MINUTES

Health, Medical & Research Committee Meeting

22-23 August 2024– Montreal, Canada

Participants:

Prof. Lars Engebretsen, Chair
Prof. Takao Akama
Prof. Xavier Bigard
Prof. Francesco Botré
Dr. Lenka Dienstbach-Wech
Dr. Matthew Fedoruk (by videoconference)
Prof. Andrew McLachlan (by videoconference from 9:00 to 13:00)
Prof. Yannis Pitsiladis
Dr. Malav Shroff
Prof. Christian Strasburger
Prof. Milica Vukasinovic-Vesic

Apologies

Prof. Wayne Derman

Ex-Officio Members:

Prof. Odile Cohen-Haguenauer
Dr. Audrey Kinahan
Prof. Bruno Le Bizec
Dr. Susan White

WADA staff:

Dr. Osquel Barroso
Dr Anne Danion (day 2)
Dr Léonie Egli
Dr Simon Fortier
Dr. Irene Mazzoni
Dr Luciana Meirotti
Prof. Olivier Rabin

Ms Claire Traversa (day 2)

Dr. Alan Vernec

Observer

Prof. Fabio Pigozzi, Fédération Internationale de Médecine du Sport

Abbreviations

AAF: Adverse Analytical Finding
ABP: Athlete Biological Passport
ADO: Anti-Doping Organizations
DBS: Dried Blood Spot
DL: Decision Limit
EAG: Expert Advisory Group
ExCo: Executive Committee
GCDEAG: Gene and Cell Doping Expert Advisory Group
HMRC: Health, Medical and Research Committee
IC: In-Competition
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
WG: Working group

Day 1

Welcome

- Prof. Lars Engebretsen, Chair of the Health, Medical & Research Committee (HMRC), opened the meeting and welcomed the members. Prof Engebretsen welcomed Prof. Francesco Botre as a new member of the HMRC and subsequently introduced himself, indicating that he is a sports physician, a Professor in Orthopedics, an orthopedic surgeon in Norway and the Head of Science and Research at the International Olympic Committee (IOC) since 2007.
- Afterwards, all the other HMRC members introduced themselves:
  - Prof. Takao Akama, Professor at the Faculty of Sport Sciences at Waseda University, Japan Anti-Doping Agency (JADA) Chief Medical Officer, and Medical Director of the Tokyo 2020 Olympic and Paralympic Organizing Committee,
  - Prof. Xavier Bigard, sports physician, researcher specialized in exercise physiology, skeletal muscle physiology and biology and currently Medical Director of the Union Cycliste Internationale (UCI),
  - Prof. Francesco Botré, Director of the Rome WADA-accredited laboratory, Director of the Research and Expertise on Antidoping Sciences (REDs) and Associate Professor at the Institute of Sport Science of the University of Lausanne (Switzerland),
  - 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, Professor at the University of Sydney, Australia, pharmacist with main expertise in pharmacology, and member of Anti-Doping Australia for twenty (20) 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, as well as a member of the Executive Committee and Chair of the Scientific Commission of the Federation Internationale de Médecine du Sport (FIMS),
  - Prof. Christian Strasburger, clinical endocrinologist, Chief of Clinical Endocrinology at the Department of Medicine of Charité-Universität, Berlin; member of the Supervisory Board of the National Anti-Doping Agency (NADA), Germany, since 2016 and co-founder of the company that developed the Growth Hormone (GH) isoforms test,
  - Dr Prof. Vukasinovic-Vesic is a sports physician and Professor at the University of Belgrade and Director of Anti-Doping Serbia for the last 5 years,
  - Dr. Malav Shroff, former Olympic sailor in 2004, current President of the Asian Sailing Federation and board member of World Olympians Association,
  - Dr Matt Fedoruk, Chief Science Officer at USADA, member of the Research Board of the Partnership for Clean Competition (PCC) and member of several WADA advisory and technical working groups.
- Next, the Ex-officio members introduced themselves:
  - Prof. Odile Cohen-Haguenauer, Chair of the Gene and Cell Doping Expert Advisory Group (GCDEAG) for 12 years, geneticist and Professor in Oncology, Hôpital Saint-Louis and Faculty of Medicine, Paris, France,

- Dr. Audrey Kinahan, Chair of the WADA List Expert Advisory Group (LiEAG) and PhD in pharmacy with a vast experience in clinical trials as assessor of the Irish and European Medicines Regulation authorities,
- Prof. Bruno Le Bizec, Member and recently appointed Chairman of the WADA Laboratory Expert Advisory Group (LabEAG) since January 2024, analytical chemist, Head of LABERCA, French National Reference Laboratory monitoring forbidden growth promoters in farm animals and organic pollutants in food.
- Dr Susan White, Chair of the TUE Expert Advisory Group (TUEEAG), sports and exercise physician, Chair of the Australian Sports Drug Medical Advisory Committee.

– Next, the observer introduced themselves:

- Prof. Fabio Pigozzi, President of the FIMS, President of the Italian NADO and Professor at the Italian National Sports University.

– Finally, the members of WADA Science & Medicine Department present on day 1 introduced themselves: Prof Olivier Rabin, Senior Executive Director in charge of the Science & Medicine Department for twenty two (22) 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 Luciana Meirotti, Head of Research, , veterinarian and immunologist; Dr Léonie Egli, Senior Manager, Research, human physiologist, lead the initial development the WADA DBS program and Dr Simon Fortier, Manager, Research, genomics and drug discovery.

Disclosure of conflicts of interest

– Prof. Engebretsen noted that there could be some conflicts of interest when discussing the project proposals pertaining to the Research Call for grants. 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.

Presentation of the draft 2025 Prohibited List

– The Draft of the 2025 Prohibited List, prepared by the LiEAG, was presented by Dr. Kinahan, Chair of the LiEAG. The draft List was circulated to 1061 stakeholders from May to July. There were approximately 200 comments received, most of which were supportive of the proposed changes. Dr Kinahan commented that along the years she had been sending feedback letters to those who answered, explaining the decisions taken, especially for proposals that were not accepted. The letter was always well appreciated by the stakeholders.

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

S0: Non-Approved substances

- S-107 and S48168 (ARM210) were added as examples of the class of ryanodine receptor-1- calstabin complex stabilizers. The ryanodine receptor-1-calstabin complex servs to maintain skeletal muscle function.

S3: Beta-2-agonists

- The dosing intervals of inhaled formoterol were updated to ensure that the ergogenic effects shown in a recent publication are not achieved. These new 12-hourly dosing intervals are consistent with manufacturers' recommended use; the maximum delivered dose is unchanged at 54 micrograms over 24 hours.

S4: Hormone and metabolic modulators

- Elacestrant was added as an example of a selective estrogen blocker.
- Mitochondrial open reading frame of the 12S rRNA-c (MOTS-c) was added as an example of an AMP-activated protein kinase activator.
- S519 and S597 were added as examples of insulin-mimetics. Insulin mimetics compounds or selective insulin receptor modulators (SIRMs) mimic insulin action by binding to the insulin receptor and are not to be confused with anti-diabetics.

S5: Diuretics and masking agents

- Xipamide was added as an example

M1: Manipulation of blood and blood components

- Donation of blood or blood components (e.g. plasma, red blood cells, white blood cells, platelets and peripheral blood stem cells) including by apheresis will no longer be prohibited when performed in a collection center accredited by the relevant regulatory authority of the country in which it operates. This broadened the permission of plasma or plasma components by plasmapheresis started in January 2024. Dr Kinahan stressed that the Athlete Biological Passport (ABP) hematological group was consulted for possible effects on the hematological parameters and the largest changes possible would occur with blood donations, always permitted, and were transient. The LiEAG took extra precautions by including the need to be performed in an accredited collection centre. The proposal was welcome by the stakeholders.

M3: Gene and cell doping:

- A minor editorial change was made for clarity.

S6: Stimulants:

- Hydrafinil (fluorenol) was changed from S6.B to S6.A, as this substance is more potent than modafinil and is not licensed for medical use.
- Midodrine and tesofensine were added as examples of specified stimulants.
- It was clarified that guanfacine is not prohibited.

P1: Beta-blockers:

- Based on information provided by the International Ski and Snowboard Federation (FIS) on the lack of performance enhancing effects, the skiing/snowboarding disciplines of ski jumping, freestyle aerials/halfpipe and snowboard halfpipe/big air were removed from this category.

Monitoring Program:

- Fentanyl and tramadol were added to monitor patterns of out-of-competition (OOC) use.

The HMRC discussed the changes proposed by the LiEAG. The HMRC members agreed with most of the modifications, but some members discussed the scope of application of the change, questioning the risk of misuse of apheresis, but were reassured by the restriction to certified official centers. A vote confirmed the majority in support of this change.

The HMRC approved the proposed draft 2025 List, Explanatory Note and Monitoring Program as recommended by the LiEAG. These versions would be recommended to the WADA Executive Committee (ExCo) for approval at their 12 September meeting.

Perspectives of the Prohibited List revisions for 2025 and beyond

- Dr. Kinahan informed the HMRC of subjects that were being addressed by the LiEAG for possible changes in the future:

Prohibition of stimulants at all times:

- Dr Kinahan informed the HMRC of a working hypothesis by the LiEAG to prohibit Stimulants at all times
- The following steps were proposed before giving further consideration to this hypothesis:
  - The LiEAG would publish an extensive literature review on the PE benefits of Stimulants OOC
  - Look at prevalence information e.g. in Doping Control Forms etc.
  - A detailed plan on how each type of substance would be managed
  - TUE considerations: the change is not expected to impact medications for chronic conditions. There is no intention to create TUEs for OTC medicines as the aim was to have therapeutically based thresholds in place.
- The work ahead was extensive and would take more than 1 year to conceptualize and several years to implement. However, in order to continue and invest the time and effort, the LiEAG wanted to know if the HMRC would support the initiative.
- The HMRC discussed the idea.
- . Overall, the HMRC was supportive of the proposal that the LiEAG should progress their evaluation of the potential for in-competition use of stimulants to be performance enhancing, considering that a number of aspects required further investigation

Weight management drugs:

- Dr Kinahan recalled that at last year's HMRC meeting, she informed the Committee that there were plans to discuss the role of substances used for weight management, not only in weight category sports but also for other instances like, for example, sports with high power to weight ratio.
- Dr Kinahan updated the HMRC on the advances made during the last year on the subject:
  - In the literature, there were studies investigating controlling weight to improve performance, not only in weight category sports.
  - The types of drugs the LiEAG initially would be looking at were:
    - Selected GLP 1 agonists and anti-diabetics
    - Diuretics
    - Stimulants
    - Emerging Weight Management Drugs
- For now, the LiEAG was mainly concentrating on semaglutide, which was included in the 2024 Monitoring Program (MP) to investigate prevalence.
- The HMRC believed it was an important subject and encouraged the LiEAG to continue working on it.
- Prof Engebretsen thanked Dr Kinahan for the presentations.

Reporting on the new review process of scientific research projects

- Dr. Luciana Meirotti, Head of Research, explained the new review process for the Call for Scientific Research Grants.
- From 2001 to 2023 there was only an annual call for research, structured so that the final review coincided with the HMRC meeting in late August/early September and the approval with the September ExCo meeting. In this long process, the call opened in late November, the reviews took place between March and June and the final decision was communicated in early October.
- To make the process more dynamic, starting this year, the Call for Grants will be open all year-round and there will be 3 review cycles per year, scheduled to coincide for approval with the 3 ExCo meetings.
- The process starts with an Expression of Interest (EOI) where the researcher presents an abridged grant proposal. Following review by 2 external and also by internal reviewers, pertinent grants with at least 2 positive reviews are selected and a full proposal is requested. The full grant is then reviewed by 3 external reviewers. Once this is done, the results are compiled by the Research Team, discussed within the Science & Medicine Department, classified by funding recommendations and scores, and presented to the HMRC. The HMRC members had access to the full applications and respective reviews ahead of the meeting. When necessary, WADA provides information on overlaps, previous failures, or immediate needs. Following the discussion and evaluation by the HMRC, the recommendations for selected projects are presented to the ExCo.
- The new format was well received by the anti-doping researchers.
- There are several pros for this new scheme:
  - more applications are being received
  - quicker review, as EOI are short applications.
  - EOI is a filtering step of low-quality applications
  - possibility for the researchers to improve and resubmit a proposal, as they are provided with the reviewers' comments.
- There are also several cons:
  - High demand and short deadlines for review (externals, internals and HMRC)
  - Increased workload and short deadlines for the WADA team
  - Difficulty to estimate budget per cycle
  - No in-person discussions for all cycles (only for one cycle per year)
- Potential improvements include virtual live discussion of full applications with the HMRC, improved financial and human resources.
- The HMRC thanked Dr Meirotti and discussed the information presented. Overall, the HMRC agreed there was an improvement in the agility and the feedback could increase the quality of resubmissions. The review process was solid. There were concerns of the workload for the HMRC members and the reviewers and the way to balance budget distribution for the 3 rounds.

Review and recommendations for the 2024 WADA Call for Scientific Research Projects

- Dr Léonie Egli and Dr Simon Fortier presented each of the 32 full applications from 2024 Cycle-1 that comprised a summary of each research proposal, a compilation of the 3 external reviews, the score and WADA remarks if appropriate.
- The 2024 Cycle1 was launched on 19 December 2023 and ran until 29 March 2024. Seventy-two (72) EOIs were received, 33 researchers were invited to apply for full application and 32 did.
- The grants were ordered by the number of positive and negative recommendations and by score (given by external reviewers) and were discussed in that order.
- HMRC members with conflicts of interest on particular projects stepped out during those discussions.
- The HMRC considered the recommendations from the external reviewers and WADA comments (if any) for each grant. As a result, 14 projects were selected and recommended for funding.
    - Five projects from Category A: Detection of doping substances/methods: methodologies in analytical chemistry
    - Five projects from in Category C: Pharmacological studies of doping substances/methods
    - Two projects from Category D: The Athlete Biological Passport.
    - One project from Category E: Detection of doping substances/methods: molecular biology, “Omics” and miscellaneous methodologies
    - One project from Category F: Scientific innovations to improve anti-doping programs
- Some conditions were imposed on some grants, for example:
    - Justification of some expenses
    - Do additional structural characterization.
    - Budget and length of grant reduced for proof of principle as the project was considered risky.
    - Number of testing subjects may be low: conditional to power analysis
    - Add DBS testing and another steroid marker
    - For a few grants, reduce budgets as they seem overestimated
- Some feedback was provided to improve some of the non-approved grants, such as to collect more preliminary data or wait until completion of a previous project, use in vivo, rather than in vitro systems, etc.
    - The HMRC concluded the discussions on the projects and would submit the recommendations for approval of funding of the selected projects during the WADA ExCo meeting on 12 September 2024.

2023-2024 Research projects outcomes and impact assessment

- Prof. Engebretsen introduced the subject, stressing the importance to show that the funds invested in research have a direct applicability in antidoping. Without science, including research, the fight against doping would not be possible.

2023-2024 Research project outcomes:

- Dr Meirotti summarized the outcomes of key projects completed in the last 12 months:
  - A 3-year project on glucocorticoids excretion through different routes of administration and using different drugs allowed to establish the minimum reporting levels (MRL) and washout periods.
  - A study that developed a high-throughput method for the detection of small molecular prohibited substances decreased analytical time to less than 2 minutes, representing a method improvement.
  - Another study improved the sensitivity and specificity of detecting intact phase-II steroid metabolites by LC-MS
  - 4 studies expanded the testing menu for black market follistatins and myostatins in urine and blood.
  - New markers of the steroid profile were identified to improve detection of testosterone administration combined with alcohol consumption.
  - During the first year of a study, a method revealing gene doping with CRISPR/Cas through the detection of sgRNA was developed.
  - The first-year report of another project described the development of a confirmation method for recombinant EPO analysis in individuals with the variant *EPO* c.577del gene. The method was applied at the Beijing and Paris Olympics.
  - For DBS detection there were:
    - 8 ongoing research projects funded by the DBS Consortium on hypoxia-inducible factors (HIF), small peptides, mRNA markers, glucocorticoids, hCG and DNA analysis
    - 1 ongoing research project co-funded with PCC
    - 7 ongoing research projects from WADA's annual call on stimulants, the detection of steroid abuse, carbonic anhydrase inhibitors and confounders in the detection of erythropoietin abuse
- Regarding the Dried Blood Spot (DBS) Working Group (WG) immediate interests, research focused on:
  - HIF activating agents
  - Small peptides
  - Excretion study with boldenone esters/contaminated meat
  - Excretion study on nandrolone preparations with enriched carbon isotopic ratios (CIR).
  - Excretion studies for substances with MRL (stimulants, glucocorticoids, narcotics and cannabinoids), prioritizing substances that can only be or are better detected in blood.

Impact assessment

- Regarding the impact assessment of WADA-funded projects Dr Meirotti informed that 35 projects were approved in 2023, 23 from the Annual Call, 7 from the special Calls and 5 targeted.
- 83% originated from Europe, 9% from North America, 6% from Asia and 3% from Oceania.
- There were 126 applications in 2024, up from the 114 in 2023 and about double from the lowest point in 2022.
- Since the last HMRC meeting, 41 articles related to WADA-funded grants were published. In total 610 articles have been published since the research grant program started in 2004.

- One way to quantitatively evaluate research impact was using bibliometrics, which was the number of times that a journal article was cited by other papers. This indicated the level of interest and influence of the work.
- The other way was using altmetrics, based tracking online platform activity including news, social media, academic networking and policy documents. Altmetrics assessed the attention received by research outputs within the academic community and general public.
- Using these tools, it was found that there have been 171 articles published in 66 journals in the last 4 years and 714 citations.
- The Impact Factor (citations/number of articles published) ranged from 0.8 to 14.7.
- The main journal where this research was published is Drug Testing and Analysis, with 45 publications in the last 4 years.
- The most cited publication was the study on the longitudinal evaluation of testosterone detection in women and the most mentioned publication (news, social media, etc) was the study on tramadol effect on performance enhancement.
- The main disciplines of the readers were in chemistry, medicine and dentistry, sports and recreation, biochemistry, genetics and molecular biology and pharmacology, toxicology and pharmaceutical science.
- There were other methods to measure impact such as doing complete metrics (paid sources), testing figure analysis, surveys of WADA accredited laboratories and ADOs for perception on biggest impact of scientific advances, cross-referencing bibliographies, but they required additional sources (monetary and human resources).
- The HMRC discussed the outcomes. It was admitted that anti-doping was a small community and the budgets available for research were extremely small compared to other disciplines, even considering other funding sources like Japan Anti-Doping Agency (JADA) and PCC in the USA. That is why WADA funding was so critical to advance anti-doping science. There were suggestions to use more social media to call the attention of the public or to create a consortium to attract more scientists.

Research Perspectives for the next 5 years

– Prof Rabin presented the priority and strategic research areas:

- DBS: there were high priority research topics underway and a DBS working group was created to steer research and applicability of the technique
- Artificial intelligence (AI): there were focused projects underway, e.g. analysis of erythropoietin or sample swapping, as well as a global approach, led by the WADA Innovation Board on how AI developed elsewhere could benefit antidoping in terms of guiding principles for the responsible use of AI as well as recommendations on the interest, resources, and priority level of innovative AI ideas.
- Partnerships: WADA continued to solidify and expand collaboration with external partners:
  - Fonds de Recherche du Quebec for projects on biomarkers and AI, as Montreal is a hub for these disciplines
  - PCC: to avoid redundancies and co-fund projects of mutual interest
  - NIDA/NIH: for research on cannabinoids including health impact and minor cannabinoids.
  - UNODC: collaboration to identify new psychoactive substances (NPS)

- Pharmaceutical industry: to be informed of emerging medicines with doping potential and be proactive at detecting them.
- Innovation and state-of the-art anti-doping methods require investment and the biggest research budgets occurred between 2007 and 2009. Following the 2009 economic crisis, the budget was at its lowest in 2015 and slightly recovered in 2023. It is expected to increase in the next years but that will depend on WADA's financial situation and contribution payments.
- The HMRC agreed that research was fundamental to the advancement of anti-doping science and that more funds were needed.

Report from the Laboratory Expert Advisory Group

– Prof Bruno Le Bizec, new Chair of the LabEAG, gave an update on their activities during 2024:

- The LabEAG is composed of 12 members: 4 representatives from WADA-accredited laboratories and 8 independent experts from ADOs, accreditation bodies, and related analytical fields (forensics, food safety, metrology and analytical chemistry). The 2024 LabEAG includes 2 new members: Prof Leo Zhang, Director of the National Anti-Doping Laboratory in Beijing, China, and Mr Brian Brookman, Proficiency Testing Consultant, London, UK. There is also one observer, Prof. Rosa Ventura, Director of the Catalonian Anti-Doping Laboratory, Barcelona, Spain.
- The key activities of the LabEAG consist in drafting and reviewing the WADA Laboratory Standards (International Standard for Laboratories (ISL), Technical Documents (TD), Technical Letters (TL), Technical Notes (TN) and Laboratory Guidelines), assess laboratory performance and compliance with WADA Laboratory standards; evaluate laboratory performance in the WADA External Quality Assessment Scheme (EQAS); provide recommendations regarding laboratory accreditation and Athlete Biological Passport (ABP) laboratory approval to the WADA decision bodies as well as reviewing selected WADA-funded research projects and provide recommendations for application.
- Since the previous HMRC meeting (August 2023), the LabEAG held 2 virtual meetings and 2 in-person meetings. Another virtual meeting is scheduled for 16 September 2024 to address pressing issues, and the next in-person meeting will take place on 25-27 November 2024 in Montreal, Canada.
- There are currently 30 WADA-accredited laboratories. The Bloemfontein**,** South Africa, laboratory is currently suspended up to 01 March 2025. There are 2 probationary laboratories: a) Athletes' Anti-Doping Laboratory (Almaty, Kazakhstan), b) Egyptian Doping Control Laboratory (Cairo, Egypt).
- There were 2 candidate anti-doping laboratories: a) Shanghai Anti-Doping Laboratory, Shanghai, China, seeking full accreditation in addition to their proposed approval for the ABP, 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 2 WADA-approved laboratories for blood testing in support of the ABP: a) Egyptian Doping Control Laboratory (Cairo, Egypt), b) Cerba Lancet Kenya Laboratory (Nairobi, Kenya); There are 2 ABP applicant laboratories: a) Laboratoire Mohammed VI antidopage in Casablanca (Morocco), b) Ethiopian Public Health Institute Laboratory in Addis-Ababa (Ethiopia). An ABP laboratory is a laboratory not otherwise accredited by WADA, but is approved by WADA to apply the analytical method and processes in support of the hematological module of the ABP program.
- The ISL is undergoing a review process since the end of last year. The ISL Drafting Team members include Dr. Osquel Barroso (WADA Science) as the drafter. Prof. Bruno Le Bizec as the Chair, and as members, Dr. Yvette Dehnes (Director Oslo, Norway, laboratory and LabEAG), Prof. Henrique Pereira

(Director Rio de Janeiro, Brazil, laboratory; Lab EAG; President of World Association of Anti-Doping Scientist (WAADS); Dr. Bruno Garrido (National Research Council Canada; LabEAG), Mr. Thierry Boghosian (WADA Science), Mrs. Marissa Sunio (WADA Legal).

- Regarding the EQAS, the Blind EQAS includes 3 rounds of 5 blind urine samples released annually (2 already completed, the other scheduled for later this year).
- In the Double-blind EQAS, 5 samples are presented annually as athletes' genuine samples and distributed to laboratories by ADOs or Delegated Third Parties on behalf of WADA (1 round completed, 2nd round started in June and 3rd round is scheduled for later this year).
- EQAS samples' contents are discussed between WADA and a LabEAG subgroup that does not include Laboratory Directors.
- There were additional EQAS for the:
  - Bloemfontein laboratory: to address issues with previous EQAS rounds
  - Shanghai laboratory: as part of the Pre-Probationary Test (PPT).
  - Paris laboratory: as part of pre-Olympic assessment and during the Olympic and Paralympic Games
- The purpose of 2-3 rounds per year of the Educational EQAS is to harmonize the identification and reporting of substances and improve analytical capabilities. There are also monthly rounds of EQAS for ABP blood samples in collaboration with CSCQ (EQAS provider in Switzerland).
- On 20 December 2023, following an audit performed by 2 independent experts, WADA declared compliance of its EQAS with the ISO/IEC 17043:2023 standard, "*Conformity assessment —General requirements for the competence of proficiency testing providers*". Within the framework of this self-declaration, conformity of the EQAS Management System will be continuously reviewed and evaluated every 2 years.
- There is a DBS special project steered by the DBS Technical WG, managed by Dr. Valeria Catalani (WADA Science), under the supervision of Dr. Barroso. To date, the WG discussed, at their 1st meeting in May 2024, DBS collection devices specifications; DBS harmonized menu and Minimum Required Performance Limits (MRPLs), proposed changes to the International Standard for Testing (IST) relevant to DBS testing; proposed changes to the TD2023DBS and the 1st Educational EQAS on DBS. Next meeting is scheduled for October 2024.
- Since September 2023, laboratory assessments were done for Lisbon (Portugal), as a condition for reinstatement of accreditation; Dresden (Germany), due to change in directorship; Montreal (Canada), due to change in directorship and as regular assessment, Paris (France): 2nd and 3rd on-site assessment for Major Event (Olympic and Paralympic Games 2024); Ghent (Belgium), as a regular assessment; Shanghai (China) as PPT of a candidate laboratory, and Sydney (Australia) due to change in directorship and as regular assessment.
- The LabEAG also reviewed and discussed several final reports of research projects related to analytical techniques. In addition, there was a questionnaire on laboratory research and development activities and the information provided is currently being analyzed.
- WADA ISL 2021, Article 4.4.2.8, *Maintain Professional Liability Insurance Coverage* establishes that Laboratories shall provide documentation to WADA that professional liability risk insurance coverage is maintained for no less than two (2) million USD annually. At the Laboratories' request, WADA is assisting in obtaining the insurance coverage. Currently, 14 Labs are participating in the WADA Laboratory Group Insurance, provided by Berkshire Hathaway Inc. while all others make their own arrangements. The proof of insurance is verified annually by WADA.

- Finally, Prof Le Bizec thanked the members of the WADA LabEAG for their time, dedication and expertise and the WADA Laboratories Division team for their support, commitment and hard work. The HMRC thanked Prof Le Bizec for the update.
- The HMRC discussed the activities of the LabEAG. It was noted that it was desirable that new laboratories were outside Europe, but the stringent requirements, need of monetary and human resources and in some instances, the insurance, were very challenging.
- Dr Barroso explained that with the resources available it is not possible to do more than 1 on-site visit every 2 months, and on Olympic years it was necessary to do at least 2 extra visits. Regarding the EQAS samples, they were planned 2 years in advance. To date, the DBS collection device has not been chosen, and it was possible that more than 1 would be recommended. For the moment, the conditions to collect DBS samples for DNA or RNA have not been established.

Report from the Gene and Cell Doping Expert Advisory Group

– Prof. Odile Cohen-Haguenauer, Chair of the Gene and Cell Doping Expert Advisory Group (GCDEAG), gave an update on their activities during 2024:

- 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 GCDEAG welcomed a new member, Dr Anna Blakney, from the School of Biomedical Engineering, University of British Columbia, Canada, while this year will mark the end of the membership for Dr Lee Sweeney, from the University of Florida, USA as well as hers.
- The terms of reference did not change from last year's and 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;
  - advising WADA on the implementation of new assays aiming at improving detection of gene doping;
  - assisting the HMRC reviewing progress reports of WADA-funded studies and evaluating grant applications.
- The GCDAEG was in general satisfied with the current definition of Gene and Cell Doping in the Prohibited List but for next year they will discuss whether it would be necessary to add a line on the "potentiated" cells. There was a minor revision on M3.1 to avoid repeating "alter".
- 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, usually in muscle or systemic.
- The window of detection will depend on:
  - the route of administration, e.g. *in vivo:* free circulating foreign nucleic acid sequences versus integrated DNA of long persisting episomes in non-dividing cells, or *in vitro* gene-manipulated cells

- the type of technology e.g. gene editing machinery (CRISPR-Cas/Prime), or gene transfer vector shuttling *in vivo*

- The actionability of the detection includes the target and sensitivity and depends on:
  - foreign transgenic cassettes: genes, regulatory sequences
  - shuttle vector-related sequences
  - systemic traffic leaving fingerprint e.g. immune response to vector or exogenous protein (e.g., designer nucleases, saRNA replicon)
- There are different approaches for detection:
  - Direct detection:
    - Nucleic acids with strong focus on DNA-based strategies
    - Gene Editing (CRISPR-Cas or Prime), looking for changes in sequence/scars
    - Known genes but also regulatory sequences as targets.
  - Indirect detection:
    - Immune response to vectors or exogenous protein product
    - Altered posttranslational modification patterns (e.g., product of intramuscular transgene cDNA)
    - Longitudinal changes in biomarkers
- The GCDEAG recommended strategy to improve detection is:
  - Two steps detection scheme:
    - First an indirect detection looking for systemic adeno-associated virus (AAV) signs such as immune response to vectors which is much higher than of the transgenic product;
    - Followed by direct detection of nucleic acids such as changes in sequences (including due to gene editing) or unknown sequences;
    - Subsequently, human and clinical samples should be tested;
    - Finally, the method should be adjusted to transfer to antidoping laboratories.
- The recommended strategy studies for indirect detection were:
  - Immune response to AAV vectors:
    - Dr Giuseppe Ronzitti's study is progressing very well, targeting unequivocal detection of AAV-mediated gene doping based on antibody and cell-based immune response to a variety of AAV capsids. The response produced by AAV-based gene transfers in human trials has much higher titers than natural infection.
  - Immune response to RNA-based delivery:
    - Should target antibodies against vectors e.g. LNPs (Lipid nanoparticles) and/or antibodies against replicon-related nonstructural proteins.
- The recommended strategy studies for direct detection are:
  - Next generation sequencing (NGS)
    - Targeted (known) and multiplexing analyzed sequences
    - Whole genome sequencing (WGS): changes in sequence unknown/due to gene editing

- CARMEN/SHERLOCK based direct detection
  - CRISPR precision technology applied to diagnosis
  - Targeted multiplexed nucleic acids sequences
- Cell-free DNA (cfDNA) based direct detection
- Self-amplifying RNA (saRNA)

- To target this type of research, the GCDEAG gave a series of recommendation for a call for grants that opened in January 2023. The Request for Applications (RFA) was directed to projects using sequencing and multiplex-CRISPR-based method to detect gene doping. There were 13 expressions of interest (EOI) and 4 were selected for funding following review of the full applications that cover a wide range of techniques. One is a follow-up of Dr Ronzitti's project to develop a pan-AAV ELISA to identify recombinant AAV exposure.
- Future challenges for gene doping detection 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, but target techniques that will stay rather than the fashionable, e.g.
    - gene editing: CRISPR-Cas mediated prime-editing e.g. ex-vivo manipulation of stem cells
    - RNA-based delivery: addressing self replicating RNAs. Dr Blackney, new member of the GCDEAG is an expert in this domain.
- The GCDEAG was working on a publication to recapitulate the evolution of the threat of gene and cell doping in sport. Prof Cohen Haguenauer thanked the HMRC as well as Prof Rabin and Prof Ted Friedmann, former Chair of the GCDEAG, for the possibility of being part of this important expert group.
- The HMRC thanked Prof. Cohen-Hagenauer for the presentation and discussed the data. To date there was not much evidence that gene doping was being used by athletes. In this regard, the effectiveness of some of these techniques in doping was not proven, and there were classic doping means that were accessible. It was envisaged that only a small number of anti-doping laboratories will be dedicated to gene doping testing due to the expertise required and the costs. It was recommended to do a list of genes that are more likely to be used for doping, so their detection is prioritized at the research level.

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 total number of members is 10.
- There were 2 meetings, one virtual held on 10 April, and the other in-person, on 19-20 August 2024.
- The number of new TUEs registered in ADAMS for 2023 were 3744, about 500 more than the precedent year.
- By class, one third were for glucocorticoids (GC), one third for stimulants, and one third for the rest, with the most common being hormone and metabolic modulators. This distribution was similar to previous years.

- Up to 1 July 2024, there were 6535 active TUEs in ADAMS, the majority (39%) for stimulants, followed by hormone and metabolic modulators (25%). Only 14 % were for glucocorticoids, which reflect the short duration of TUE for this class.
- When looking at the diagnostic categories, almost 34 % are for nervous system diseases, about 17% for endocrine and metabolic diseases followed closely by diseases of the musculoskeletal system. These are the categories as presently defined in ADAMS and are very broad and rather arbitrary.
- The NADOs that had the most TUEs approved were Italy and Spain. This was related to a broader definition of the athletes that require TUEs and not to a higher use of prohibited drugs.
- A better way of measuring the number of TUEs would be through prevalence, defined as the proportion of athletes with valid TUE among all athletes at a specific event or time period. This is difficult without a denominator because the number of athletes subjected to anti-doping rules constantly change. However, the Olympic Games provided an opportunity to measure as the athlete pool was well defined In this regard, over the last 4 Olympic Games the total TUE prevalence was 0.9% while in the last 4 Paralympic Games it was 2.76 %,
- During summer Olympics, TUEs for glucocorticoids (mainly musculoskeletal conditions), stimulants (mainly for ADHD) and metabolic modulators (mainly insulin) were the most prevalent, while in the summer Paralympic Games, in addition to the aforementioned, TUEs for narcotics and diuretics were also prevalent. For the Winter games, there were relatively more TUEs for beta-2-agonists. The majority of TUEs were granted by a NADO and there were no TUE for EPO and only 1 for testosterone.
- A paper published in May 2020, authored by Alan Vernec and David Healy (Science and Medicine, WADA) found similar prevalence during 5 Olympic/Paralympic games between 2010 and 2018. There was also no association between being granted a TUE and the likelihood of winning a medal.
- TUEs entered into ADAMS are monitored and screened by WADA medical staff. If there are concerns the TUE undergoes a full WADA TUEC review. International Federations and Major Event organizers also review TUE granted by NADOs when athletes move to international level. They may reject a TUE granted by a NADO if it does not meet requirement of the International Standards for TUE.
- The full review occurs when: WADA Medical decides to review; when an athlete disputes the NADO or Federation decision; or at the request of a NADO or athlete for a national level athlete, in which case the review is not mandatory. Each review is done by a 3-person panel: the Chair (member of TUEEAG), another clinical expert, and a 3rd member, ether another clinical expert or TUEEAG member. WADA Legal is also involved in the review. The most common reasons for review are inadequate information or incorrect diagnosis.
- Dr White also addressed the 4.3 Cases: which occur when the NADO or International federation asks WADA to support an approval even if the not all 4.2 or a 4.1 criteria were met. These are exceptional circumstances where it would be manifestly unfair and against the spirit of the Code to not grant a TUE. The majority were related to cases when ISTUE criteria 4.2 were met but not any of the retroactive criteria; a minority were related to cases where the ISTUE 4.2 was not satisfied, like a wrong diagnosis. Cases were complex and consumed a lot of time.
- There was also material to assist physicians like the TUE Guidelines and Checklists, reviewed annually as well as resources like Factsheets and E-Learning courses in ADEL (Anti-Doping Education and Learning Platform).
- The HMRC thanked Dr White for the presentation. Many members were thankful for the Guidelines as they are very useful tools for physicians and TUE Committees. There were questions on whether there were patterns of certain TUE requests by country and sport, but it did not seem to be the case.

Review on muscle memory hypothesis

- Ms Claire Traversa, who has been a summer intern and worked on a temporary contract at the Science and Medicine Department, and is a PhD student at McGill University, with interest in muscle physiology, was tasked to do a narrative literature review on muscle memory during her internship.
- Although Central Nervous System (CNS) memory, based on increased synaptic connection, was implicated in sports memory skills, muscle memory included a physiological imprint seen at the muscle level as well.
- Muscle cells contain multiple nuclei (myonuclei). Satellite cells (SC's) lay dormant until activation e.g. during muscle regeneration, muscle growth and other muscle cellular processes. Activated SC's can proliferate and differentiate for different functions by undergoing cell division; including providing new myonuclei to existing muscle cells which can remain stable for 15 years or more.
- Each myonuclei serves a domain of cytoplasm for transcriptional output, so an increase in myonuclei increases the transcriptional ceiling of the muscle fiber and consequently muscle protein synthesis and increased sarcomere size (hypertrophy).
- A single bout of resistance training can activate SC's for up to 90 hours post-exercise but myonuclei increase is thought to only occur in hypertrophy threshold levels greater than 20%. This threshold must be exceeded quickly, aggressively, and continuously over time to induce myonuclear increase in number. New myonuclei are not lost due to muscle atrophy.
- When anabolic androgenic steroids (AAS) are combined with exercise, muscle hypertrophy is more evident than in exercise alone and the hypertrophy threshold is achieved faster. In addition, muscle mass is regained faster in those who previously consumed AAS and stopped, than in individuals who never used AAS.
- In addition to the myonuclear permanence, associated mechanisms may involve epigenetic changes affecting gene expression, resulting from structural changes to DNA and/or histones (i.e. methylation).
- Even if the predominantly used fiber types are different in resistance and endurance sports, AAS may be used in both types of sports. Oxidative muscle fibers, predominant in endurance exercise, experience preferential SC accumulation and myonuclear accretion compared with glycolytic fibers. However, it is unknown if higher SC and myonuclei counts may provide a lasting performance benefit in endurance sports as well.
- WADA is very interested in the subject and has funded 4 projects over the years, 1 is finished and 3 were ongoing. One was assessing the morphological and epigenetic changes, one was looking into the effects of no detraining once AAS were stopped, while the other was investigating the rate of muscle protein synthesis and the comparison of genetic expression between AAS users versus nonusers in resistance training.
- Other subjects that needed to be addressed were:
  - Investigating effects of other anabolic performance enhancing compounds
  - Cycling on/off substances
  - Investigating other sports/ fiber types
  - Sex differences
  - Legal anti-doping consequences
  - If there is a measurable return to baseline
- The HMRC thanked Ms Traversa for the excellent review of the subject and presentation.

World Anti-Doping Code update

- Mr Julien Sieveking, Director of WADA Legal Department, gave an update on the 2027 Code review, focusing on subjects that are of particular interest and pertinence to the HMRC.
- At present, the 1st draft of the revised Code is being circulated to stakeholders for consultation until mid-October. After that, there will be 2 more rounds of consultation. Therefore, the update to the HMRC should be considered preliminary.
- Some of the articles of more specific interest to the HMRC that may be revised include:
    - Sanctions linked to Substances of Abuse
    - Purpose of the analysis of samples and related analytical data
    - Further analysis of samples prior or during Results Management
    - Definition of sources of contamination
    - Definition of Technical Letter
- Mr Sieveking outlined some of the proposed changes. The red-lined version of the 1st draft is posted in WADA website for those who want more details.
- The HMRC thanked Mr Sieveking for the update.

Update on International Standard for Laboratories (ISL) review process

- Dr Osquel Barroso gave an update on the ISL review process.
- The ISL Working Group (ISL WG) is composed by several members of the LabEAG, and the WADA Laboratory Division Team and Legal Department (see page 14).
- The process was started in September 2023 to engage the ADOs and the 1st ISL Working Group meeting took place in November 2023. On 22 December 2023, the ADO engagement phase ended, and the drafting phase was initiated. This phase concluded in May 2024 and on 21 May 2024 the draft was posted for stakeholder consultation, which is ongoing.
- The next steps are:
    - 11 October 2024: end of 1st stakeholder consultation phase
    - 1st half of 2025: 2nd stakeholder consultation phase
    - 1-5 December 2025: approval of revised World Anti-Doping Code/International Standards at World Conference on Doping in Sport – Busan, Korea
    - 1 January 2027: revised Code/IS come into force.
- Some of the proposed modifications include:
    - Better description of Laboratory Standards (TD, TL, Laboratory Guidelines, Technical Notes)
    - Improved Code Definitions of Atypical Finding, Decision Limit, MRL and TL.
    - Sixteen TDs will be listed in the ISL, 3 of them new (TD EQAS, TD on Method Validation, TD or Laboratory Performance Evaluation). These new TDs will include more detailed instructions about each procedure and the flexibility to update/modify without having to change the ISL.

- The ISL section 4 (laboratory accreditation and ABP approval) will be split in 3 parts, with detailed instructions for each process:
  - Laboratory accreditation
  - ABP laboratory approval
  - Olympic Games/ major event accreditation
- Section 5.0 on the application of ISO/IEC 17025 to the analysis of doping control samples will be extended to ABP laboratories
- It is proposed to have a new section 7.0 on accredited laboratory and ABP laboratory monitoring and performance evaluation activities.
- Some changes to the laboratories disciplinary procedures are proposed as well as the inclusion of the ISL Code of Ethics as a new section 8.
- The HMRC thanked Dr Barroso for the update.

Update in the International Standard for TUEs (ISTUE)

- Dr Alan Vernec gave an update on the ISTUE revision.
- The ISTUE WG was composed of Ms Elizabeth Riley, Chair and Chief Drafter, Legal counsel, IPC, Dr Susan White, Dr Alan Vernec, Dr David Healy and Mr Alexandre Czusdi-Vallee, Legal, WADA
- On January 2024, WADA launched the First Drafting Phase of the 2027 World Anti-Doping Code and International Standards Update Process. As part of this phase, WADA published the stakeholders' feedback received during the 'Stakeholder Engagement Phase' initiated in September 2023, provided mainly by NADOs from Europe and North America.
- This feedback was the basis for discussions during the ISTUE WG meeting in March.
- The selected proposed amendments include:
  - Restructuring of Article 4.2 which defines the conditions in which a TUE can be granted. One major proposal would include removing the requisite of using permitted alternative treatments.
  - Less restrictive application of Article 4.1b
  - Clarification of ISTUE Article 4.3 process
  - Guidance on TUE Committee formation
  - NADO TUE appeal panels
  - Clarifications on ADO responsibilities, e.g. decision reporting, athlete guidance.
- The 1st draft consultation to stakeholders was ongoing until October 2024
- The 2nd drafting phase will take place between October and December this year, reserving an optional drafting phase between January and April 2025.
- The final draft will be presented for approval at the World Conference in November 2025.
- The HMRC thanked Dr Vernec for the update.

Closing remarks

- Prof. Engebretsen informed the HMRC that this year marked the end of Dr. Audrey Kinahan as Chair of the LiEAG and of Prof Odile Cohen Haguenauer as Chair of the GCDEAG. Both have been members of such EAGs for many years and due to the Statute of Limitation that establishes a maximum membership duration of 12 years, their tenures came to an end. Prof Engebretsen thanked Dr Kinahan and Prof Cohen Haguenauer for their invaluable contribution, for their style and their love and dedication to science.
- Prof Rabin added that it was difficult to summarize how WADA relied on experts of such high caliber. He remarked that Dr Kinahan always brought the collective will with respect and scientific principles and was extremely grateful for her work, including her availability to present the information to laymen at the WADA symposium. With regards to Prof Cohen Haguenauer, Prof Rabin stressed the importance of her expertise in gene therapy and recalled her journey from the very beginning at the Banbury conference in 2002 when gene doping was a theoretical possibility until now when it may be becoming a reality. Along those years WADA developed a test to detect gene doping and additional technologies were being developed.
- Dr Kinahan thanked the words expressed and said she was impressed by the people she worked with at both the HMRC and ListEAG to have the vision and inspiration to improve anti-doping science.
- Prof Cohen Haguenauer remarked that it was extremely important to meet people with the scientific knowledge and evidence-based science as well as to be free to express their views. She thanked WADA staff and particularly Prof Rabin, Prof Arne Ljungqvist, former Chair of the HMRC and ListEAG, and Prof Ted Friedman, former Chair of the GCDEAG.
- The HMRC thanked both and gave them a standing ovation.

Calendar for meeting 2025

- August: TBD based on ExCo and HMRC meetings

Closing of meeting

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