Development and activities of the fight against doping

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Abstract Although doping has a long history of use to enhance performance in competition, the sports community has long fought against it, as it destroys the spirit of athletic integrity. Doping is of course currently prohibited, and the World Anti-Doping Agency (WADA) was established in 1999. WADA quickly created the World Anti-Doping Code (WADC) as a universal rule on anti-doping. This code has 5 International Standards by which all sports participants must abide. The Prohibited List International Standard is the definitively accepted list of prohibited substances and methods in sports; and athletes and support personnel should familiarize themselves with the most recent edition. All athletes to whom prohibited substances or methods are administered for legitimate therapeutic use should obtain a Therapeutic Use Exemption (TUE). Doping Control, referring to all processes related to doping tests, is conducted through In-Competition Testing and Out-of-Competition Testing. Japan established its own Japan Anti-Doping Agency (JADA) in 2001. JADA performs approximately 5,000 doping tests annually, and the Japanese incidence of anti-doping rule violations may be significantly less than the global average. The “JADA Car”, produced by JADA, is the world’s first mobile multi-function anti-doping unit. JADA launched its sports pharmacist system in 2010, and has since certified more than 5,000 sports pharmacists. The Japanese national high school curriculum currently involves anti-doping education, and will continue to promote anti-doping activities in Japan.

Keywords: World Anti-Doping Agency (WADA), Japan Anti-Doping Agency (JADA), World Anti-Doping Code (WADC), Therapeutic Use Exemption (TUE), Prohibited List, Doping Control

History of Doping and Anti-Doping Activities

Doping is defined as the illegal use of drugs or other such methods to win competitions. It is said that a fortified drink, “dop”, drunk at fights by the indigenous people of Africa, is the origin of the word “doping”¹. The use of performance-enhancing drugs in an Amsterdam canal swimming event in 1865 is the oldest recorded instance of athletic doping. In 1886, a fatal cycling accident occurred due to the use of doping stimulants²,³. Another cycling fatality from stimulant use at the 1960 Rome Olympics prompted the International Olympic Committee (IOC) to discuss the need for Olympic anti-doping regulations from the perspective of protecting athlete health⁴. The IOC began formal doping control with the Mexico Summer Olympic Games and Grenoble Winter Olympic Games in 1968. Initially, only stimulants and narcotics were tested for, with anabolic androgenic steroids first examined at the Montreal Olympics in 1976. Many positive doping tests have been reported in the Olympic Games since 1968⁵ (Table 1).

In 1988 a famous incident occurred, with Ben Johnson, a sprinter, winning the 100 m final at the Seoul Olympics, setting an amazing new world record of 9.79 seconds, and being disqualified for doping three days later. A large number of erythropoietin preparations were found in the Tour de France in 1998. The rights of the clean athlete were further protected when Adrian Annus, a hammer thrower, was stripped of his gold medal at the 2004 Summer Olympic Games in Athens for a doping violation, the medal instead going to Koji Murofushi. In 2013, people were again shocked by the case of Lance Armstrong, a famous cyclist.

International anti-doping activities have been promoted since the 1960s by the IOC. However, since the IOC is itself the organizer of the Olympic Games, concerns were raised regarding the neutrality and transparency of its self-managing doping control. Additionally, anti-doping activity was seen to be the work of not just the elite sports world, but broader society in general. The World Anti-Doping Agency (WADA) was therefore established in 1999 as an independent international agency through the contributions of the IOC and various countries⁶. Japan contributed 1,502,800 USD to WADA in 2012, an amount second only to the United States⁷. WADA unifies and promotes anti-doping activities across almost all sports...
and countries.

In Japan, the Japan Amateur Sports Association started anti-doping activities after the Tokyo 1964 Olympics, and doping tests were performed domestically for the first time at the Sapporo 1972 Winter Olympics. In 2001, the Japan Anti-Doping Agency (JADA) was founded and unified a concrete, Japanese anti-doping system7).

As government initiatives against doping grew, the International Convention against Doping in Sport was adopted by the 33rd UNESCO General Conference in 2005 and implemented on February 1, 2007, following ratification from 30 countries, including Japan. The Japanese Ministry of Education, Culture, Sports, Science & Technology (MEXT) accredited JADA as its National Anti-Doping Organization in 2007. The Basic Act on Sport was then enacted in June 2011, which decreed that the government should promote anti-doping activities in conjunction with JADA, leading MEXT to formulate the Sport Basic Plan8).

Anti-Doping Rules and Definition of Doping

There are several reasons that doping is prohibited. Athletes have been noted as having an intrinsic value called “the spirit of sport”9) (Table 2). Doping is fundamentally contrary to this intrinsic spirit, and therefore damages athletic integrity. In addition, performance-enhancing substances may cause a variety of adverse health effects, and must therefore be prohibited in order to protect athlete health. Lastly, as elite athletes are noted figures and admired by the youth, doping sends a poor message to society, possibly encouraging drug abuse2).

The World Anti-Doping Code (WADC) is the universal authority on anti-doping. The WADC was adopted in 2003, and subsequently revised, effective from 2009.

Table 1. Doping tests in Olympics

<table>
<thead>
<tr>
<th>SUMMER OLYMPICS</th>
<th>WINTER OLYMPICS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td><strong>Place</strong></td>
</tr>
<tr>
<td>1968</td>
<td>Mexico City</td>
</tr>
<tr>
<td>1972</td>
<td>Munich</td>
</tr>
<tr>
<td>1976</td>
<td>Montreal</td>
</tr>
<tr>
<td>1980</td>
<td>Moscow</td>
</tr>
<tr>
<td>1984</td>
<td>Los Angeles</td>
</tr>
<tr>
<td>1988</td>
<td>Seoul</td>
</tr>
<tr>
<td>1992</td>
<td>Barcelona</td>
</tr>
<tr>
<td>1996</td>
<td>Atlanta</td>
</tr>
<tr>
<td>2000</td>
<td>Sydney</td>
</tr>
<tr>
<td>2004</td>
<td>Athens</td>
</tr>
<tr>
<td>2008</td>
<td>Beijing</td>
</tr>
<tr>
<td>2006</td>
<td>Turin</td>
</tr>
</tbody>
</table>

In Beijing, 7 cases during the Games, 7 horse doping cases, and 5 cases by further analysis.

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Table 2. The “spirit of sport” is characterized by these values

- Ethics, fair play and honesty
- Health
- Excellence in performance
- Character and education
- Fun and joy
- Teamwork
- Dedication and commitment
- Respect for rules and laws
- Respect for self and other participants
- Courage
- Community and solidarity

World Anti-Doping Code, 2009

The WADC identifies eight items as indicators of doping (Table 3), including a positive doping test, proof of doping by testimony, refusal to undertake doping tests, and acts of staff complicity. In addition, the WADC has five International Standards, which are “Prohibited List”10), “Testing”11), “Therapeutic Use Exemptions”12), “Laboratories”13), and “The Protection of Privacy and Personal Information”14). The WADC and 5 International Standards are universal anti-doping rules to which all sport participants are held (Fig. 1). Any athlete who violates these regulations is subject to sanctions. The WADC and International Standards are revised every several years, with the “Prohibited List” revised annually. We must therefore refer to the most recent version of the WADC, which can be easily obtained via the WADA website. A translated Japanese version can be accessed on the JADA website as well.
The WADC Prohibited List is the sole list of prohibited substances and methods. The annual Prohibited List is valid from January 1st to December 31st of a given year. WADA considers including a substance or method on the Prohibited List when the substance or method in question meets any two of the following three criteria: (1) the substance or method has the potential to enhance athletic performance; (2) the substance or method represents a potential health risk to the athlete; (3) WADA determines that the use of the substance or method violates the spirit of sport. A substance or method is also included on the Prohibited List if the substance or method has the potential to mask the use of other prohibited substances or methods.

As the Prohibited List is revised annually, we here describe the current version. The 2013 Prohibited List is composed of three categories (Table 4). SUBSTANCES AND METHODS PROHIBITED AT ALL TIMES (IN-AND OUT-OF-COMPETITION) comprise prohibited Substances (S) and Methods (M) for both In-Competition and Out-of-Competition doping tests. In-Competition refers to the period commencing twelve hours before a competition to the end of such a competition and the sample collection process (defined in WADC). Out-of-Competition doping tests are performed with no advance notice at a practice site or athlete accommodations. SUBSTANCES AND METHODS PROHIBITED IN-COMPETITION are prohibited for only In-Competition doping tests. SUBSTANCES PROHIBITED IN PARTICULAR SPORTS are prohibited only for the sports listed in this category. All prohibited substances are Specified Substances except for those substances in classes S1, S2, S4.4, S4.5, S6.a, and Prohibited Methods M1, M2 and M3. Class S1 is ANABOLIC AGENTS, and S2 is PEPTIDE HORMONES, GROWTH FACTORS AND RELATED SUBSTANCES. The period of ineligibility...
for the violation of Specified Substances can possibly be reduced in certain circumstances.

**S1. ANABOLIC AGENTS**

“Anabolic” refers to the synthesis of organic substances such as protein. Anabolic agents generally have muscle-building effects. Anabolic Androgenic Steroids (AAS) and Other Anabolic Agents are listed in S1. AASs are androgens and related substances, and are classified as either exogenous or endogenous AASs. A doping violation results if exogenous AASs are detected in an athlete. However, as endogenous AASs are normally physiologically present in the body, an athlete is considered to have committed a doping violation only when it is demonstrated by a specific assay that endogenous AASs in the sample were produced outside the athlete’s body. AASs are contained in tonics and topical applications for facial hair growth, as well as supplements that can be purchased via the Internet. Clenbuterol is an example of an Other Anabolic Agent, and incidents of clenbuterol food contamination occurred in 2011.15)

**S2. PEPTIDE HORMONES, GROWTH FACTORS, AND RELATED SUBSTANCES**

Erythropoietin (EPO) increases erythrocytes and enhances endurance. Chorionic Gonadotrophin (CG) and Luteinizing Hormone (LH) stimulate endogenous androgen production and increase muscle volume.

**S3. BETA-2 AGONISTS**

Beta-2 agonists are essential medicines for treating asthma. It is reported that the prevalence of asthma (including exercise-induced bronchospasm) is relatively high in athletes. With regards to the balance between doping regulations and the need for legitimate therapeutic use, minor changes have been effected for the regulation of beta-2 agonists. In the 2013 Prohibited List, all beta-2 agonists are prohibited, except for inhaled salbutamol, inhaled formoterol, and salmeterol (Table 5). It should be noted that tulobuterol is a beta-2 agonist and tulobuterol patches are used for asthma or severe coughs.

**S4. HORMONE AND METABOLIC MODULATORS**

This group contains aromatase inhibitors, selective estrogen receptor modulators (SERMs), other anti-estrogenic substances, insulin and Peroxisome Proliferator Activated Receptor δ (PPARδ) agonists (e.g., GW 1516). These substances are used to treat breast cancer, osteoporosis, infertility and diabetes. In 2013, WADA was alerted that GW 1516, an experimental drug later withdrawn due

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**Table 4. 2013 Prohibited List**

| SUBSTANCES AND METHODS PROHIBITED AT ALL TIMES (IN- AND OUT-OF-COMPETITION) |
|-------------------------------|------------------|---------------|
| S0. NON-APPROVED SUBSTANCES    | S1. ANABOLIC AGENTS |
| S2. PEPTIDE HORMONES, GROWTH FACTORS AND RELATED SUBSTANCES | S3. BETA-2 AGONISTS |
| S4. HORMONE AND METABOLIC MODULATORS | S5. DIURETICS AND OTHER MASKING AGENTS |
| M1. MANIPULATION OF BLOOD AND BLOOD COMPONENTS | M2. CHEMICAL AND PHYSICAL MANIPULATION |
| M3. GENE DOPING               |                  |

**SUBSTANCES AND METHODS PROHIBITED IN-COMPETITION**

| S6. STIMULANTS |
| S7. NARCOTICS |
| S8. CANNABINOID |
| S9. GLUCOCORTICOSTEROIDS |

**SUBSTANCES PROHIBITED IN PARTICULAR SPORTS**

| P1. ALCOHOL |
| P2. BETA-BLOCKERS |

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**Table 5. Medications for Asthma**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Category</th>
<th>Inhalation</th>
<th>Other Routes (oral, intravenous, patch, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>salbutamol</td>
<td>S3. BETA-2 AGONISTS</td>
<td>○</td>
<td>×</td>
</tr>
<tr>
<td>formoterol</td>
<td>S3. BETA-2 AGONISTS</td>
<td>○</td>
<td>×</td>
</tr>
<tr>
<td>salmeterol</td>
<td>S3. BETA-2 AGONISTS</td>
<td>○</td>
<td>—</td>
</tr>
<tr>
<td>other Beta-2 agonists</td>
<td>S3. BETA-2 AGONISTS</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>glucocorticosteroids</td>
<td>GLUCOCORTICOSTEROIDS</td>
<td>○</td>
<td>×</td>
</tr>
<tr>
<td>clenbuterol</td>
<td>S1. ANABOLIC AGENTS</td>
<td>—</td>
<td>×</td>
</tr>
</tbody>
</table>

○: permitted ×: prohibited —: not applicable
to its carcinogenicity\(^{16}\), was being sold on the black market and used by some athletes.

**S5. DIURETICS AND OTHER MASKING AGENTS**

Masking agents conceal the use of other prohibited substances or prohibited methods. Diuretics are used for weight reduction and to dilute the concentration of prohibited substances in a urine sample. Diuretics are often prescribed for hypertension. Plasma expanders and desmopressin change blood plasma volume and hematocrit, masking the effect of EPO. Glycerin loading is prohibited for plasma expander action. Probenecid, a medicine for hyperuricemia (gout), suppresses the urinary excretion of other prohibited substances.

**M1. MANIPULATION OF BLOOD AND BLOOD COMPONENTS**

Blood transfusions are prohibited, as increasing erythrocyte levels enhance endurance performance. Blood cleansing is prohibited under M1. Oxygen supplementation is, however, not prohibited.

**M2. CHEMICAL AND PHYSICAL MANIPULATION**

A previous case was recorded where an athlete submitted another individual’s urine sample instead of his own in a doping test. Intravenous infusions and/or injections of more than 50 mL per 6 hour period are prohibited except in the case of legitimate medical treatment.

**S6. STIMULANTS**

Stimulants are classified as Non-Specified Stimulants (Non-Specified Substances) or Specified Stimulants (Specified Substances). Non-Specified Stimulants include amphetamines, cocaine and modafinil. ephedrine, pseudoephedrine and methylephedrine are classified as Specified Stimulants, included in medicines for the common cold and rhinitis. Ma huang and nux vomica are raw materials used in herbal medicine, which include Specified Stimulants. It should be noted that there are many kinds of supplements containing methylhexanamine\(^{17}\).

**S9. GLUCOCORTICOSTEROIDS**

Glucocorticosteroids are steroids other than ASSs. Because glucocorticosteroids have strong anti-inflammatory effects, they are often used for treatment. Glucocorticosteroids administered by systemic routes (oral, intravenous, intramuscular and rectal) are prohibited, but glucocorticosteroids administered by non-systemic routes (intraarticular / periarticular / peritendinous / epidural / intrathecal / intradermal injections and inhalation) are not.

**Therapeutic Use Exemptions**

Therapeutic Use Exemptions (TUE) constitute permission to use prohibited substances or methods for therapeutic purposes. Athletes who have not been granted TUEs cannot use prohibited substances or methods even for legitimate therapeutic purposes. If an athlete requires the use of prohibited substances or methods for emergency therapeutic purposes, he/she may apply for a TUE retroactively. When a prohibited substance is detected in a doping test sample, it is very important to ascertain whether or not the athlete has been granted a TUE. If so, the doping test is negative, if not, it is positive (Fig. 2).

International athletes submit their TUE applications to their respective International Federations, and national athletes submit their applications to their National Anti-Doping Organizations (JADA in Japan) (Table 6). Not all
Testing Authorities conduct doping tests and usually manage the results. Testing Authorities are Anti-Doping Organizations such as the International Olympic Commit-

Table 6. Roles of International Federation and National Anti-Doping Organization in TUE application

<table>
<thead>
<tr>
<th>Athletes who may request TUEs</th>
<th>International Federation</th>
<th>National Anti-Doping Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athletes in the International Federation's Registered Testing Pool</td>
<td>Athletes participating in an International Event for which a TUE granted pursuant to the International Federation's rules is required</td>
<td>Athletes in the National Anti-Doping Organization's Registered Testing Pool</td>
</tr>
</tbody>
</table>

TUE applications are approved. Relevant TUE Committees review each TUE application and decide according to the International Standard for TUE criteria (Table 7). Each TUE Committee should include at least three physicians.

JADA receives more than 100 TUE applications annually (Fig. 3). JADA has annually published the TUE guidebook for medical doctors since 2007, and has prepared a “Medical Information Form for Beta-2 Agonists” for applicant convenience.

Doping Control

Doping Control refers to all steps and processes related to doping tests (Fig. 2). Those steps consist of test distribution planning, sample collection and handling, laboratory analysis, therapeutic use exemptions, results management, and hearings. “Testing” collectively refers to the parts of the Doping Control process involving test distribution planning, sample collection, sample handling, and sample transport to the laboratory. Testing is conducted pursuant to the WADC International Standard for Testing. Sample collection and sample handling are carried out by Doping Control Officers at Doping Control Stations. Doping Control Officers operating in Japan have been trained and certified by JADA.

Fig. 3 TUE applications to JADA
Abbreviated TUE process abolished in 2009.

Table 7. Criteria for TUE

A TUE will be granted only in strict accordance with the following criteria:

a. The Athlete would experience a significant impairment to health if the Prohibited Substance or Prohibited Method were to be withheld in the course of treating an acute or chronic medical condition.

b. The therapeutic use of the Prohibited Substance or Prohibited Method would produce no additional enhancement of performance other than that which might be anticipated by a return to a state of normal health following the treatment of a legitimate medical condition. The use of any Prohibited Substance or Prohibited Method to increase “low-normal” levels of any endogenous hormone is not considered an acceptable therapeutic intervention.

c. There is no reasonable therapeutic alternative to the use of the otherwise Prohibited Substance or Prohibited Method.

d. The necessity for the use of the otherwise Prohibited Substance or Prohibited Method cannot be a consequence, wholly or in part, of the prior use, without a TUE, of a substance or method which was prohibited at the time of use.
doping tests were carried out and 2,885 Adverse Analytical Findings (1.2%) were reported.

The National Sports Festival is the largest annual national sports event in Japan. Doping control for the National Sports Festival started in Shizuoka in 2003. Twenty-four In-Competition Tests were carried out at the 67th Winter Games in January 2012, and 173 In-Competition Tests and 50 Out-of Competition Tests were performed at the 67th Games in Gifu in October 2012. A single positive case has not been detected at the National Sports Festivals since 2003, showing that most Japanese athletes are clean.

Japanese Initiatives in Anti-Doping

JADA has set up a “JADA Car” that serves as a multifunction anti-doping mobile unit. The JADA Car has 3 functions, a Doping Control Station, a laboratory for blood analysis, and an educational outreach booth. The JADA Car can perform both doping tests and anti-doping educational programs anytime, anywhere.

JADA additionally launched the sports pharmacist system in 2010. Pharmacists train in basic sports medicine and anti-doping, and then are certified as sports pharmacists. These certified sports pharmacists are experts in prohibited substances, and advise athletes and anyone involved in sports. Over 5,000 sports pharmacists have been certified by JADA and are currently working.

The Japanese national high school curriculum for 2013 includes anti-doping education. Students learn the values of athletics and the basic principles of anti-doping. We expect that this curriculum will increase the appreciation of athletic values in Japanese society and promote anti-doping activities.

References


