

# Points to Consider

Identification of Compounds with  
Potential for Doping Abuse and  
Sharing of Information  
with WADA

## 2 FIELDS 1 GOAL

Protecting the Integrity of Science and Sport



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# POINTS TO CONSIDER

## Identification of Compounds with Potential for Doping Abuse and Sharing of Information with WADA

### 1. INTRODUCTION

#### 1.1 Background and Rationale

With the increasing focus on assuring safe use provisions throughout the lifecycle of medicines, it is difficult for drug developers to believe that there is a growing group of users and their enablers for whom safe use provisions are irrelevant. With the increased rewards on offer to sportsmen and women in the modern era, athletes are under increasing pressure to achieve better, faster, longer and stronger performances. With the difference between being the best and the “also ran” becoming smaller and smaller, the temptation to look for alternative ways to achieve a competitive edge increases with every passing year. Performance-enhancing drugs have probably been a part of top-flight sport for decades in the modern Olympics era. In order to maintain a level playing field, drug testing is now an everyday part of the professional athlete’s life. However, as tests have become more sophisticated so, too, have the cheats. Today it is not only the more traditional steroids and beta-blockers being abused. Almost any new drug is being viewed as possibly having the potential to enhance performance in one or more sports.

The World Anti-Doping Agency (WADA) is the independent international organization created in 1999 to promote, coordinate and monitor the fight against doping in sport in all its forms. In order to do this effectively, WADA needs the cooperation of the biotechnology and pharmaceutical industries to proactively identify products with the potential for abuse, and to develop testing methods to detect illegal use.

Such collaboration has, until recently, been initiated on an ad hoc basis. To mark a formal commitment to the collaboration between the biotechnology and pharmaceutical industries and WADA, IFPMA and WADA signed a joint agreement in July 2010 [1], followed shortly thereafter by similar agreements between WADA and a number of individual companies, as well as endorsement by U.S. BIO in June 2011.

## 1.2 Purpose of this *Points to Consider* Document

The purpose of this booklet is to provide practical guidance for identifying pipeline compounds with a potential for sports-related abuse and for sharing this information with the World Anti-Doping Agency (WADA). The advice provided in this booklet represents current best practices and has been agreed with WADA. This includes template documents for Confidentiality Agreements and a Memorandum of Understanding [2] to facilitate interactions between companies and WADA, which are based on several years of experience in collaboration between WADA and industry. Signature of such an agreement, however, is not a prerequisite for collaboration with WADA.

This booklet also applies to compounds that fail to complete all drug development stages, and do not achieve commercial viability, since these fall into a less well-controlled “grey zone.” While compounds that complete all stages of development and are granted marketing authorization are highly visible, well documented and well regulated, experience has shown that those for which development is discontinued may provide substantial doping abuse potential while having low visibility and less control and oversight. Such compounds are particularly attractive to “high-profile abusers” because they are thought to be unknown, hence undetectable, and are likely to be part of a tailor-made doping regimen, thus conferring significant competitive advantage.

To optimize the chances of adoption and implementation, any procedure developed by a company should provide a balance between theoretical stringency and the day-to-day realities of the work in both WADA and the biotechnology and pharmaceutical industries. Thus, the intention is to provide a simple, intuitive and transparent process that:

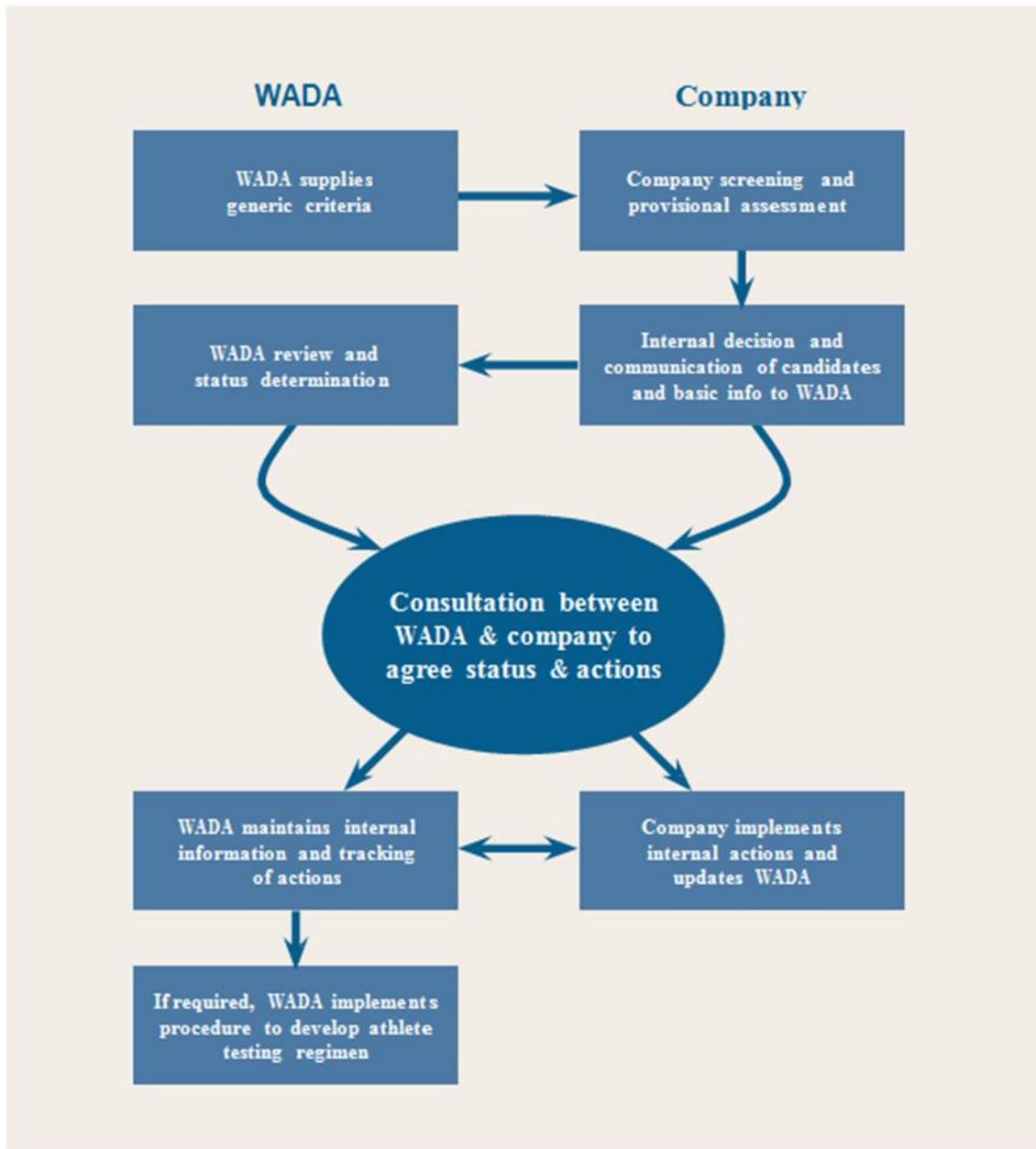
- Optimizes effectiveness and efficiency
- Avoids undue workload
- Protects proprietary information
- Ensures that time, effort and resources are focused on compounds with genuine abuse potential as opposed to hypothetical “noise”
- Avoids creation of a standalone bureaucracy

In keeping with these criteria, many of the processes described in this document can be integrated easily into a company’s existing processes for assessing compounds for other kinds of abuse (e.g., physical and psychological addiction, misuse and diversion/counterfeiting).

## 2. PROCESS OVERVIEW

Figure 1 provides an overview of the process and information flow.

**Figure 1. Overview of Process and Information Flow**



### 3. IDENTIFICATION OF COMPOUNDS WITH DOPING ABUSE POTENTIAL

#### 3.1 Basis for Identification

The WADA Code [3] (Section 4.3) defines the high-level criteria that determine whether a compound should be included in the Prohibited List. This, together with the Prohibited List [4], provides useful guidance in identifying the classes of agents that have a mechanism of action or effects that may be misused for performance enhancement. For novel compounds not covered by the Prohibited List, however, such potential is difficult to assess and is more reliant on observed effects. In this context, it is useful to consider the types of effects that may lead to enhanced performance in different types of sports. These effects vary according to the sport, and include, but may not be limited to, pro-cognitive or pro-cardiorespiratory effects. The in-house review process for individual compounds, depending on the stage of development (i.e., amount of data available), can apply one or more approaches:

- **Structure:** possibility for comparison with chemical structures of existing performance-enhancing agents
- **Mechanism of action:** identification of potential mechanisms likely to yield performance enhancement (e.g., various measures of enhanced physical or mental endurance, stimulatory effects, muscle growth, stimulation of haematopoietic cell production, reduced susceptibility to muscle or tendon injury)
- **Observed effects in animals or humans:** this may include unexpected effects such as CNS stimulatory effects (e.g., insomnia, euphoria, aggression), increased energy levels, reduction in fatigue, loss of appetite, increase of appetite, weight loss, etc., that may be indicative of potential for misuse

#### 3.2 In-house Review Process and Assessment of Doping Abuse Potential

##### 3.2.1 Rating of Doping Potential

Compounds should be assessed in-house by the company at different stages of development and rated for their potential for doping abuse. Subsequent actions would be determined on the basis of this rating, which may change during the course of nonclinical and clinical development. An example of such a rating system is provided in Table 1.

To minimize “noise” and unnecessary workload, WADA would be notified only of those compounds with likely or confirmed doping potential (categories C and D in the example).

**Table 1. Doping Potential Ranking and Associated Actions (Example)**

Status ranking*	Actions
A. No or negligible doping potential	<ul style="list-style-type: none"> <li>Routine monitoring during development – do not inform WADA</li> </ul>
B: Possible doping potential	<ul style="list-style-type: none"> <li>Monitoring during development, with additional assessments to further evaluate risk – do not inform WADA</li> </ul>
C: Probable doping potential	<ul style="list-style-type: none"> <li>Enhanced safety risk evaluation within company</li> <li>Assessment of risk during formal in-house reviews</li> <li>Consultation with WADA to further evaluate risk and supply additional data</li> </ul>
D. High risk of doping potential	<ul style="list-style-type: none"> <li>Defined in consultation with WADA</li> <li>“Task force”</li> <li>Dedicated safety risk evaluation</li> <li>Measures to control drug access</li> <li>Detailed info to WADA on detection measures, clinical indicators and other support</li> <li>Frequent communication between company &amp; WADA</li> </ul>

\* a compound may switch ranking during the course of development depending on the accruing data

Risk assessment templates have been developed to help companies establish anti-doping risk assessment procedures. These comprise:

- **Risk Assessment Checklist** [5]: MS Word table that outlines mechanisms and observed effects likely to yield performance enhancement, plus a listing of categories derived from the WADA Prohibited List.
- **Structural Similarity Tool** [6]: MS Excel database that includes substances on the WADA Prohibited list along with corresponding structures and Simplified Molecular Input Line Entry System (SMILES) nomenclature. SMILES is a chemical notation system designed for chemical information processing that can be integrated into chemical software platforms used by the biotechnology and pharmaceutical industries to conduct substructure searches of their compound collections.
- **Compound Anti-Doping Status Report** form [7]: MS Word table that can be used to track risk assessment status for individual compounds.

These tools can be downloaded from the IFPMA website by clicking on the links provided in the references list. These are provided in a generic format that can be

customized to complement procedures adopted from this “*Points to Consider*” guidance by an individual organization.

### **3.2.2 Products in Non-Clinical Development**

It is anticipated that sufficient evidence for characterization of doping abuse potential would be provided by standard biochemical and *in vitro* and *in vivo* pharmacological characterization, without requiring additional studies.

To a great extent, consideration of risk at very early stages will be based on structure and mechanism of action (see Section 3.1).

It is recommended that consideration of doping abuse potential be included in routine review by internal bodies, such as a nonclinical safety review committee.

### **3.2.3 Products in Clinical Development**

It is recommended that the review of data relevant to doping abuse potential be included prospectively in the routine safety risk evaluation and management for each compound, based on considerations under Section 3.1, and that regular safety review within the company address the question of doping abuse potential.

For compounds for which a doping abuse potential has been identified on the basis of nonclinical development, data collection and/or analysis in clinical trials can be adapted to make specific provision for adequate follow up, as would be the case for any nonclinical safety concerns.

For products proceeding to health authority filings, the absence of, or potential for, doping abuse can be documented in regulatory submissions pertaining to misuse potential and risk management, e.g. EU Risk Management Plan Sections II SVI.3 (*Potential for Misuse for Illegal Purposes*) and II SVI.5 (*Potential for Off-label Use*) [8].

### **3.2.4 WADA Consultation**

Information is shared with WADA on a voluntary basis. It is recommended that WADA be contacted only for those compounds for which in-house review indicates a likely or probable doping abuse potential. It is not intended to involve WADA in in-house review procedures or to share information on compounds without at least a probable doping risk potential (see Section 3.2.1).

## **4. SHARING OF INFORMATION WITH WADA**

### **4.1 Procedure**

1. A designated contact person from the company contacts the WADA Science Department in writing at its dedicated e-mail address: [science@wada-ama.org](mailto:science@wada-ama.org).
2. An initial contact either in writing (documents) or verbally (teleconference) will allow WADA to rapidly assess the doping potential of the compound(s).
3. If the doping potential is confirmed by WADA, a confidentiality agreement (CDA) is signed, unless a blanket agreement covering multiple programmes is already in place, in which case the protections afforded by that agreement may be sufficient.
4. When the CDA is in place, specific confidential information is provided in order for WADA to complete its assessment process.
5. At the end of the assessment process, if deemed necessary, WADA will provide the company with a list of information and specific resources (i.e., reagents) needed to further develop an anti-doping method.

### **4.2 Timing**

Initial and updated information is supplied as it becomes available. There is no requirement for routine reporting or updating to WADA, e.g., annual report.

### **4.3 Nature and Format of Information to be Shared with WADA**

In WADA and for each company, it is recommended that a key contact person be designated to simplify and streamline general communications. All information exchanged between the company and WADA about compounds having doping potential would be conveyed via the identified contact persons.

If a compound is determined to have genuine doping potential, additional dedicated communication channels would be established.

The product Investigator Brochure (IB) may be a suitable vehicle for information, although it contains information that a company may not wish to share. Alternatives may be an extract from the IB or a standard form providing key information.

Information would be shared only with WADA and not with any third parties such as other biotechnology or pharmaceutical companies. Security of the information within WADA to prevent unauthorized access would be assured.

Protection of proprietary information would be achieved by means of a confidentiality agreement. To minimize administrative workload, a generic template, to cover all compounds of interest at the company, has been developed with WADA for use as a starting point [2]. This may be adapted or added to, as appropriate, for a given situation.

#### **4.4 Decision on Doping Potential**

On the basis of the review process defined above, the company performs an internal assessment of doping abuse potential. An example of a ranking system and associated actions is provided in Table 1. For those agents with at least a probable assessment, the information described in Section 4.3 is supplied to WADA.

Based on the information received, WADA will define the doping potential of the compound(s) and will agree on the next steps with the company. If a genuine doping abuse potential is confirmed by WADA, the actions described in Section 5 will be undertaken.

### **5. ACTIONS IN CASE OF GENUINE DOPING ABUSE POTENTIAL**

#### **5.1 In-house Measures**

Once a genuine doping risk has been identified in agreement with WADA, it may be useful to set up within the company a dedicated subteam of the product team for each compound with an identified doping risk potential. This group would be responsible for sharing information and materials with WADA.

It may be of utility to maintain a “reference resource centre” with examples of best practices, etc., within the appropriate department within each company. This would advise and support product teams as they review and evaluate compounds, act as the initial go-between for the company and WADA and support a product team in setting up the dedicated task force, if this is called for.

#### **5.2 WADA Needs for Testing Strategy**

WADA will provide the list of information and specific resources needed in order to develop an anti-doping method, and will identify the process and anticipated timeline to be followed. Particular emphasis will be placed on the intervention, if needed, of external parties (e.g., WADA accredited laboratories).

The company and WADA will exchange information on the drug development and on the development and implementation of the anti-doping method(s) at a frequency agreed by the two parties. This will include:

- Full information on mechanism of action, structure, receptor targets, abuse potential, preclinical and clinical indicators, pharmacokinetic and pharmacodynamic characteristics, as required by the individual case
- Information on detection (concentrations in blood or tissue, surrogate indicators, diagnostic tests, etc.)
- Support in validating detection methods (e.g., excretion studies to validate anti-doping methodology)

- Supply of materials requested for testing (e.g., specific reagents, reference samples, etc.)
- Information on anti-doping test development, any potential improvement in the detection method and the implementation of the method in anti-doping activities (provided by WADA to the company)

### **5.3 Company Actions to Control Access**

Storage and transport of bulk materials or finished product, including both commercial and clinical trial supplies, represent potential vulnerabilities that can be exploited to divert materials for inappropriate use.

#### **5.3.1 Control of Manufacturing Information**

This should be governed by internal company-specific procedures.

#### **5.3.2 Bulk Materials**

Access to bulk materials is governed by internal company-specific procedures.

If development is discontinued, secure storage or secure destruction measures should be developed and communicated to WADA.

#### **5.3.3 Clinical Trial Supplies**

Experience has shown that clinical trial facilities may be vulnerable to diversion of clinical trial supplies with doping potential from their intended use in clinical trials to misuse for doping purposes by athletes or their entourage.

Existing company standard operating procedures for control of clinical trial supplies may provide sufficient protection. However, in the case of compounds where, for example, unused material could be collected from containers discarded after administration (e.g., residue in used vials), additional measures may be required to collect and destroy such material. Additional information to the staff at the investigational site on the doping potential of a new drug in clinical trials and recommendations for enhanced vigilance in control of drug dispensing, storage conditions or supply management may be helpful under such circumstances. Such measures would be determined on a case-by-case basis.

#### **5.3.4 Access to Commercial Product**

Special measures may be required to ensure that commercial product is used only for the authorized purpose. Examples of such measures include controlled dispensing and prescription measures, or patient registries. Such measures would be determined on a case-by-case basis.

WADA should be notified if drug supplies disappear or are stolen, including information on quantity, location, batch numbers, etc.

## 6. IMPLEMENTATION

Each company should define its own internal process for review of doping abuse potential for compounds, consistent with applicable regulatory requirements and the company's Standard Operating Procedures.

In terms of WADA interaction, implementation of this "*Points to Consider*" booklet can be staged to prioritize late-phase development compounds (Phase IIb-III), progressing to early development phase compounds in the later stages of implementation.

## 7. REFERENCES

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