NOTE: AS REFERENCED IN WADA'S MEDIA RELEASE OF 11 JULY 2018, ON 15 MAY, WADA PROVIDED THE FOLLOWING NOTE TO UCI ON THE SALBUTAMOL REGIME, ADDRESSING THE SUBSTANCE OF MR. FROOME'S QUESTIONS.

15 MAY 2018

WADA STATEMENT ON THE SALBUTAMOL THRESHOLD/DECISION LIMIT

1. HISTORICAL BACKGROUND

1.1 The List Pre-World Anti-Doping Code

Before January 2004, the International Olympic Committee (IOC) was responsible for establishing the anti-doping rules on behalf of the international sport movement. The IOC List of Prohibited Substances and Prohibited Methods (IOC List) was an annex to the Olympic Movement Anti-Doping Code (OMAC).

According to WADA's records, salbutamol was included in the IOC List as a prohibited stimulant in 1991, with the anabolic properties of salbutamol being acknowledged in the 1994 IOC List.

In the final IOC List in 2003, salbutamol was prohibited in Section A, subsection b (Stimulants), which indicated that "*Prohibited substances in class A.b include the following examples with both their L- and D-isomers : formoterol***, salbutamol***, salmeterol*** and terbutaline*** …and related substances*". This List also included a footnote in the section B, Anabolic Agents, which clarified *"***permitted by inhaler only to prevent and/or treat asthma and exercise induced asthma. Written declaration of asthma and/or exercise-induced asthma by a respiratory or team physician is necessary to the relevant medical authority*". In addition, salbutamol was also prohibited in Section C.2 as "Other anabolic agents" and a footnote read that *"For salbutamol, a concentration in urine greater than 1000 nanograms per milliliter of non-sulphated salbutamol constitutes a doping violation".* In this regard, section IV of the 2003 IOC List entitled "*Summary of urinary concentrations above which a doping violation has occurred*" indicated "*Salbutamol (as anabolic agent) > 1,000 nanograms/milliliter*".

On the basis of the above, even before 1 January 2004, when the World Anti-Doping Code (WADC) and its related International Standards, including the International Standard for the List of Prohibited Substances and Methods (Prohibited List), came into force, salbutamol was prohibited for urinary concentrations higher than 1,000 ng/mL (*i.e.* 1 µg/mL), and its use required the athlete to provide an explanation of their respiratory medical condition to the sport authorities.

The IOC threshold of 1,000 ng/mL was established as a conservative cut-off to distinguish between inhaled (permitted) and oral (prohibited) administration of salbutamol[1]. It was derived from routine doping

[1] The introduction of the 1,000 ng/mL threshold to distinguish oral from inhaled use of salbutamol reflected findings from numerous animal and human studies, which showed anabolic properties of β2-agonists when administered by systemic routes but not following the intake of therapeutic dosages by inhalation. In this regard, in humans, oral salbutamol increased performance and affected metabolism and selected anabolic hormones during submaximal cycling to exhaustion (Collomp *et al*., 2000 a & b; van Baak *et al*, 2000) and augmented strength in resistance training

control analytical data, which the IOC had compiled over many years, the published salbutamol excretion studies available at the time (see below), as well as a number of cases that the IOC Medical Commission had reviewed when in charge of the anti-doping rules.

By the early 2000s, the Barcelona anti-doping laboratory published two excretion studies (Ventura *et al*., 2000; Berges *et al*., 2000) conducted with asthmatic and non-asthmatic volunteers, who had been exposed to 200, 400 or 1600 µg of inhaled salbutamol and 4, 16 or 20 mg of oral salbutamol. No volunteer using inhaled salbutamol in those studies exceeded 1,000 ng/mL in urine when non-sulfated (Ventura *et al*, 2000) or free enantiomeric salbutamol (Berges *et al*, 2000) were measured by gas chromatography-mass spectrometry (GC-MS) (Ventura *et al*, 2000) or high performance liquid chromatography – mass spectrometry (HPLC-MS) (Berges *et al*, 2000). On the basis of the results of these studies, the research teams recommended establishing a urinary threshold at 500 ng/mL of non-sulfated or free racemic salbutamol to distinguish oral from inhaled use. In addition, Berges *et al* proposed determining the ratio of *S*(+) to *R*(-) free salbutamol enantiomers, and to use a discriminant function when urinary concentrations were higher than 500 ng/mL to distinguish between routes of administration. Consequently, in 1999, the IOC introduced a threshold of 500 ng/mL of salbutamol to distinguish between inhaled and oral administration and a year later, in April 2000, this threshold was increased to 1,000 ng/mL, which was considered a conservative level (Fitch, 2006). Therefore, by 2001, under the applicable IOC rules, any case with urinary concentrations higher than the 1,000 ng/mL threshold was considered an anti-doping rule violation.

In 2004, a case report published by Schweizer *et al.* from the Lausanne laboratory claimed that an athlete had surpassed the 1,000 ng/mL threshold value and recommended a review of this value. After further discussion between WADA and the authors, it was noted that there had not been a strict control of the dose intake during the study; moreover, assuming that the athlete had inhaled 900 µg of salbutamol in 5 hours, this was clearly not in accordance with medical guidelines for the treatment of asthma.

1.2 Evolution of the rules for β2-agonists and more specifically salbutamol under the WADC Prohibited List

As of 1 January 2004, when the WADC and its associated International Standards came into force, WADA became responsible for the harmonization of anti-doping policies worldwide. During the initial stages,

(Martineau *et al*., 1992; Caruso *et al*, 1995). During that period, studies done in animal models showed, for example, that systemic salbutamol induced skeletal muscle hypertrophy and increased muscle mass (Carter & Lynch, 1994; Cepero *et al*., 1998 & 2000) and antagonized cachexia (Carbo *et al*., 1997).

Following the adoption of the WADC and the publication of the Prohibited List by WADA, a number of other studies continued to show the performance enhancing effects of oral salbutamol, including, for example, resistance exercise and maximal anaerobic power (Caruso *et al*, 2005 & 2008; Le Panse *et al*., 2005, 2006 & 2007; Collomp *et al.,* 2005; Hostrup *et al*., 2016).

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play true

WADA had to ensure continuity in anti-doping practice and incorporated many of the rules included in the OMAC, in particular for the prohibited substances and methods, to avoid major disruptions in doping control and confusion for its stakeholders. More specifically for salbutamol, the WADA List Expert Group (LiEG), supported by the WADA Health, Medical and Research Committee (HMRC) and by the WADA Executive Committee, agreed to maintain the prohibition of salbutamol when measured in excess of a urinary threshold concentration of 1,000 ng/mL (the "**Threshold**").

Accordingly, in the 2004 Prohibited List, under section S6 (Beta2 agonists), it was stipulated that "*All beta2 agonists including their D- and L-isomers are prohibited except that formoterol, salbutamol, salmeterol and terbutaline are permitted by inhalation only to prevent and/or treat asthma and exercise-induced asthma/bronchoconstriction. A medical notification in accordance with section 8 of the International Standard for Therapeutic Use Exemptions is required*". Section S6 continued with the following paragraph: "*Despite the granting of a TUE, when the laboratory has reported a concentration of salbutamol (free plus glucuronide) greater than 1,000ng/mL, this will be considered as an adverse analytical finding unless the athlete proves that the abnormal result was the consequence of the therapeutic use of inhaled salbutamol*". On the basis of the foregoing, the WADA approach to the regulation of salbutamol allowed athletes who exceeded the urinary threshold of 1,000 ng/mL to demonstrate that the result had resulted from inhaled, therapeutic use.

Other than changing β2-agonists from category S6 to S3 in January 2005, which was a purely administrative change, from 2005 to 2009 there were no major changes and only minor adjustments to the wording of the β2-agonists section of the Prohibited List, including for salbutamol.

As time passed, it was observed by WADA that many salbutamol prescriptions, received as part of Therapeutic Use Exemption (TUE) applications, were labeled "*as needed*" or "*as required*", with no maximum daily dose indicated. To address this situation, WADA introduced the notion of the maximum inhaled daily therapeutic dose of salbutamol that athletes could take, in line with the manufacturer's recommendations, in the 2010 Prohibited List[2]. By taking this approach, athletes could use inhaled salbutamol without a TUE; however, it limited such use to approved therapeutic doses, thus minimizing the risk of overdosing and surpassing the urinary threshold.[3]

The maximum daily dose was based on the salbutamol manufacturer's recommendation for a therapeutic regime by inhalation and as described in reference pharmacopeias (*e.g.* see MIMS Ireland, 2004; Compendium of Pharmaceuticals and Specialties 2005; Martindale 2011). It was introduced to address

[2] Section S3. β2-agonists of the 2010 Prohibited List indicated: "*All beta-2 agonists (including both optical isomers where relevant) are prohibited except salbutamol (maximum 1600 micrograms per 24 hours) and salmeterol by inhalation which require a declaration of Use in accordance with the International Standard for Therapeutic Use Exemptions*".

[3] However, the principle of a urinary threshold concentration for salbutamol was strictly maintained in the 2010 Prohibited List: "*The presence of salbutamol in urine in excess of 1,000 ng/mL is presumed not to be an intended therapeutic use of the substance and will be considered as an Adverse Analytical Finding unless the Athlete proves through a controlled pharmacokinetic study, that the abnormal result was the consequence of the use of a therapeutic dose (maximum 1600 micrograms over 24 hours) of inhaled salbutamol*".

the problem of athletes using inhaled salbutamol in excessive doses after being prescribed an "*as needed*" or "*as required*" regimen of salbutamol. In addition, the possibility of a controlled excretion study had been introduced for the first time in the 2009 Prohibited List, acknowledging *de facto* the inter-individual variability in the excretion of salbutamol observed in recent research studies.

The clarification of the origin of the 1600 μg/day maximum daily dose for inhaled salbutamol was introduced in the 2011 Prohibited List with the reference in the core text to "*in accordance with the manufacturers' recommended therapeutic regime*". In other words, not only was there a maximum of 1600 μg/day but this dose was to be taken in accordance with the therapeutic regime (*e.g.* not as a single dose).

Subsequently, from 2012 to 2016, the wording for salbutamol in section S3 of the Prohibited List remained unchanged, with the exception of minor cosmetic adjustments.

In 2017, the number of examples of β2-agonists in the Prohibited List was expanded to specifically mention the names of other substances that fell within this non-exhaustive category (i.e., higenamine). Also, for salbutamol in particular, it was specified that the maximum daily dose of "*1600 micrograms over 24 hours*" was "*not to exceed 800 micrograms every 12 hours*". This rule was introduced to be more in line with good medical practice in terms of therapeutic use of salbutamol (GINA; Parsons *et al* 2013), as well as to address observations from recent studies indicating that the inhalation of salbutamol in high dosages, over a short period of time, could lead, in some cases, to urinary concentrations in excess of the Decision Limit of 1,200 ng/mL[4] (Dickinson *et al*, 2014; Haase *et al*., 2016).

In 2018, a more precise requirement for the maximum allowed daily dose of salbutamol was included in the Prohibited List that is currently in force. It reads: *"…salbutamol, maximum 1600 micrograms over 24 hours in divided doses not to exceed 800 micrograms over 12 hours starting from any dose*". For both the 2017 and 2018 Prohibited Lists, explanations were provided in the respective Summary of Modifications, which accompanied the publication of each of the Prohibited Lists, in order to better inform and guide the sports community on the appropriate use of salbutamol to avoid excessive dosing and potential adverse analytical findings (AAFs; Summary of Modifications, 2017 and 2018).

In parallel to reviewing the Prohibited List on an annual basis, from the outset, WADA specifically reviewed the thresholds of the relevant substances with the aim of refining and consolidating the applicable values as required. This was particularly the case for β2-agonists and more specifically for salbutamol as early as 2003-2004, when WADA started to commission research teams to generate original data on salbutamol excretion.

1.3 Consolidation of the salbutamol threshold over the years

As indicated above, the IOC rules on salbutamol prescribed that any finding for a urinary concentration of salbutamol higher than 1,000 ng/mL was considered as an anti-doping rule violation. However, as also mentioned, it was very clear in the context of use of salbutamol that many athletes were prescribed

[4] The concept of Decision Limit is explained in section 3.2 below.

salbutamol "*as needed*" or "*as required*", as reported on their TUE applications. Such use was not in line with good medical practice for treatment of asthma (*e.g.* GINA Guidelines) and created a significant risk of overexposure to salbutamol. As a result, it was possible for athletes to surpass the anti-doping analytical threshold when excessive doses of inhaled salbutamol were used, even if the athlete was following a legitimate physician's prescription.

As early as September 2003, shortly before WADA became responsible for establishing the Prohibited List, WADA undertook a review of the relevance of the 1,000 ng/mL threshold and commissioned, under its research program, excretion studies with the support of Prof McKenzie's research team. Two studies were conducted with inhaled single doses of salbutamol of 200, 400 and 800 μg (Sporer *et al*. 2008a and 2008b). Even though the administration was by a one-off single dose and not spread over several hours, none of the volunteers exceeded the 1,000 ng/mL threshold in those studies.

In addition, in 2006, Pichon and colleagues published an article with volunteers exposed to 200 μg, 3 times/day over three days *"in order to distinguish the results of a preventive treatment for exercise-induced asthma from doping practices"*. Based upon the low excreted salbutamol concentrations, the conclusion of the study was that the urinary salbutamol threshold should be lowered to 250 ng/mL.

In the following years, WADA continued to support studies on inhaled and oral use of salbutamol and its effect on athletic performance, as well as to further explore the relationship between inhaled doses and urinary excretion of this β2-agonist. Several WADA-sponsored studies were conducted by the group of V. Backer in Copenhagen from 2008 to today, aiming at better defining the relationship between various regimens of β2-agonists and the pharmacokinetics of their urinary excretion.

In these studies by Backer, doses of 800 μg (4 x 200 μg and 1 x 800 μg), 1600 μg (4 x 400 μg) 8 mg 40 x 200 μg of inhaled salbutamol were administered to asthmatic or non-asthmatic volunteers or non-competing athletes in various sports (Mareck *et al*. 2011 ; Elers *et al*. 2010, Elers *et al*. 2011; Elers *et al*., 2012a). All the studies concluded that urinary concentrations of salbutamol were below the Decision Limit. The Decision Limit was only breached in one study designed to administer inhaled salbutamol equivalent to an oral dose (40 x 200 μg = 8 mg) (Elers *et al*., 2012b), which was consistent with concentrations found following oral administration of 8 mg (Pichon et al., 2006; Mareck *et al*. 2011 ; Elers *et al*. 2010; Hostrup *et al*., 2014).

As a world-renowned expert in the field, Prof. Vibeke Backer was invited to present and discuss the results of her research studies at the April 2013 meeting of the LiEG.

In parallel to WADA's sponsored studies on salbutamol excretion, a study of Elers and colleagues published in 2010 (Elers *et al*., 2010) exposed volunteers to 800 μg of inhaled salbutamol and concluded that the results "*support that a limit of 1,000 ng/mL is sufficiently high to secure a low risk false positive"* but noted that *"50% false negative were observed"* with oral administration of 8 mg salbutamol. Other studies observed that the Decision Limit meant that a number of samples would be considered as negative following oral (prohibited) administration of salbutamol (Ventura *et al*., 2000; Mareck *et al*., 2011; Elers *et al*., 2012a; Hostrup *et al*, 2014). Correction of some of the diluted samples for the urinary specific gravity

(SG) of 1.020, as suggested by the authors, would render the concentrations of salbutamol above the Decision Limit and flag these samples as AAFs following the prohibited administration of salbutamol. (Hostrup *et al*., 2014).

In recent years, WADA has continued its efforts to explore the conditions influencing salbutamol excretion by commissioning additional studies with different research teams. In particular, salbutamol administration studies conducted by the groups of Backer and Dickinson investigated the effect of exercise, hot environment and dehydration, as factors that could affect the excretion of salbutamol in urine (Dickinson *et al*, 2014 a; Dickinson *et al*., 2014 b; Haase *et al*., 2016). In these studies, single doses of 800 μg or 1600 μg inhaled salbutamol were administered, and the analysis of salbutamol excreted in urine confirmed the high inter-individual variability of salbutamol urinary excretion and revealed that when high doses of 1600 μg were administered in one intake (and in combination with exercise and dehydration), some individuals could temporarily exceed the Decision Limit (0 out of 7 in Dickinson *et al*., 2014b; 16 of 30 in Dickinson *et al*., 2014a; and 17 of 117 (with correction for SG) in Haase *et al*., 2016). Despite these results, the authors considered that the limits established by WADA were adequate to distinguish inhaled use of salbutamol in therapeutic doses from over-dosing by inhalation or oral administration of salbutamol (Dickinson *et al* 2014 a & b).

At about the same time, another study was published by Pillard and colleagues (Pillard *et al*., 2015), in which inhaled salbutamol was administered for four (without exercise) and five (with exercise) consecutive days at 200 μg every 6 h three times per day (total daily dose 600 μg) following GINA and ATS guidelines. The study recommended lowering the salbutamol threshold to 507 ng/mL and correcting the urinary concentrations for the SG of the urine sample.

The most recent studies conducted under the WADA research program, in particular by the groups of Backer and Jacobson (ongoing and unpublished studies), were primarily aimed at studying the pharmacokinetics of several β2-agonists when administered by inhalation alone or in combination, as well as to evaluate the measuring of enantiomeric salbutamol as a means to distinguish oral from inhaled administration. In Jacobson's study, following the administration of acute or chronic high doses (800 μg or 1600 μg) of inhaled salbutamol, some samples appear to have exceeded the Decision Limit. However, the exact conditions in which such situations occurred remain unclear (clarifications are currently being sought from the investigator). In the Backer study, following a unique dose of 1600 μg inhaled salbutamol (alone or in combination with other β2-agonists), 6 out of 37 samples exceeded the Decision Limit and this number was reduced to 4 when concentrations were corrected for SG. No sample exceeded the Decision Limit 6 h after administration. However, as noted by Backer, it can be expected that many of the samples that exceeded the Decision Limit in that study would not have done so under the current rule that prohibits exceeding 800 μg of inhaled salbutamol over 12 hours.

1.4 Measurement of salbutamol urinary concentration

Salbutamol is excreted in urine as a combination of unchanged (parent compound) and phase-II metabolites (mainly as the sulfated metabolite). The relative proportion of the different molecular forms depends on dosage and route of administration, as well as on the genetics of the individual, as judged by

the observed inter-individual variability in salbutamol excretion. Due to the first-pass metabolism in the gastrointestinal tract, the proportion of sulfated salbutamol excreted in urine is higher (~ 50%) after oral administration (Morgan *et al*., 1986; Hussey, Donn and Powell, 1991). Salbutamol is not metabolized extensively in the lungs (Hindle and Chrystyn, 1992); therefore, following inhalation, salbutamol is mainly excreted as the parent compound, while the glucuronidated metabolite may be excreted in much lower proportions (Mareck *et al*., 2011). However, a significant fraction (up to 60-70%) of inhaled salbutamol may be swallowed (depending on user experience, delivery device, etc.), which would lead to an increased proportion of the sulfated metabolite excreted in urine.

In doping control, measurement of urinary concentrations of salbutamol is based upon the determination of the free (unchanged) and glucuroconjugated fractions of salbutamol. Historically, the analysis has been done by gas chromatography-mass spectrometry (GC-MS), following the pre-treatment (hydrolysis) of the sample using an enzyme (glucuronidase) in order to excise the glucuronide moiety of the minor phase-II metabolite. As a result, non-sulfated salbutamol content, including the unchanged parent compound and the free salbutamol released from the glucuroconjugated metabolite, is quantified.

As mentioned in sections 1.1 and 1.2 above, the IOC, pre-WADA 1,000 ng/mL threshold for salbutamol had been determined based on the measurement of non-sulfated salbutamol by GC-MS. WADA continued to apply this approach, and these target analytes were also analyzed in the later excretion studies described in paragraph 1.3 above, which have been used to monitor the WADA-established Decision Limit for salbutamol.

Nevertheless, the relevance of the sulfate fraction has been indirectly explored through a few studies using chiral analysis (Berges *et al.,* 2000, and two WADA-sponsored studies (Fiacco *et al*., 2012 and Jacobson-unpublished results). In this regard, the R(-) enantiomer undergoes a higher rate of sulfation after oral intake, therefore the non-metabolized S(+) enantiomer would be excreted in a greater proportion than the non-metabolized R(-) (Boulton *et al* 1996; Walle *et al*., 1993). Results from Fiacco's study confirmed the initial results by Berges *et al.* in 2000 on the feasibility of the chiral analysis; however, it concluded that the ratios of the non-metabolized or metabolized (sulfated fraction) salbutamol enantiomers would not have a marked benefit to distinguish permitted and prohibited administrations of salbutamol, since it strongly depended on the percentage of the inhaled dose that is swallowed. In the study by Jacobson, analysis of chiral ratios only provided a modest increase in diagnostic performance over existing approaches.

2. CONCEPT OF THE CONTROLLED EXCRETION STUDY

It is important to note that, starting from the first WADA Prohibited List in 2004, the Threshold of 1,000 ng/mL was no longer considered as a strict Threshold because, unlike for some other threshold substances (e.g. hGH, pseudoephedrine), surpassing the Threshold did not automatically lead to the assertion of the

finding as an AAF[5]. It was considered by WADA from the outset that the 1,000 ng/mL is a reasonable value to allow appropriate medical use of inhaled salbutamol by the vast majority of asthmatic athletes while deterring the risk of abuse of salbutamol by inhalation in excessive doses or by systemic routes of administration. In other words, in a situation where there is overlap in the urinary concentrations of salbutamol following its use by allowed or prohibited routes of administration, WADA's objective was to define a Threshold, which would permit the therapeutic use of inhaled salbutamol while serving as a means to deter the abuse of this substance by prohibited, performance-enhancing routes of administration.

Numerous studies have revealed the high variability in salbutamol urinary excretion between individuals. As known for some other substances, it appears that some individuals would have a stronger propensity than others to excrete higher concentrations of free salbutamol when exposed to a similar regime of administration of this substance. To account for the possibility of different metabolizers, even if rare, the Prohibited List allows athletes to request a controlled excretion study when salbutamol urinary concentrations exceed the Decision Limit of 1200 ng/mL. This offers the athlete the possibility to demonstrate that his/her unusual personal metabolism leads to a higher excretion of salbutamol (*i.e.* above the Decision Limit) even when salbutamol is taken by inhalation following an appropriate therapeutic regime.

It is important to note than any athlete with a urinary concentration higher than the Decision Limit for salbutamol can request a controlled excretion study. The study can be conducted in a WADA-accredited laboratory that has the capability to handle the protocol of such a study. Controlled excretion studies will aim at reproducing the conditions of intake of salbutamol (*e.g.* doses, frequency, time intervals) as well as any other reasonable known (*i.e.* demonstrable) conditions or circumstances that could reasonably have caused the salbutamol AAF.

3. INTEGRATION OF THE MEASUREMENT UNCERTAINTY

3.1 Compliance decisions for Threshold Substances: Thresholds, Measurement Uncertainties and Decision Limits

The standards of Laboratory performance of the WADA-accredited laboratories are defined in the WADA International Standard for Laboratories (ISL) and its associated Technical Documents (TDs). These sets of rules aim to harmonize the production of valid test results and evidentiary data and the reporting of analytical findings.

[5] The 2004 Prohibited List indicated, in section S6. Beta-2 Agonists: "*Despite the granting of a TUE, when the Laboratory has reported a concentration of salbutamol (free plus glucuronide) greater than 1000 ng/mL, this will be considered as an adverse analytical finding unless the athlete proves that the abnormal result was the consequence of the therapeutic use of inhaled salbutamol*".

Prohibited Threshold Substances are substances, included in the Prohibited List, for which an AAF can be reported only if they are detected in a concentration that is in excess of a defined Threshold value. Therefore, the confirmatory analyses for the presence of prohibited Threshold Substances requires the application of fully quantitative tests, which produce analytical results with sufficient accuracy and statistical confidence to allow unequivocal application of anti-doping regulatory compliance decisions. Such specific compliance decision rules are currently established in the WADA TD on Decision Limits (TDDL), which is based on the application of GUM (Guide to the Expression of Uncertainty in Measurement) principles described in the EURACHEM/CITAC Guide on Use of Uncertainty Information in Compliance Assessment[6].

In this context, it is important to understand the difference between a Threshold and a Decision Limit, explain the role of the uncertainty of the measurement in the calculation of the Decision Limit, and describe how these concepts have been historically applied in the anti-doping testing field.

Several empirical approaches may be used for establishing the Threshold for prohibited Threshold Substances, depending on the origin of the substance (exogenous or endogenously produced by the body) and whether it is prohibited at all times or only in-competition. Thus, for salbutamol (an exogenous β2-agonist prohibited at all times, except if taken by inhalation in a dose not exceeding 800 µg every 12 hours), the Threshold was established by the IOC prior to the first Prohibited List and WADC coming into force in 2004 (as described above in section 1.1). The Threshold, set at a concentration value of 1,000 ng/mL (of parent compound plus its glucuroconjugated form) allows, to a great extent, differentiating permitted use by inhalation from abuse at supratherapeutic inhaled doses or administration by prohibited routes (*e.g.* oral). This Threshold was further verified by controlled excretion studies, in which the drug was administered to healthy individuals in permitted, inhaled therapeutic doses (see, in particular, section 1.3 above).

In order to report an AAF for a Threshold Substance, the result of the analysis shall demonstrate that the concentration of the Threshold Substance in the sample exceeds the Threshold with a certain level of statistical confidence (at least 95%).

In this regard, two different approaches have been historically applied by WADA when defining compliance decision rules for Threshold Substances.

3.2 Rule applied until 1 September 2010

The ISL v 6.0 from Jan 2009 (and similar previous versions of the ISL) established, in Article 5.2.4.3.1.6 that "*The mean value of the results of three Aliquots for the "A" Sample finding for Threshold Substances minus the value of the measurement uncertainty determined by the Laboratory [underwritten for emphasis] must exceed the relevant Threshold.*"

[6] EURACHEM/CITAC Guide. Use of uncertainty information in compliance assessment. First edition. Ellison SRL, Williams A (Eds) (2007).
http://www.eurachem.org/guides/pdf/Interpretation_with_expanded%20 uncertainty_2007_v1.pdf

This compliance rule to determine an AAF for Threshold Substances can be mathematically expressed as:

$$y - U95\% > T$$

where: *y*: mean concentration of the substance obtained from measuring 3 Aliquots of the "A" Sample (*i.e.* the measurement result);
U95%: the expanded uncertainty of the measurement result[7];
T: the threshold for the substance (e.g. 1,0 µg/mL for Salbutamol)

The expression of the measurement result *y* and its expanded uncertainty *U* as $y \pm U_{95\%}$ defines an interval within which the 'true' value of the target analyte in the sample is believed to lie with a 95% level of confidence. Therefore, if $y - U_{95\%}$ is higher than the Threshold, then it can be concluded that the measurement result *y* exceeds the Threshold with at least 95% statistical confidence, and therefore such result shall be reported as an AAF.

However, this approach, while scientifically and methodologically correct, had an important drawback for anti-doping applications. In the early stages after the introduction of the WADA External Quality Assessment (EQAS) program, it became evident that the differences between Laboratories in the estimation of the MU for Threshold Substances were considerable. It was clear that guidance was required to estimate the MU of the measurement and to decide with reasonable certainty when the Threshold was exceeded to declare an AAF.

In other words, whereas there was a clearly defined Threshold for each Threshold Substance, compliance decisions could vary between Laboratories based on their different estimates of the MU: while in one Laboratory a given result expressed as $y - U_{95\%}$ may have constituted an AAF, in a second Laboratory, with a higher MU estimate, this same measurement result would have been reported as negative. This created a perception of unfairness and confusion amongst athletes and other WADA stakeholders.

3.3 **Rule applied from 1 September 2010**

On 1 September 2010, the first version of the WADA TD on Decision Limits for the Confirmatory Quantification of Threshold Substances (TD2010DL) became effective. The scope of the document was to

[7] The Measurement Uncertainty (MU), expressed either as the combined standard uncertainty u_c or the expanded uncertainty $U_{95\%}$ (which defines an approximate 95% confidence range in which the true value of the measurement result is expected to be found, and is obtained by multiplying the u_c by a coverage factor $k = 2$) defines the quality or fitness-for-purpose of a measurement. It provides an objective basis for demonstrating the equivalence of results obtained by different laboratories and for the assessment of conformity with a threshold value.

The estimation and use of the MU associated with results obtained by a quantitative procedure is a requirement that the anti-doping laboratories must fulfill as part of their quality assurance measures (in compliance with ISO/IEC 17025 accreditation as well as with the ISL). It serves to establish the necessary confidence in the validity of the measurement results, and ensure that they provide analytical data of the expected quality.

harmonize the rules for the reporting of AAFs for Threshold Substances and described the use of MU information in the establishment of Decision Limits.

In principle, the same compliance decision rule still applied (*i.e.* that the concentration of the Threshold Substance in the sample had to exceed the Threshold with at least 95% statistical confidence). However, in order to ensure harmonization of the application of this rule across all WADA-accredited Laboratories, the concepts of Decision Limits and Maximum Acceptable Combined Standard Uncertainty ($u_{c\,Max}$) were introduced.

The $u_{c\,Max}$ for each Threshold Substance constitutes the minimum requirement to be achieved by a Laboratory for their MU (as estimated at levels close to the Threshold concentration during method validation) when reporting a result for the determination of a Threshold Substance. Whatever approach is applied by the Laboratories to estimate the MU, their estimated *u*c value at levels close to the Threshold shall not be higher than the *uc-Max* specified in the TD DL. Since the *uc* at levels close to the Threshold shall not be higher than the *uc-Max*, the reporting of the Laboratory's *uc* serves to demonstrate that the Laboratory performs the analytical procedure to determine the Threshold Substance according to the technical specifications of assay accuracy and precision.

For determination of the $u_{c\text{-}Max}$, as defined in the TD DL, WADA relies on data obtained from its EQAS program. It is considered that these types of data include contributions from all relevant sources of uncertainty and provide a conservative overall estimate of u_c, which is suitable for the intended purpose of establishing a Decision Limit above which an AAF shall be reported. Thus, the (robust) standard deviation (inter-laboratory precision, *sR)* of the participant Laboratories' results obtained from the analysis of representative samples in the EQAS can be used as a conservative estimate of the *uc* associated with an individual result.

The Decision Limit defines the value for the measurement result, obtained from testing an individual sample using a fit-for-purpose quantitative procedure, above which it can be concluded that the true value for the substance in the sample exceeds the Threshold with a statistical confidence of at least 95%. For calculating the Decision Limit, a guard zone (*g*) is added to the value of the Threshold established for a particular prohibited Threshold Substance. This guard zone takes into account the analytical uncertainty in the reported value when the method is applied to samples that contain the analyte at or near the Threshold level. Since the critical determination is whether a value measured has exceeded the established Threshold with a confidence level of at least 95%, the value of the guard band is calculated by multiplying the *u*c-*Max* for a result at levels close to the Threshold (as defined from EQAS data and specified in the TD DL), by an applicable coverage factor *k*. For a one-tailed normal distribution[8] with a

[8] Note that, in this case, a one-tailed (*i.e.* one-sided) distribution is applied (which defines the coverage factor *k* at 1.645) since the important element is to determine whether the result is higher than the Threshold with 95% confidence. In other words, the only values that need be considered are those lying on one side (*i.e.* higher than) of the Threshold value. In the first approach, a coverage factor *k* of 2 is used to determine the $U_{95\%}$, since in this case a two-tailed (*i.e.* 2-sided) distribution is needed to determine the interval (on both sides of the measured value) where the true value is expected to be found.

95% coverage range, this coverage factor would correspond to 1.645. Furthermore, the calculated value of the Decision Limit (*i.e.* calculated as T plus 1.645·$u_{c\,Max}$) is rounded up to 2 significant figures.

This compliance decision rule to determine an AAF for Threshold Substances can be mathematically expressed as:

$$\boldsymbol{y > DL}, \textit{ i.e.}$$

$$\boldsymbol{y > T + 1.645 \cdot u_{c}\text{-}Max}$$

where: y: mean concentration of the substance obtained from measuring 3 Aliquots of the "A" Sample (*i.e.* the measurement result);
u_c-*Max* : maximum allowed uncertainty at levels close to the threshold, as determined by WADA from data obtained from Laboratory analysis of representative EQAS samples
T: the threshold for the substance.

Applying this formula to the determination of salbutamol, considering the T = 1,000 ng/mL and a u_c-*Max* of 100 ng/mL (*i.e.* 10% of the T), results in a value of 1,160 ng/mL, which after rounding up to 2 significant figures produces a Decision Limit at 1,200 ng/mL. Therefore, any sample with a urinary concentration of salbutamol higher than 1,200 ng/mL is considered to have exceeded the Threshold with a statistical confidence of at least 95%, and shall be reported as an AAF for salbutamol.

This approach, while methodologically equivalent to the first approach applied before 1 September 2010, ensured a better harmonization of the reporting of results by Laboratories through:

1- The definition of a unique Decision Limit for each Threshold Substance, to be applied by all Laboratories; and
2- The establishment of a maximum acceptable value of the MU, ensuring the accuracy and precision of Laboratory quantitative determinations to the levels expected to conclude an AAF with at least 95% confidence when the measured value of the Threshold Substance in the sample exceeds the Decision Limit.

This compliance decision rule, initially set out in the TD2010DL, was later included in the revised ISL v 7.0 from January 2012, which established in Article 5.2.4.3.1.6 that "*For Threshold Substances, Adverse Analytical Finding or Atypical Finding decisions for the "A" Sample finding shall be based on the mean of the measured analytical values (e.g. concentrations) … of three Aliquots which shall exceed the value of the relevant Decision Limit*".

In conclusion, in order to include a robust Decision Limit for several quantitative analyses in the field of anti-doping, the laboratory experts proposed a harmonized approach in line with international guidelines which led to a systematic application of a requisite 95% of confidence applied to the established thresholds of all quantitative analysis in anti-doping. For the specific case of salbutamol, this interval of confidence applied the Threshold of 1,000 ng/mL and established a Decision Limit at 1,200 ng/mL. In routine practice, any urinary concentration of salbutamol below the Decision Limit of 1,200 ng/mL is not considered an AAF and therefore not reported by WADA accredited laboratories as such. Conversely, any

urinary concentration of salbutamol above the Decision Limit of 1,200 ng/mL shall be reported by anti-doping laboratories as an AAF.

4. SPECIFIC GRAVITY

The measurement of SG is a means to take into account the concentration of the athlete's urine samples and indirectly reflects the hydration status of the athlete at the time of the sample collection.

Historically, SG correction was applied for the quantitative analysis of endogenous threshold substances when values of SG were higher than 1.020 (which is considered to be the reference SG value for a normally hydrated athlete). This approach benefited athletes, since concentrations would only be corrected in cases of concentrated urine (therefore resulting in a lower adjusted concentration), while the same correction was not applied to diluted urine (which would result in higher adjusted concentrations).

The LabEG recently decided to propose a systematic correction of concentrations for all threshold substances (endogenous and exogenous, including salbutamol) when SG is higher than 1.020. This decision was introduced in the TD2018DL, which was approved by the WADA Executive Committee in November 2017 with a deadline for implementation (*i.e.* effective date) on 1 March 2018.

5. CONCLUSIONS

The Threshold of 1,000 ng/mL for salbutamol was adopted from the IOC rules in place before 1 January 2004 to distinguish permitted therapeutic inhaled use of salbutamol from abuse by excessive inhalation or oral administration. However, one important change that WADA made from the outset was that exceeding the urinary threshold concentration was no longer automatically considered as an anti-doping rule violation. This change reflected the possibility that certain athletes could, albeit rarely, exceed the Threshold in view of their particular metabolism of salbutamol (in particular, when no maximum allowed dose had been set yet and medical prescriptions often referred to use "as needed").

The Threshold value of 1,000 ng/mL has been constantly reviewed and confirmed as appropriate over the years by multiple research studies conducted by different investigators, many of which had been commissioned by WADA.

It is well acknowledged that due to inter-individual variability in the excretion of salbutamol, the Threshold at 1,000 ng/mL and Decision Limit at 1,200 ng/mL are not hard values, which could be used to unequivocally determine an anti-doping rule violation, as can be the case for other threshold substances. One of the primary purposes of this "soft" Threshold is to distinguish between systemic use (where there is evidence of anabolic effects) and therapeutic use by inhalation. Studies have consistently revealed that the vast majority of athletes taking salbutamol within the maximum allowed therapeutic inhaled dose will not exceed the Decision Limit. In contrast, it has been demonstrated that a proportion of athletes taking salbutamol by prohibited systemic routes will excrete salbutamol in urine at concentrations below the Decision Limit; this has resulted over the years in numerous calls for the Decision Limit to be reduced.

In conclusion, the Threshold/Decision Limit for salbutamol does not purport categorically to distinguish between two mutually exclusive options such as doping and not doping. Rather, this Decision Limit has been established at a reasonable level to allow the use of inhaled salbutamol therapeutically by athletes without the need to apply for a TUE and with a minimal risk of producing an AAF. At the same time, this Decision Limit acts as an adequate detector and deterrent of the abuse of salbutamol for performance enhancement purposes. After years of research, monitoring and verification of the salbutamol system since the IOC model, various generations of WADA's LiEG members have considered the Threshold of 1,000 ng/mL and later the Decision Limit of 1,200 ng/mL to be at an appropriate level to achieve this dual purpose. It is important to understand that this balancing act is, to some extent, a qualitative exercise integrating the specific anti-doping expertise of the specialists that are called upon to make this determination, in particular the LiEG, but also the HMRC experts and, ultimately, the members of the WADA Executive Committee as representatives of the sport and government interests in the fight against doping in sport.

For analytical results exceeding the Decision Limit, the possibility of conducting a controlled excretion study, simulating as much as reasonably practicable the known conditions on the day of the positive doping test, is a step accessible to all athletes. This allows the athlete to demonstrate that he/she has a rare metabolism that can lead to excreting salbutamol in urine at or around the reported level in excess of the Decision Limit further to an inhaled dose within the prescribed maximum. If so demonstrated, the AAF would be nullified.

For more than 15 years since the inception of the WADC and the Prohibited List, the Threshold of salbutamol has remained unchanged at 1,000 ng/mL. However, the anti-doping rules defining the permitted therapeutic use of inhaled salbutamol have significantly evolved over this time: from the simple application of the Threshold at 1,000 ng/mL to determine an anti-doping rule violation, to a system which:

i) includes the analytical measurement uncertainty to define a compliance Decision Limit at 1,200 ng/mL;
ii) provides athletes with the opportunity to overturn the AAF through a controlled pharmacokinetic study; and
iii) requires the correction of urinary salbutamol concentrations for SG (for concentrated urines) to determine an adverse analytical finding for salbutamol.

The evolution of the rules established by the anti-doping regulatory bodies to allow the therapeutic use of inhaled salbutamol has also been significant: from no dose limitation and a considerable risk of excessive intake when athletes were prescribed use of inhaled salbutamol "*as needed*" or "*as required*", to a prescribed maximum daily dose as recommended by the manufacturer (*i.e*. 1600 μg inhaled salbutamol daily), to the more recent requirement not to exceed 800 μg of inhaled salbutamol over any 12 hour period in fractionated doses.

Anti-doping experts consider that the rules currently in force, including the possibility for athletes to request a controlled excretion study in case of an adverse analytical finding for salbutamol, are fair and balanced. Such rules support good medical practice for the therapeutic use of inhaled salbutamol, and represent at the same time a strong deterrent factor to prevent its abuse for doping purposes.

6. CONSULTATION AND PEER REVIEW

The Threshold for salbutamol was in place before WADA became responsible for the world anti-doping program. Indeed, it was adopted (albeit with refinements) from the IOC at a time when Code Article 3.2.1 (on the presumed validity of analytical methods or decision limits approved by WADA following consultation with the relevant scientific community and being subject to peer review) did not even exist in the WADC. However, it is WADA's firm opinion that the Threshold/Decision Limit for salbutamol has been subject to significant consultation and peer review with the scientific community over the years.[9]

The Threshold implemented by the IOC was based on a recommendation from the IOC Medical Commission, which took into account the studies published in the scientific literature and anti-doping data available at the time. Based on its own review of the existing literature, the WADA LiEG and the HMRC adopted this Threshold (although softened it by removing the automatic consequence of doping, if exceeded). Over the years and as set out above, WADA has continuously commissioned a significant amount of research projects, resulting in peer-reviewed and published studies, to ascertain the correlation between the salbutamol administration regime (dose, frequency and mode of administration), the corresponding urinary concentration levels and the potential for performance enhancement. On each occasion, WADA and its committees (in particular the List and the Laboratory Expert Groups) discussed and reviewed the results of the research with the investigators and concluded that the Threshold was adequate. Indeed, none of the research teams has ever recommended that the Decision Limit be increased; rather, it has been proposed on numerous occasions that the level be lowered, as it was not sufficiently sensitive for systematically detecting systemic use of salbutamol. The scientists that have conducted these studies and been involved in those discussions include some of the world's most renowned specialists in the field, such as D. McKenzie and V. Backer. In addition, the various List and Laboratory Expert Groups, and HMRC that have reviewed and refined the salbutamol system over the years (always confirming the basic Threshold of 1,000 ng/mL) have comprised more than 110 scientists from around the world with particular expertise in anti-doping, pharmacology and sports physiology. In particular, the List Expert Groups have included several experts on β2-agonists (see section 8 below) and analytical science.

[9] According to the Cambridge Dictionary, peer review is defined as "*the process of someone reading, checking, and giving his or her opinion about something that has been written by another scientist or expert working in the same subject area*".

Each year, the modified Prohibited List drafted by the LiEG for the following calendar year, together with explanations of any modifications to the current version of the List, are circulated to WADA stakeholders for comments pursuant to Article 4.1 of the WADC. The WADA stakeholders, such as International Federations and National Anti-Doping Organizations, have medical commissions composed of scientists with expertise in different fields, including anti-doping science. Comments received from the stakeholders are considered by the LiEG, and the new Prohibited List is further reviewed and approved by the HMRC before it is recommended for adoption to the WADA Executive Committee.

In short, therefore, the Threshold for salbutamol has been subject to ongoing monitoring and refinement in a process that has been public and transparent for WADA's stakeholders; in particular, it has been debated and approved by different generations of the WADA LiEG, which itself has taken into account the evolving body of peer-reviewed and published literature, the recommendations from (and discussions with) research teams that have been commissioned by WADA and also the comments received from WADA's stakeholders. Similarly, the Decision Limit has been the subject of review by the Laboratory Expert Group, and has been ratified in various versions of the TDDL. Like any other TD, the TDDL has also been circulated to the stakeholders for review, including all the ADOs and their experts in the field of analytical science, before being approved by the WADA Executive Committee. The Decision Limit, despite being in place for eight years, has never been subject to challenge to WADA's knowledge.

The current version of the 'salbutamol system', which inter alia (i) accounts for analytical measurement uncertainty, (ii) provides for adjustment based on the SG of concentrated samples, (iii) gives specific indications on the maximum allowed inhaled doses and (iv) affords athletes the opportunity to conduct a controlled study in order to seek to overturn an adverse analytical finding, is as balanced and fair to athletes as it has ever been.

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7. REFERENCES

- Berges et al., (2000) Clin Chem. 46:1365
- Boulton et al., (1996) Br J Clin Pharm. 41 :35
- Carbo et al (1997) Cancer Lett. 115:113
- Carter & Lynch (1994) Metabolism. 43:1119
- Caruso et al (1995) Med. Sci Sports Exerc 27:1471
- Caruso et al, (2005) J Strength Cond Res. 19:102.
- Caruso et al, (2008) J Strength Cond Res. 22:1156.
- Cepero et al (1998) J Pharm Pharmacol. 50:1059
- Cepero et al, (2000) Comp Biochem Physiol C Toxicol Pharmacol. 126:45.
- Collomp et al (2000a) Int J Sports Med 21: 480
- Collomp et al (2000b) J Appl Physiol 89: 430.
- Collomp et al., (2005) Int J Sports Med. 26:513.
- Compendium of Pharmaceuticals and Specialties (2005) Canadian Pharmacists Association.
- Dickinson et al, (2014a) Clin J Sport Med :482
- Dickinson et al., (2014b) J Sport Sci Med, 13:271
- Elers et al., (2010) Med Sci Sports Exerc 42:244
- Elers et al., (2011) Int J Sport Med 32:574
- Elers et al., (2012a) Clin J Sport Med 22:140
- - Elers et al., (2012b) Scan J Sport Med 22 :232
- EURACHEM/CITAC Guide. Use of uncertainty information in compliance assessment. First edition. Ellison SRL,Williams A (Eds) (2007). www.eurachem.org/guides/pdf/
- Fiacco et al, (2012) Proceedings of the Manfred-Donike-Workshop 20 ; 30th Cologne Workshop on Dope Analysis p.164
- Fitch (2006) Clin Rev Allergy Immunol. 31(2-3):259
- GINA Guidelines- http://ginasthma.org/
- Haase et al., (2016) Drug Test Anal. 8:613
- Hindle and Chrystyn, (1192) Br J Clin Pharmacol 34:311
- Hostrup et al., (2014) Drug Test Anal. 6:528.
- Hostrup et al., (2016) Scand J Med Sci Sports. 26:8
- Le Panse et al., (2005) Int J Sports Med. 26:518
- Le Panse et al., (2006) Br J Sports Med 40:627
- Le Panse et al., (2007) Br J Sports Med. 41:430.
- Martindale, 2011 Edition, Pharmaceutical Press, London.
- Mareck et al., (2011) Drug Test Analysis, 3:820.
- Martineau et al., (1992) Clin Sci (Lond) 83:615-21.
- MIMS Ireland , (2004), pp 240.
- Parsons et al., (2013) Am J Respir Crit Care Med 187:1016
- Pichon et al., (2006) Int J Sports Med. 27:187.

- Pillard et al., (2015) Resp Res 16:155.
- Schweitzer et al (2004) Clin J Sport Med.14:31
- Sporer et al., (2008a) Med Sci Sports Exerc. 40:149.
- Sporer et al., (2008b) Clin J Sport Med. 18:282
- Summary of Modifications, Prohibited List https://www.wada-ama.org/en/resources/science-medicine/prohibited-list-documents
- Van Baak et al., (2000) Med. Sci. Sports Exerc., 32:1300
- Ventura et al, (2000) Ther Drug Monit.22:277.
- Walle et al., (1993) Drug Metab Dispos 21:76

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8.0 Composition of WADA Scientific Committees

8.1 Composition of WADA Health, Medical and Research Committees (2001-2018)

2000	
LJUNGQVIST, A	SWE
AYOTTE, C	CAN
DE ROSE, E	BRA
DRINKWATER, B L	USA
FITCH, K	AUS
FRIEDMANN, T	USA
KOSS, J O	NOR
MUELLER, K	GER
SALTIN, B	DEN
WADLER, G	USA

2001	
LJUNGQVIST, A	SWE
AYOTTE, C	CAN
DE ROSE, E	BRA
DRINKWATER, B L	USA
FITCH, K	AUS
FRIEDMANN, T	USA
IRIE, M	JPN
KOSS, J O	CAN
MBANYA, J C	CAM
MUELLER, K	GER
SALTIN, B	DEN
WADLER, G	USA

2002	
LJUNGQVIST, A	SWE
AYOTTE, C	CAN
DE ROSE, E	BRA
DRINKWATER, B L	USA
FITCH, K	AUS
FRIEDMANN, T	USA
IRIE, M	JPN
MUELLER, K	GER
MBANYA, J C	CAM
SALTIN, B	DEN
WADLER, G	USA

2003	
LJUNGQVIST, A	SWE
AYOTTE, C	CAN
DE ROSE, E	BRA
DRINKWATER, B L	USA
FITCH, K	AUS
FRIEDMANN, T	USA
IRIE, M	JPN
MUELLER, K	GER
MBANYA, J C	CAM
SALTIN, B	DEN
WADLER, G	USA

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2004	
LJUNGQVIST, A	SWE
AYOTTE, C	CAN
DE ROSE, E	BRA
FITCH, K	AUS
FRIEDMANN, T	USA
HAMILTON, C	USA
HORTA, L	POR
KONO, I	JPN
MBANYA, J C	CAM
POPOV, A	RUS
SALTIN, B	DEN
SCHAMASCH, P	FRA

2005	
LJUNGQVIST, A	SWE
DE ROSE, E	BRA
FITCH, K	AUS
FRIEDMANN, T	USA
GERRARD, D	NZL
HAMILTON, C	USA
HEDMAN, B	GER
HORTA, L	POR
KONO, I	JPN
MBANYA, J C	CAM
PLUIM, B	NED
SCHAMASCH, P	FRA

2006	
LJUNGQVIST, A	SWE
DE ROSE, E	BRA
FRIEDMANN, T	USA
GERRARD, D	NZL
HAMILTON, C	USA
HEDMAN, B	GER
HORTA, L	POR
KONO, I	JPN
MBANYA, J C	CAM
PLUIM, B	NED
SCHAMASCH, P	FRA

2007	
LJUNGQVIST, A	SWE
CATLIN, D	USA
DE ROSE, E	BRA
FRIEDMANN, T	USA
GERRARD, D	NZL
PASCUAL, T	ESP
HORTA, L	POR
JOHANSEN, P W	NOR
KONO, I	JPN
MBANYA, J C	CAM
PLUIM, B	NED
SANDO, B	AUS
FRIEDMANN, T	USA

WORLD ANTI-DOPING AGENCY
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2008	
LJUNGQVIST, A	SWE
CATLIN, D	USA
DE ROSE, E	BRA
DVORAK, J	SUI
JOHANSEN, P W	NOR
KONO, I	JPN
MBANYA, J C	CAM
NOAKES, T	RSA
PASCUAL, T	ESP
PLUIM, B	NED
SANDO, B	AUS
SCHAMASCH, P	FRA
FRIEDMANN, T	USA
GERRARD, D	NZL
HORTA, L	POR
WADLER, G	USA

2009	
LJUNGQVIST, A	SWE
DE ROSE, E	BRA
DVORAK, J	SUI
HADIDI, K	JOR
JEGATHESAN, M	MAS
JOHANSEN, P W	NOR
KONO, I	JPN
MBANYA, J C	CAM
NOAKES, T	RSA
PASCUAL, T	ESP
PLUIM, B	NED
SCHAMASCH, P	FRA
FRIEDMANN, T	USA
GERRARD, D	NZL
HORTA, L	POR
WADLER, G	USA

2010	
LJUNGQVIST, A	SWE
DE ROSE, E	BRA
DVORAK, J	SUI
HADIDI, K	JOR
JEGATHESAN, M	MAS
JOHANSEN, P W	NOR
KONO, I	JPN
MBANYA, J C	CAM
PASCUAL, T	ESP
PLUIM, B	NED
SPILIOPOULOU, C	GRE
FRIEDMANN, T	USA
GERRARD, D	NZL
PASCUAL, T	ESP
WADLER, G	USA

2011	
LJUNGQVIST, A	SWE
DE ROSE, E	BRA
DI GIANFRANCESCO, A	ITA
DVORAK, J	SUI
HADIDI, K	JOR
HANDELSMAN, D	AUS
JEGATHESAN, M	MAS
JOHANSEN, P W	NOR
KONO, I	JPN
PASCUAL, T	ESP
PLUIM, B	NED
SPILIOPOULOU, C	GRE
FRIEDMANN, T	USA
SAX, A	LUX
FRIEDMANN, T	USA
BUDGETT, R	GBR

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2012	
LJUNGQVIST, A	SWE
DE ROSE, E	BRA
DI GIANFRANCESCO, A	ITA
DVORAK, J	SUI
HADIDI, K	JOR
HANDELSMAN, D	AUS
JEGATHESAN, M	MAS
PASCUAL, T	ESP
PLUIM, B	NED
SPILIOPOULOU, C	GRE
STEINACKER, J	GER
SUZUKI, H	JPN
FRIEDMANN, T	USA
PIPE, A	CAN
BUDGETT, R	GBR

2013	
LJUNGQVIST, A	SWE
DI GIANFRANCESCO, A	ITA
DVORAK, J	SUI
HADIDI, K	JOR
HANDELSMAN, D	AUS
JEGATHESAN, M	MAS
PASCUAL, T	ESP
PLUIM, B	NED
SALLIANT, G	FRA
SPILIOPOULOU, C	GRE
STEINACKER, J	GER
SUZUKI, H	JPN
FRIEDMANN, T	USA
GERRARD, D	NZL
MILLER, J	FRA
PIPE, A	CAN

2014	
LJUNGQVIST, A	SWE
DI GIANFRANCESCO, A	ITA
DVORAK, J	SUI
HADIDI, K	JOR
HANDELSMAN, D	AUS
JEGATHESAN, M	MAS
PASCUAL, T	ESP
SALLIANT, G	FRA
SPILIOPOULOU, C	GRE
STEINACKER, J	GER
SUZUKI, H	JPN
VELOSO, J	URU
FRIEDMANN, T	USA
GERRARD, D	NZL
MILLER, J	FRA
PIPE, A	CAN

2015	
FOURNEYRON, V	FRA
DI GIANFRANCESCO, A	ITA
DVORAK, J	SUI
ENGEBRETSEN, L	NOR
HADIDI, K	JOR
HANDELSMAN, D	AUS
JEGATHESAN, M	MAS
PASCUAL, T	ESP
SALLIANT, G	FRA
SPILIOPOULOU, C	GRE
STEINACKER, J	GER
SUZUKI, H	JPN
FRIEDMANN, T	USA
GERRARD, D	NZL
MILLER, J	FRA
PIPE, A	CAN
HARCOURT, P	AUS

WORLD ANTI-DOPING AGENCY
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2016	
FOURNEYRON, V	FRA
DI GIANFRANCESCO, A	ITA
DVORAK, J	SUI
ENGEBRETSEN, L	NOR
HADIDI, K	JOR
HANDELSMAN, D	AUS
JEGATHESAN, M	MAS
MOUNTJOY, M	CAN
PASCUAL, T	ESP
REYES, O	COL
STEINACKER, J	GER
STRASBURGER, C	GER
FRIEDMANN, T	USA
GERRARD, D	NZL
MILLER, J	FRA
KINAHAN, A	IRL
HARCOURT, P	AUS

2017	
ERDENER, U	TUR
DI GIANFRANCESCO, A	ITA
EKSTROM, L	SWE
ENGEBRETSEN, L	NOR
HANDELSMAN, D	AUS
JEGATHESAN, M	MAS
MOUNTJOY, M	CAN
PASCUAL, T	ESP
REYES, O	COL
STEINACKER, J	GER
STRASBURGER, C	GER
SUZUKI, H	JPN
FRIEDMANN, T	USA
GERRARD, D	NZL
WAN, T	HKG
KINAHAN, A	IRL
HARCOURT, P	AUS

2018	
ERDENER, U	TUR
DI GIANFRANCESCO, A	ITA
EKSTROM, L	SWE
ENGEBRETSEN, L	NOR
HANDELSMAN, D	AUS
MOUNTJOY, M	CAN
NAKITANDA, A	UGA
ORBERTZOVA, M	BUL
PASCUAL, T	ESP
REYES, O	COL
STRASBURGER, C	GER
SUZUKI, H	JPN
GERRARD, D	NZL
WAN, T	HKG
KINAHAN, A	IRL

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8.2 Composition of List Expert Groups (2003-2018)

2003	
LJUNGQVIST, A	SWE
DE ROSE, E	BRA
FITCH, K	AUS
HANIG, J	USA
KUIPERS, H	NED
MUELLER, K	GER
PIPE, A	CAN
SEGURA, J	ESP
VAN DUGTEREN, G R	RSA
VERBIEST, P	BEL
WADLER, G	USA

2004	
LJUNGQVIST, A	SWE
DVORAK, J	SUI
HANIG, J	USA
MIRFENDERESKI, R	FRA
MUELLER, K	GER
ROELANDT, R	BEL
SALTIN, B	DEN
SCHAMASCH, P	FRA
SUZUKI, H	JPN
WADLER, G	USA

2005	
LJUNGQVIST, A	SWE
BUDGETT, R	GBR/SUI
DVORAK, J	SUI
HANIG, J	USA
MIRFENDERESKI, R	FRA
MUELLER, K	GER
PIPE, A	CAN
ROELANDT, R	BEL
SCHAMASCH, P	FRA
SQUIRRELL, A	AUS
SUZUKI, H	JPN
WADLER, G	USA

2006	
WADLER, G	USA
BUDGETT, R	GBR/SUI
DVORAK, J	SUI
MIRFENDERESKI, R	FRA
MUELLER, K	GER
PIPE, A	CAN
ROELANDT, R	BEL
SCHAMASCH, P	SUI
SUZUKI, H	JPN

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2007	
WADLER, G	USA
BUDGETT, R	GBR/SUI
DVORAK, J	SUI
HANIG, J	USA
PIPE, A	CAN
ROELANDT, R	BEL
SAUGY, M	SUI
SCHAMASCH, P	SUI
SUZUKI, H	JPN

2008	
WADLER, G	USA
BUDGETT, R	GBR/SUI
HANIG, J	USA
HUESTIS, M	USA
KINAHAN, A	
LAGIER, G	FRA
PIPE, A	CAN
ROELANDT, R	BEL
SAUGY, M	SUI
SCHAMASCH, P	SUI
SUZUKI, H	JPN

2009	
WADLER, G	USA
BUDGETT, R	GBR/SUI
HANIG, J	USA
HUESTIS, M	USA
KINAHAN, A	IRL
LAGIER, G	FRA
PETROU, M	CYP
PIPE, A	CAN
SAUGY, M	SUI
SCHAMASCH, P	SUI
SUZUKI, H	JPN

2010	
WADLER, G	USA
BUDGETT, R	GBR/SUI
HANIG, J	USA
HUESTIS, M	USA
KINAHAN, A	IRL
LAGIER, G	FRA
PETROU, M	CYP
PIPE, A	CAN
PITSILADIS, Y	GBR
SAUGY, M	SUI
SCHAMASCH, P	SUI
SUZUKI, H	JPN

2011	
BUDGETT, R	GBR/SUI
BIDLINGMAIER, M	GER
FINKLE, B	USA
HANIG, J	USA
HUESTIS, M	USA
KINAHAN, A	IRL
LAGIER, G	FRA
PETROU, M	CYP
PITSILADIS, Y	GBR
SAUGY, M	SUI
SCHAMASCH, P	SUI
SUZUKI, H	JPN

WORLD ANTI-DOPING AGENCY
play true

2012	
BUDGETT, R	GBR/SUI
BERGLUND, B	SWE
BIDLINGMAIER, M	GER
FINKLE, B	USA
HANIG, J	USA
HUDZIK, T	USA
HUESTIS, M	USA
KINAHAN, A	IRL
McCORMACK, R	CAN
PETROU, M	CYP
PITSILADIS, Y	GBR
SAUGY, M	SUI
SCHAMASCH, P	SUI

2014	
PIPE, A	CAN
BERGLUND, B	SWE
BIDLINGMAIER, M	GER
BOTRE, F	ITA
BUDGETT, R	GBR/SUI
CULLER, M	USA
FINKLE, B	USA
HUDZIK, T	USA
HUESTIS, M	USA
KINAHAN, A	IRL
McCORMACK, R	CAN
STUART, M	GBR
THEVIS, M	GER

2013	
PIPE, A	CAN
BERGLUND, B	SWE
BIDLINGMAIER, M	GER
BUDGETT, R	GBR/SUI
FINKLE, B	USA
GMEINER, G	AUT
HUDZIK, T	USA
HUESTIS, M	USA
KINAHAN, A	IRL
McCORMACK, R	CAN
PETROU, M	CYP
PITSILADIS, Y	GBR
SCHAMASCH, P	SUI
THEVIS, M	GER

2015	
PIPE, A	CAN
BERGLUND, B	SWE
BIDLINGMAIER, M	GER
BIGARD, X	FRA
BOTRE, F	ITA
BUDGETT, R	GBR/SUI
CULLER, M	USA
FINKLE, B	USA
HUDZIK, T	USA
HUESTIS, M	USA
KINAHAN, A	IRL
STUART, M	GBR
THEVIS, M	GER

WORLD ANTI-DOPING AGENCY
play true

2016	
KINAHAN, A	IRL
BACKER, V	DEN
BIDLINGMAIER, M	GER
BIGARD, X	FRA
BUDGETT, R	GBR/SUI
CULLER, M	USA
FINKLE, B	USA
HUDZIK, T	USA
HUESTIS, M	USA
STUART, M	GBR
TETTEY, J	GHA/GBR
THEVIS, M	GER
THIEME, D	GER

2017	
KINAHAN, A	IRL
BIDLINGMAIER, M	GER
BUDGETT, R	GBR/SUI
CULLER, M	USA
FINKLE, B	USA
HARCOURT, P	AUS
HUDZIK, T	USA
HUESTIS, M	USA
STUART, M	GBR
TETTEY, J	GHA/GBR
THEVIS, M	GER
VAN DEN HOOGENBAND, C R	NED
WEBBORN, N	GBR

2018	
KINAHAN, A	IRL
BIDLINGMAIER, M	GER
BUDGETT, R	GBR/SUI
CULLER, M	USA
HARCOURT, P	AUS
HUDZIK, T	USA
HUESTIS, M	USA
SCHUMACHER, O	GER
SPRIET, L	CAN
STUART M,	GBR
TETTEY, J	GHA/GBR
THEVIS, M	GER
WEBBORN, N	GBR

WORLD ANTI-DOPING AGENCY
play true

8.3 COMPOSITIONS OF LABORATORY EXPERT GROUPS (2002-2018)

2002	
BOWERS, L	USA
BARNETT, M	USA
FIGVED, S E	NOR
HILDERBRAND, R	USA

2004	
AYOTTE, C	CAN
BOWERS, L	USA
HEMMERSBACH, P	NOR
KAZLAUSKAS, R	AUS
MILLER, J	FRA
SCHAMASCH, P	FRA

2003	
AYOTTE, C	CAN
BOWERS, L	USA
COWAN, D	GBR
GARLE, M	SWE
MILLER, J	FRA
NOLAN, S	NZL
SCHAMASCH, P	FRA
SEGURA, J	ESP
UEKI, M	JPN

2005	
HORTA, L	POR
BOWERS, L	USA
HEMMERSBACH, P	NOR
KAZLAUSKAS, R	AUS
MILLER, J	FRA
SCHAMASCH, P	FRA
WU, M	CHN

WORLD ANTI-DOPING AGENCY
play true

2006	
HORTA, L	POR
BOWERS, L	USA
HEMMERSBACH, P	NOR
KAZLAUSKAS, R	AUS
MILLER, J	FRA
SCHAMASCH, P	FRA
WU M,	CHN

2007	
HORTA, L	POR
BOTRE, F	ITA
BOWERS, L	USA
KAZLAUSKAS, R	AUS
MILLER, J	FRA
SIEKMANN, L	GER
SQUIRRELL, A	AUS
WU, M	CHN

2008	
HORTA, L	POR
BOTRE, F	ITA
BOWERS, L	USA
KAZLAUSKAS, R	AUS
MILLER, J	FRA
SIEKMANN, L	GER
SQUIRRELL, A	AUS
WU, M	CHN

2009	
HORTA, L	POR
BOWERS, L	USA
GEORGAKOPOULOUS, C	GRE
KAZLAUSKAS, R	AUS
MILLER, J	FRA
ROSSI, F	ITA
SCHANZER, W	AUS
SQUIRRELL, A	AUS
WESTWOOD, S	AUS

2009	
HORTA, L	POR
BOWERS, L	USA
GEORGAKOPOULOUS, C	GRE
KAZLAUSKAS, R	AUS
MILLER, J	FRA
ROSSI, F	ITA
SCHANZER, W	AUS
SQUIRRELL, A	AUS
WESTWOOD, S	AUS

2010	
PASCUAL, T	ESP
AYOTTE, C	CAN
BOWERS, L	USA
GMEINER, G	AUT
MILLER, J	FRA
ROSSI, F	ITA
SCHANZER, W	GER
SQUIRRELL, A	AUS
WESTWOOD, S	AUS

WORLD ANTI-DOPING AGENCY
play true

2011	
PASCUAL, T	ESP
AYOTTE, C	CAN
BOWERS, L	USA
GMEINER, G	AUT
MILLER, J	FRA
ROSSI, F	ITA
SCHANZER, W	GER
SQUIRRELL, A	AUS
WESTWOOD, S	AUS

2012	
PASCUAL, T	ESP
AYOTTE, C	CAN
GMEINER, G	AUT
MILLER, J	FRA
ROSSI, F	ITA
SCHANZER, W	GER
SQUIRRELL, A	AUS
WAN, T	CHN
WESTWOOD, S	AUS

2013	
MILLER, J	FRA
AYOTTE, C	CAN
KUURANNE, T	FIN
ROSSI, F	ITA
SCHANZER, W	GER
SEGURA, J	ESP
SQUIRRELL, A	AUS
WAN, T	CHN
WESTWOOD, S	AUS

2014	
MILLER, J	FRA
KUURANNE, T	FIN
McINTURFF, T	USA
ROSSI, F	ITA
SAUGY, M	SUI
THIEME, D	GER
VAN EENOO, P	BEL
WAN, T	CHN
WESTWOOD, S	AUS

WORLD ANTI-DOPING AGENCY
play true

2015	
MILLER, J	FRA
KUURANNE, T	FIN
LE BIZEC, B	FRA
McINTURFF, T	USA
ROSSI, F	ITA
SAUGY, M	SUI
THIEME, D	GER
VAN EENOO, P	BEL
WAN, T	CHN
WESTWOOD, S	AUS

2016	
MILLER, J	FRA
AYOTTE, C	CAN
CAVANAGH, R	USA
GOEBEL, C	AUS
KUURANNE, T	FIN
LE BIZEC, B	FRA
McINTURFF, T	USA
ROSSI, F	ITA
WAN, T	CHN
WESTWOOD, S	AUS

2017	
WAN, T	CHN
AYOTTE, C	CAN
CAVANAGH, R	USA
GOEBEL, C	AUS
KUURANNE, T	FIN
LE BIZEC, B	FRA
ROSSI, F	ITA
SCHULZE, J	SWE
TURNER, L	GBR
WESTWOOD, S	AUS

2018	
WAN, T	CHN
COHEN, A	DEN
GOEBEL, C	AUS
GOTZMANN, A	GER
KUURANNE, T	FIN
LE BIZEC, B	FRA
SCHULZE, J	SWE
TURNER, L	GBR
VAN EENOO, P	BEL
WESTWOOD, S	AUS