

The List of Prohibited Substances and Methods in Sport: Structure and Review Process by the World Anti-Doping Agency

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Abstract

The List of Prohibited Substances and Methods (the List) is the International Standard that determines what is prohibited in sport in- and out-of-competition. The official text of the List is produced by the World Anti-Doping Agency (WADA), the international independent organization responsible for promoting, coordinating and monitoring the fight against doping in sport. The drafting of the annual List is a highly interactive and consultative process involving scientific and medical experts in anti-doping, sport federations and governments. In this article, the elements that compose the List as well as the process behind its annual revision and update are presented.

Historical Background

Efforts to enhance athletic performance using means other than training can be dated back to the ancient Olympic Games. There is evidence that during these Games athletes would ingest animal parts, plants and potions to improve their physical prowess (1,2). In modern era sports, use of performance-enhancing substances became apparent at the end of the 19th century. In the earlier half of the 20th century, the use of performance-enhancing drugs was limited to stimulants and alcohol. In such context, the International Association of Athletics Federations (IAAF) banned the use of stimulants in track-and-field competitions in 1928. During World War II, amphetamines were extensively employed to combat fatigue and enhance alertness by soldiers, and as a consequence, the use of stimulants in sport increased thereafter. More recently in the 1960s, anabolic steroids made their appearance in the drug market. By then it was obvious that drug abuse for the purpose of performance enhancement was spreading among many sports (1–3).

Although a number of fatalities had been attributed to doping along the years, it was not until the death of Danish cyclist Knut Jensen in the 1960 Olympic Games that more systematic anti-doping measures started to be implemented. Several countries passed laws against doping in the mid 1960s and the Council of Europe adopted a resolution against doping in sport in 1967. Around that time, sport federations such as the Federation Internationale de Football Association (FIFA), in 1966, as well as the Union Cycliste Internationale (UCI) and the Union Internationale de Pentathlon Moderne (UIPM), in 1967, began compiling the first lists of substances prohibited in their respective sports. In addition, the International Olympic Committee (IOC) created a Medical Commission to fight doping in sport in 1967. Soon after, the IOC Medical Commission issued the first list of banned substances for the 1968 Olympic Games in Grenoble (Winter Games) and Mexico (Summer Games) and doping tests started to be conducted in Olympic Sports (1–2,4).

The initial list contained stimulants and narcotics only but later, other categories of substances (e.g., anabolic agents, diuretics, peptide hormones, and glucocorticosteroids) and methods (e.g., blood doping, pharmacological, chemical, and physical manipulation) were progressively added to the yearly-revised IOC list (2). Until 2003, the IOC list of Prohibited Classes of Substances and Prohibited Methods was applied to sports within the Olympic Movement. There were disparate efforts from sport federations and governments and the creation of national anti-doping agencies in different countries to combat doping in sports. However, a number of anti-doping conventions held in the mid-1980s recognized the necessity to coordinate anti-doping rules and regulations in order to effectively fight doping in sport. Following the Festina Scandal during the 1998 Tour de France, when a large number of doping substances were found in the trunk of a physiotherapist of the Festina Team car by customs officials (5,6), it became more evident that doping had become a major public health

concern. It became evident that more cooperation was needed between governments and sports authorities and that anti-doping rules should be harmonized through an independent anti-doping agency. Consequently, the IOC convened the First World Conference on Doping in Sport in February 1999 in Lausanne, Switzerland. The major outcome of this meeting was the establishment of the World Anti-Doping Agency (WADA) in November 1999, to promote and coordinate internationally the fight against doping in sport in all its forms (1,4).

The Prohibited List Under WADA

Periodic update of the List

Following the adoption of the first World Anti-Doping Code (the Code) at the 2nd World Conference on Doping in Sport in March 2003 in Copenhagen, Denmark, WADA assumed the responsibility of maintaining, updating, and publishing the List of Prohibited Substances and Methods (the List) in sport. The List is one of the five International Standards developed under the Code to ensure harmonization and best practice of the anti-doping program (7,8). The List is updated and published by WADA at least annually. The annual List updating process is highly interactive between WADA and the Code signatories. The first level of this process involves the Prohibited List Committee. This 12-member Committee is composed of an international panel of sports medicine doctors and scientists, including pharmacologists, toxicologists, physiologists, chemists, and biologists (9). The Members of this Committee are replaced periodically and are chosen from independent experts who are nominated by WADA's President, Director General, and the Chairman of the WADA's Health, Medical, and Research (HM&R) Committee.

The Prohibited List Committee meets three times per year. During the first meeting, usually held in late January or early February, the Committee compiles comments received about the recently published List, gathers information on new doping trends and new drugs on the market and comments from WADA stakeholders and discusses possible changes to the List. Whenever needed, the Committee invites external scientific or medical experts to gain deeper knowledge on a particular subject. Also, Committee Members regularly collect information from the scientific literature and/or the sport field on specific issues. This information is presented to the Committee as position papers or oral presentations. In addition to the data available from the scientific literature, the Committee also considers information generated by WADA's Scientific Research Program. Grants funded by WADA include those aimed at identifying new designer drugs (e.g., 1-testosterone) and masking agents (e.g., finasteride) and at determining potential ergogenic effects of pharmaceutical drugs (e.g., sildenafil). Furthermore, developing interaction between WADA and the pharmaceutical and biotechnology industries allow the Prohibited List Committee to gain insight on new drugs under development with potential doping effects. Several EPO-like drugs such as Mircera™, Dynepo™, and Hematide™, as well as Selective Androgen Receptor Modulators (SARMs) and Hypoxia

Inducible Factor (HIF) stabilizers are good examples of this sharing of information.

During the second meeting of the Prohibited List Committee, which usually takes place in April, the proposed changes are further discussed and incorporated into the draft of the following year's List. The draft List is then circulated among hundreds of WADA's stakeholders and associates (i.e., governments, anti-doping organizations, sport federations, WADA accredited anti-doping laboratories) for a consultation period of about three months. These stakeholders, who also consult the advice of their medical/scientific committees or the opinion of staff scientists and medical doctors, review the draft of the List and provide their views and recommendations directly to WADA, by the end of July. WADA's Science Department compiles the comments in order to allow the Prohibited List Committee to review, evaluate, and discuss all stakeholders' assessments during their early September meeting. Following the completion of this process, the Committee presents a consolidated draft of the List to the HM&R Committee in early September.

The HM&R Committee is also composed of medical doctors and scientists with extensive expertise in the field of anti-doping (10). The HM&R Committee reviews and discusses the List as well as the proposed changes and, if deemed necessary, makes further modifications during its annual early September meeting. The draft of the List, after endorsement by the HM&R Committee, is then presented to WADA's Executive Committee in mid-September.

The 12-member Executive Committee is WADA's policy-making body. It is equally composed of representatives from the Olympic Movement and governments of the world (11). The List is traditionally presented by the Chairman of the HM&R Committee with the support of WADA's Science Director. The Executive Committee reviews the List and introduces further changes, makes final decisions if necessary and then formally approves the List Standard. The List is then published on WADA's website on October 1st, at the latest, each year, that is at least three months before coming into effect on January 1st of the following year. Simultaneously, the List is distributed to stakeholders and sent to UNESCO as stipulated in the Convention of Doping in Sports. In doing so, stakeholders can examine the changes introduced and proceed accordingly to the integration of the new List in their respective regulations or legislations. In addition to the regular annual review, the Code also has a provision for reviewing and publishing the List as often as necessary (12) so as to fast-track and include new substances/methods or classes of substances/methods that would suddenly become available for doping abuse and would not be already covered by the List. An example of this would be the discovery of a new designer drug. During the seven years the Code has been in effect, the List has been revealed as sufficiently well drafted and flexible to cover the designer drugs discovered to date (e.g., tetrahydrogestri- none, desoxymethyltestosterone, methylhexanamine), so the fast-track mechanism has not been necessary as of yet. However, this disposition remains essential to ensure reactivity of anti-doping authorities in a world where increasing numbers of illegal designer drugs are produced every year (13).

Criteria to include substances or methods in the List

In compliance with the Code, a substance or method has to fulfill at least two of the following three criteria to be considered for inclusion in the List: 1. Potential to enhance or proof of enhancing sports performance; 2. Evidence of a potential or actual health risk to the athlete; and 3. Use violates the spirit of sport as described in the Code.

None of the criteria alone is sufficient to consider adding a substance or method to the List. During the recent revision of the Code in 2009 (8), there were discussions on whether it should be mandatory for the substances or methods included in the List to be performance-enhancing and therefore make this criterion the primary one supported by one of the two others. However, it was the decision of the vast majority of stakeholders that the three criteria should remain with equal weight. Otherwise, physiological means of enhancing performance, including exercise itself or proper diet would potentially be considered as prohibited. Designer drugs are another example of why it would be impractical to make performance enhancement of a drug compulsory. In this regard, it would be unethical to set up experimental studies in humans for substances not approved by health authorities for human administration.

The first two criteria listed clearly have a scientific and medical basis while the third is rooted in ethical and societal perspectives. Therefore, the Prohibited List Committee may have to occasionally consult WADA's Ethical Issues Expert Panel. An example can be found during the discussions concerning the possible inclusion of artificially induced hypoxic conditions in the List. In this case, the Prohibited List Committee determined that artificially induced hypoxic conditions could be performance-enhancing, but it did not seem to represent a significant risk for athletes' health. The Ethical Issues Expert Panel had therefore to be consulted on the third criteria.

In addition to the aforementioned group of substances and methods, any drug or method capable of masking the use of a prohibited substance or method is also included in the List.

Although the classes of substances and methods that currently compose the List reflect the opinion of the majority of Code signatories, the inclusion of some classes (e.g., cannabinoids, glucocorticosteroids, or beta-2-agonists) is not unanimously supported. Some stakeholders believe that there is not sufficiently strong scientific evidence that these substances are performance-enhancing in sports; however, as mentioned above, the inclusion of a substance or method in the List relies upon more than just one criterion.

Categories and subcategories under the List

Categories. The categories of Substances included in the latest List are Non-approved substances; Anabolic agents; Peptide hormones, growth factors, and related substances; Beta-2-agonists; Hormone antagonists and modulators; Diuretics and other masking agents; Stimulants; Narcotics; Cannabinoids; Glucocorticosteroids; Alcohol; and Beta-blockers. The prohibited Methods are Enhancement of oxygen transfer, Chemical and physical manipulation, and Gene doping (14).

Timing of prohibition and sports specificities. The substances and methods on the List are prohibited during certain

periods of time (14). Anabolic agents, peptide hormones, growth factors and related substances, beta-2-agonists, hormone antagonists and modulators, diuretics and other masking agents, as well as all the methods are prohibited both in- and out-of-competition in all sports. On the other hand, stimulants, narcotics, cannabinoids, and glucocorticosteroids are only prohibited in-competition in all sports. Finally, substances like alcohol and beta-blockers are prohibited in certain sports only, either at all times or in competition. Both these substances would have detrimental effects in the majority of sports, but may prove beneficial for a handful of disciplines. Therefore, it is considered unnecessary to ban them in all sports. According to the 2003 Code, the choice of requesting the banning of alcohol or beta-blockers in a particular sport was in the hands of the sport federations themselves (15). At the time the first List was established by WADA in 2004, WADA consulted all the major Federations and included such substances in accordance with their recommendations. Following the revision of the Code in 2009, WADA has the authority to prohibit alcohol and/or beta-blockers in any given sport (16).

There have been discussions on whether all substances and methods should be prohibited at all times rather than having separate categories of substances prohibited in-competition, out-of-competition or in certain sports. However, as indicated in the Code, substances prohibited in-competition are not considered to have the potential to enhance performance in future competitions and therefore there is no need to ban them outside sport events (16).

Non-specified and specified substances and methods. From 2003 until 2008, the Prohibited List identified a group of substances as being "specified". This group included, for example, most beta-2-agonists, cannabinoids, glucocorticosteroids, and several stimulants. The basis for this distinction was that these substances could cause unintentional anti-doping rule violations because of their general availability in medicinal products or because they were less likely to be successfully abused as doping agents. An anti-doping rule violation involving a specified substance could result in a reduced sanction if the athlete could prove that there was no intention of enhancing performance. The definition of what constitutes a specified or non-specified substance or method changed with the revised version of the Code in 2009. The Code currently defines that anabolic agents, hormones, certain stimulants and hormone antagonists, or other substances identified on the List as well as all methods, are non-specified. All other substances not falling into this category are considered specified. Although the terminology is equal to that used in the original version of the Code, the concept is slightly different. In the 2009 Code the definition of a specified substance is based on the application of Article 10 of the Code with respect to Sanctions to Individuals rather than on the availability or ergogenic properties of the substance or method. As such, depending on the doping case, a specified substance may or may not carry a lesser sanction than a non-specified one.

Open and closed classes. Most classes of substances and methods included in the List are open. There are several reasons for doing this. For example, the thousands of names of substances comprised under the different classes would re-

quire the publication of a List composed of hundreds of pages, which would be impractical for quick consultation. In addition, it would require constant updating of the List as there are new pharmaceutical or street drugs under those categories that come into the market periodically each year. It would also mean that a new designer drug would not be considered prohibited, as it would not be included in the List by name or even by function. To solve this problem, only a handful of representative examples are presented in the List; all other substances or methods under those classes are covered by sentences such as "...and all other substances with similar chemical structure or similar biological effect(s)", "including but not limited to...", or "and their releasing factors (when referring to prohibited substances that can be produced endogenously)" (14). An open category allows any new designer substance found or suspected to be abused by athletes or any newly approved pharmaceutical drug to be automatically prohibited if its structure or biological effects are similar to the examples listed, without the need to wait and prove that it is successfully used as a doping agent.

Only endogenous anabolic androgenic steroids and narcotics are closed classes. In the first case, the number of endogenous anabolic steroids is limited, and they are known entities. In the case of narcotics, only the most potent and addictive substances are considered doping substances under this class.

Nomenclature. Although the content of the List is scientific in nature, it is not intended to be exclusively accessible to the medical and scientific community. The List should also be easy to read and to understand by athletes and their entourage whenever they wish to consult to find out whether a substance or method is prohibited. The List should also be an educational tool for the general public, including recreational athletes, schoolchildren, and parents. As such, it is important, whenever possible, to find an appropriate compromise between the scientific terminology needed by the anti-doping laboratory personnel, sports medicine doctors, and pharmacists and common names accessible to non-scientific professionals involved in anti-doping, such as lawyers, as well as the athletes and the general public. This is particularly important in cases of street drugs, natural products, or common substances. Therefore, in several cases both the common and the chemical (international non-proprietary name-INN) names are included in the List. Examples of these are some anabolic androgenic steroids [e.g., tetrahydrogestrinone (18 α -homo-pregna-4,9,11-trien-17 β -ol-3-one); boldione (androsta-1,4-diene-3,17-dione); prasterone (dehydroepiandrosterone, DHEA)], synthetic hormones [e.g., CERA (methoxy polyethylene glycol-epoetin beta)], substances present in nutritional supplements [e.g., androstatrienedione (androsta-1,4,6-triene-3,17-dione); 6-oxo (4-androstene-3,6,17 trione)], and stimulants [e.g., carphedon (4-phenylpiracetam)].

Monitoring Program

The Monitoring Program was established to detect patterns of misuse of substances not included in the List. The substances in the Monitoring Program are published by WADA in a document separate from the List (17). The laboratories have to test for and report these substances, but the athlete is not

sanctioned if the sample contains such substance(s). The trends are compiled and analyzed by WADA's Science Department, and the results are provided to the Prohibited List Committee and some stakeholders (i.e., international federations and national anti-doping agencies). The Committee may either decide to continue with the monitoring or, if there is enough evidence of abuse, it may decide to introduce the substance onto the List. An example of the latter can be found in pseudoephedrine. This common cold medication was included in the IOC Prohibited List, but it was later withdrawn because of its ubiquity in over-the-counter medications and the lack of performance-enhancing benefits at therapeutic doses. However, the Monitoring Program demonstrated for several years that the use of pseudoephedrine had steadily increased at higher, supratherapeutic doses in certain countries and sports. These results prompted the Prohibited List Committee to consider reintroducing pseudoephedrine to the List. Before doing so, WADA conducted clinically controlled excretion studies to determine the urinary threshold value that is incompatible with the use of the drug for therapeutic purposes. As a result, pseudoephedrine was reintroduced in the 2010 List, prohibited at urinary concentrations above 150 μ g/mL.

Other substances such as caffeine, synephrine, phenylephrine, phenylpropanolamine, piperadol, and bupropion still remain under monitoring (17). Bupropion, for example, has been shown in several studies to have beneficial effects for exercise tolerance to heat (18–21). Therefore, WADA is closely monitoring this drug, but so far there have been no signs of abuse, including during major summer competitions. As a result, bupropion remains in the Monitoring Program.

Conclusions

The complexity of the List resides in the fact that it is used as a scientific, educational, and legal tool and the format is the result of a compromise to suit such heterogeneity of purposes and audiences.

The drafting and updating of the annual List of Prohibited Substances and Methods is a highly interactive and consultative process involving scientific and medical experts in anti-doping, sport federations, and governments. As a result, the substances and methods listed are thoroughly scrutinized ensuring that their inclusion is warranted vis-a-vis the criteria established in the Code and that the List remains practical in its application.

The List is the result of considering different views and expectations from WADA's stakeholders as well as adapting to the rapid evolution of science and pharmacology. Consequently, the List is an evolving document. However, by making the decisions based on science and on an open and transparent process, WADA has achieved considerable stability in the structure and worldwide application of the List since 2004. The List is a cornerstone of anti-doping activities, the most visited document on WADA's website, and will continue to evolve as science progresses and new drugs with doping potential are identified.

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