Research perspectives for the next 5 years

- Prof. Rabin presented the future directions in research for the next 5 years:
DBS
 - As presented earlier, high priority research topics were underway,

- US professional leagues were very supportive of DBS implementation, as they considered it a “game changer”,
- In this regard, it was important to strengthen the partnership with PCC on DBS to speed up development.

Artificial intelligence

- Could be useful to detect sample swapping as it already delivers promising results,
- For EPO analysis it seems to outperform the adaptive model,
- An ongoing AI model was being developed to improve testing strategies,
- The ethical, legal and social implications of using AI in anti-doping should be thoroughly evaluated.

Prevalence: currently in the research stage, the aim is to implement in the near future

- There were several requests for applications:
 - DBS and gene doping detection as detailed above
 - Certified Reference Materials, in partnership with PCC, to harmonize laboratory reporting. There were 5 grants under review
 - It was also envisaged to call for applications for muscle memory, but it may be reconsidered in light of some ongoing studies on the subject when completed.
- Partnerships were key for the advancement of anti-doping research. Currently WADA was partnering or seeking partnership with:
 - Fonds de Recherche du Quebec (FRQ)
 - Partnership for Clean Competition (PCC)
 - NIH/NIDA for cannabis and cannabinoids research
 - Different anti-doping organizations
- In order to strengthen the identification of emerging drugs, WADA was collaborating with:
 - The United Nations Office on Drugs and Crime (UNODC)
 - The World Health Organization (WHO)
 - The International Society for the Study of Emerging Drugs (ISSED)
 - WADA Intelligence & Investigations Department
 - Pharmaceutical industry, for counterfeit legal drugs (IFPMA)
 - Universite de Montreal for Internet and Dark web searches, comparison and database construction
- As presented earlier, the call for grants will be streamed continuously along the year.

The HMRC was satisfied with the 5 -year plan. There were suggestions of partnership with industry, but it could be perceived as favoring one company over another

Dried Blood Spots: state of development and perspectives

- Miss Claire Traversa, Manager, DBS Program, replacing Dr Leonie Egli on maternity leave, gave an update on the state of DBS analysis:

- The Program started in 2013 at WADA and until now there had been 20 funded projects that evaluated methods in DBS for a range of prohibited substances.
- The DBS Consortium was established in 2019, managed by Leonie Egli. The project was initiated 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.
- The DBS Steering Committee supported the research topics between 2019 – 2023. Previously, these projects formed part of the Annual Call for Grants
- Promising DBS research results from WADA-funded projects were published in recent years.
- The TD2021DBS on DBS testing and implementation became effective 1st September 2021. 69 "mock" DBS samples (venous blood on DBS cards) for steroid esters were analyzed in Tokyo 2021 and 105 DBS samples analyzed and reported under a full procedure by the Beijing Lab in 2022.
- In 2022 the focus was to further DBS development through additional research topics and publish an updated technical document. In this regard, the Special call on high priority research topics discussed earlier took place.
- The TD2023 became effective on 1 January 2023
- For 2024 the perspectives are to:
 - encourage ADOs to incorporate DBS samples into testing plans;
 - harmonize DBS sample collection devices;
 - expand the testing menu to more non-threshold substances (first without MRL, then with MRL) and develop quantitative analysis for threshold substances;
 - continue high-priority research
- Laboratory testing is very restricted to date, therefore next steps will require to:
 - expand and harmonize DBS testing menu
 - define the laboratory method performance requirements in DBS, e.g. non-threshold substances with and without MRLs, decision limits for threshold substances
 - prepare laboratory normative documents, such as laboratory guidelines, technical documents, technical letters and/or technical notes to describe the expected requirements
 - Develop DBS External Quality Assessment Scheme (EQAS)
 - Determine the minimum number of samples to be analysed by laboratories annually
- The most recent successful projects included:
 - G. Miller: verification of erythropoiesis stimulating agents analytical method developed in the Barcelona laboratory by a second laboratory (Salt Lake City). It was recommended to increase the number of samples and the volume and write a Technical Document.
 - L. Mercolini: demonstrating that long-term storage stability of peptides prone to degradation was greatly enhanced through DBS
 - A. Marchand: validated a forensic DNA method to detect DNA mixes, However the method worked in vitro but not in vivo.
- Other projects were ongoing in addition to the recently approved.

- The HMRC thanked Miss Traversa for the presentation and work. There were questions on whether DBS would replace urine testing. Miss Traversa said that it would not replace but complement urine/blood samples for substances not easily detected or unstable in these matrices, it would be an alternative matrix for increased number of tests, and would allow for mass screenings, e.g. full teams, testing in remote areas, younger athletes, etc.

Prevalence of Doping-Doping Prevalence Index (DPI): Progress report

- Mr. James Sclater, Senior Manager, Strategic Projects, gave an update on the Prevalence of Doping Project.
- This project started several years ago, gathering a Working Group (WG) that discussed the best way to address this issue. The WG designed and tested an indirect survey as a pilot project.
- The survey was considered by stakeholders to be important and to point out what actions are missing from the anti-doping program. In particular, it was helpful to find out about, for example:
 - anti-doping program effectiveness,
 - whether only unsophisticated dopers were caught
 - likeliness to be caught if tested one or repeated times
 - differences between winter and summer sports as well as non-Olympic vs Olympic
- The mandate of the WG has now ended and a new WG was formed, which will have to decide what is measured, work with the IT Department to develop the tool and work with the NADOs to use it.
- There are different DPI categories, for example:
 - AAFs, which is already established and is probably underestimated
 - ADRV
 - ABP results
 - Direct surveys
 - Indirect surveys, which mixes relevant and irrelevant questions
 - Criminology analysis like for illegal drugs
- Therefore, the WG is composed of members of testing, NADOs, IF, social science, athlete, experts in indirect surveys, ABP experts and criminologists
- The surveys will be translated into many languages.
- The HMRC thanked Mr Sclater and had some comments, mainly on the need to simplify and make clear the questions, as well as the type of questions that may be sensitive to different cultures.

Integration of Artificial Intelligence (AI) in Anti-Doping activities

- Marc-André Matton, Chief Technology Officer, gave an update on the usefulness of AI in antidoping.
- AI may be useful in anti-doping to:

- Educate
 - Do risk assessment
 - Predict doping risk behaviour
 - Correlate ADRV with education
 - Trends in ABP to predict risk
 - Etc
- AI can assist by developing a control strategy based on algorithms.
 - There is an enormous amount of data relating to doping, but needs to be cleaned up.
 - Data governance was vital for securing stakeholders.
 - They had already created a Dashboard with the State of Doping, which includes substances, sport, age, regional distribution, etc
 - In most cases only the tip of the iceberg is seen. Therefore, it is necessary to see what is below by integrating and organizing the data, understanding, evaluating, extracting and transforming it as well as identify key questions.
 - Mr Matton added that AI will not make a final decision but would be a support tool to human decision.
 - The HMRC thanked Mr Matton for the update.

Calendar for meeting 2024

- August: TBD based on Executive Committee meeting.

Closing of meeting

Prof Engebretsen thanked the members of the HMRC for their dedication and work.

The meeting was adjourned.