DOPING AUTORITEIT

Regarding: Netherlands reaction to draft 2015 Prohibited List International Standard (a shared submission of four stakeholders)

Capelle aan den IJssel, 25-07-2014

Dear Mr. Howman and members of WADA's Prohibited List Expert Group,

Thank you very much again for the invitation to review the new draft of the Prohibited List International Standard. With this letter, I would like to provide you with the comments of four Dutch stakeholders, being:

- the Ministry of Health, Welfare, and Sports,
- the Netherlands Olympic Committee*Netherlands Sports Confederation (NOC*NSF),
- the NOC*NSF Athletes' Commission, and
- the Anti-Doping Authority the Netherlands.

On behalf of these four organisations I would like to ask you to treat this letter as a fourfold contribution to your consultation process.

As usual, we have used our continuous relationship with athletes, physicians, pharmacists, and scientists over the previous year to collate our remarks and comments. In case the work of the Expert Group can be helped by explaining our proposals in more depth or by providing alternative proposals or more data we would be more than happy to assist.

With sincere greetings and the best wishes in your efforts to compile the final version of the 2015 Prohibited List,

Also on behalf of the Ministry of Health, Welfare, and Sports, the Netherlands Olympic Committee*Netherlands Sports Confederation (NOC*NSF), and the NOC*NSF Athletes' Commission,

Anti-Doping Authority the Netherlands

Herman Ram
CEO

Introduction

We thank you for the changes that were introduced in the Prohibited List last year; we feel the Prohibited List has increased in strength because of the changes that were introduced. We hope that with the continuous support of all stakeholders the process of improving the Prohibited List International Standard will continue.

In this reaction we will first elaborate on the criteria we used in the review process. Subsequently we will address our proposals. We have divided our comments in two separate paragraphs: major points of consideration and other points of consideration.

Review criteria

As always, we have followed the subsequent criteria in reviewing the Prohibited List International Standard:

- the List should optimise the possibility to catch cheating athletes and their support personnel by prioritising on the criterion of performance enhancement;
- it should minimise the impact on good-willing athletes, which means it is as short as possible, but as long as necessary;
- it should minimise the requirements for good-willing physicians and other support personnel;
- it should not interfere with guidelines of good medical practice and focus on the issue of doping in sports;
- it should be easily explainable to athletes, their support personnel and the general public, so these groups will not be alienated from anti-doping efforts in general.

Generally speaking, there are two keywords that arise from our proposals and comments: clarity and transparency. The Prohibited List should be clear to everyone involved and the anti-doping community should be able to publicly explain the outcomes of the decisions that are ultimately made by the Prohibited List Expert Group. By adhering to these characteristics, we feel that the Prohibited List will be optimally focussed, practical, and understandable to everyone involved, thereby strengthening the World Anti-Doping Program.

Major points of consideration

Thyroid Hormones

The 2015 Prohibited List is very complete. However, we want to stress the importance of adding thyroxine (T4), triiodothyronine (T3), Thyroid Stimulating Hormone (TSH) and Thyrotropin-Releasing Hormone (TRH). Although there is no hard scientific evidence that the substances have the potential to improve performance, there are persistent rumours of competitive athletes using it. Theoretically, there might be a weight-loss effect with the concomitant increased availability of energy substrates. Together with the well-known and longstanding abuse of this substance in the world of bodybuilding and fitness (e.g. McKillop, Scott Med J, 32(2):39, 1987 and Auge & Auge, Subst Use Misuse, 34(2):217, 1999) we feel there is sufficient evidence that thyroid hormones fulfil the Code-criterion 4.3.1.1 (‘Medical or other scientific evidence, pharmacological effect or experience that the substance or method, alone or in combination with other substances or methods, has the potential to enhance or enhances sport performance’). Also, it is clear that the abuse of these substances is a potential health risk (e.g. Roti et al., Endocr Rev, 14(4):401, 1993). All in all, in our view the addition of thyroid hormones to the prohibited list is long overdue.

- We would strongly suggest to add thyroxine (T4), triiodothyronine (T3), Thyroid Stimulating Hormone (TSH) and Thyrotropin-Releasing Hormone (TRH) to the 2015 Prohibited List, with the most appropriate section in the current draft version being S2.

Cannabinoids
We are of the opinion that the use of a substance that is 'most likely to have a negative impact on athletic performance' (such as cannabis), should not be part of the anti-doping program, especially when its use has been out-of-competition. Athletes, being role models to the young, should not be using marihuana nor should they engage themselves in morally objectionable activities such as speeding when driving a car or even smoking in their private lives. These activities, however, are not doping issues, and they should not lead to severe doping sanctions. We are aware of the various views that exist on this issue, but we would like to ask you to try and find a solution that is less rigorous than the current prohibition.

At a fundamental level, we feel it is unfair to sanction athletes on the basis of presence of a long-lasting metabolite in an athlete's sample when this particular substance is only prohibited in-competition. The reports of Brenneissen et al. (Anal Bioanal Chem (2010) 396:2493–2502) and Mareck et al. (Drug Test Anal (2009) 1(11-12): 505-510) give sophisticated alternative approaches to this fundamental issue in the case of cannabis. In our view it is better to address this issue on the basis of clear science, instead of the political decision to raise the decision limit for the main cannabis-metabolite in TD2013DL and TD2014DL.

Splitting up section S2
In our opinion we should be able to easily explain every section of the Prohibited List in our education sessions. This is not the case with section S2 (and in lesser extent with section S4). Over the years section S2 of the Prohibited List has grown in name and in content. In 2004 it had the short name *Peptide Hormones*, in 2014 the name of this section has evolved to the much longer *Peptide Hormones, Growth Factors, Related Substances and Mimetics*. We feel this is too long and too complex for one section. Also, the name implies this section captures all of the prohibited peptide hormones. This is not the case, as insulins are currently categorized under section S4. Besides that, we feel some of the different subsections are weakly related to each other and are better suited in other sections.

- We suggest to rename section S2 in *Erythropoietin-related substances*, to move subsection 2.3 and 2.5 to section S1. *Anabolic Agents* and to move subsection 2.4 to section S9. *Glucocorticosteroids*.

Other points of consideration

S1
Both nandrolone and 19-norandrostenedione are still listed in section S1-1a ("Exogenous AAS") even though it has been known for years that these substances can be produced endogenously. For example, Hemmersbach and colleagues stated in 2006 "The first reports of human, in vivo production of nandrolone in the ovarian follicle were published 15–20 years ago" (Biomed Chromatogr 20(8): 710-717) and Kicman has stated in 2010 "adverse findings for nandrolone are frequent, but this steroid and 19-norandrostenedione are also produced endogenously" (Handb Exp Pharmacol 2010; 195:25-64).

- We suggest that both nandrolone and 19-norandrosterone are moved to section b of S1-1. Since they can be produced endogenously, that would be a more suitable place.

S2

We support the swift actions taken by WADA to explicitly place the use of HIF-activators on the Prohibited List earlier this year. This shows WADA is taking rumours serious and is willing to take immediate actions. In our opinion this strengthens the public's opinion on power of the anti-doping community in the fight again doping. At the same time, we like to stress that mid-term amendments can require extra educational efforts (e.g. printed materials) and therefore we ask to keep these sudden amendments to a minimum.

Furthermore, we are curious about the rationale to explicitly list both xenon and argon. As far as we know, only xenon has the potential to enhance performance. However, if it is decided to include argon, it would be only logic to mention similar noble gases like helium as well.

- Please provide the rationale (scientific, practical or otherwise) for listing argon besides xenon on the Prohibited List and not including other noble gases like helium. Furthermore, please give us insight on the status of helium, is its use permitted or prohibited?

In addition, the Explanatory Notes make clear that the use of cyanocobalamin (vitamin B12) is not prohibited. However, over the years these remarks will no longer be easily available.

- In order to avoid confusion we feel it is necessary to explain the permitted status of cyanocobalamin (vitamin B12) in the Prohibited List itself. This could, for example, be done in a similar way to the remarks regarding felypressin (in section S5) or imidazole and adrenaline (in section S6).

In January 2011, we welcomed the removal of the methods of injecting "Platelet Rich Plasma" (PRP) or "Platelet Leukocyte Gel" (PLG) in therapeutic settings from this section. This was explained in the Explanatory Notes. In line with cyanocobalamin (vitamin B12), over the years these remarks will no longer be easily available. On several occasions this has given rise to confusion in our medical community, especially since PRP fits into the current definition of "gene doping", which includes "the use of normal … cells".

- In order to avoid confusion we feel it is necessary to explain the permitted status of therapeutical PRP and PLG in the Prohibited List itself. This could, for example, be done in a similar way to the remarks regarding felypressin (in section S5) or imidazole and adrenaline (in section S6).

Section S2 is extended with the group 'Non-erythropoietic EPO-Receptor agonists'. However, we have no information that this group of substances is misused, nor that it has the power to increase performance.

- Please provide the rationale for introducing the group 'Non-erythropoietic EPO-Receptor agonists' in section S2.

For editorial reasons, subsection 2.5 ends with the phrase "…and other substances with similar chemical structure or similar biological effects". However section S2 itself already starts with the phrase "The following substances, and other substances with similar chemical structure or similar biological effect(s), are prohibited:". That is why we feel the phrase at the end of subsection 2.5 should be removed (if this section remains unchanged in structure; see our previous comment on 'Splitting up section S2').

- We suggest to remove the phrase "…and other substances with similar chemical structure or similar biological effects" at the end of subsection 2.5.

Also for editorial reasons, all enumerations in the Prohibited List are in alphabetical order, except the enumerations in section S2.

- We suggest to place the enumerations in section S2 in alphabetical order, in line with the rest of the Prohibited List.

S3
The rules for all inhaled β2-agonists should be in line with each other. Over the past few years, scientific literature has well established that inhaled β2-agonists have no proven performance enhancing effect on endurance, strength and sprint performance in healthy athletes (see e.g. Pluim et al., Sports Med 41(1): 39-57, 2011). In this light, it is very surprising to have different rules for salbutamol, salmeterol, and formoterol on one hand, and the other inhaled β2-agonists on the other hand. In fact, this demarcation in the anti-doping rules is interfering in a physician's decision to prescribe certain medication.

- We strongly suggest that WADA will allow the use of all inhaled β2-agonists when taken by inhalation in accordance with the manufacturers' recommended therapeutic regimen.

S4
No changes have been proposed, but our comment from last years is still valid: the decision to move insulins to section S4 without copying the words "releasing factors" and "other substances with similar chemical structure or similar biological effect(s)" means that the substances exenatide and liraglutide are permitted per 1-1-2013. We are curious about the backgrounds that have led to this decision.

- Please provide the rational (scientific, practical or otherwise) for permitting two substances that have been banned in the past.
- For editorial reasons: for the sake of consistency, it would be better to conclude each subsection with a semicolon (;) and to conclude the final subsection (in this case 5) with a period (.), just like has been done in sections S3 and M3.

S5
- For editorial reasons: in listing the examples of plasma expanders it would be better to say "…intravenous administration of albumin, dextran, hydroxyethyl starch **and/or** mannitol…" instead of **and**, since this implies that it might only be prohibited when all substances are intravenously administrated.

M2
Subsection 2.2 deals with the intravenous infusions and/or injections of fluids, which directly effects the composition of blood and blood components. For this reason we feel this subsection should be relocated from M2 to M1.

- We suggest to relocate subsection 2.2 to section M1. *Manipulation of blood and blood components,* preferably integrated in subsection 1.3:

    3. *Any form of intravascular manipulation of the blood or blood components by physical or chemical means, including but not limited to, the intravenous infusions and/or injections of more than 50mL per 6 hour period except for those legitimately received in the course of hospital admissions, surgical procedures or clinical investigations.*

Next to that, we welcome the addition of 'surgical procedures' in this subsection.

M3
The texts on Gene Doping remain unchanged, which on the one hand is good since the annually occurring changes over the last few years made this method difficult to

interpret. But on the other hand, the current text is still too vague and gives little clarity on what is permitted. For example, if you prohibit to use of normal cells with the potential to enhance sport performance, without giving any further explanation, you imply that the ingestion of any type of food (e.g. meat consumption) is by definition prohibited. Also, the current text seems to include therapies such as PRP (see our comments made above in section S2) and allergen immunotherapy, despite the fact that they are permitted. We feel that this should not be the case

- We ask WADA to improve the definition of Gene Doping, so it will give more clarity on what is permitted and what is not, and/or to provide some examples of potential gene doping violations to help us in the interpretation of the definition.

S7
No changes have been proposed, but our comment from last years is still valid: to our knowledge, the abuse of this category of substances is very, very limited and if they are abused, it constitutes medical malpractice more than doping use (i.e. it is not a case where an unfair competitive edge is being sought). Frankly, we only encounter this section in combination with (questions about) abundant poppy seed use or TUE-applications regarding surgery and concomitant painkillers.

- We suggest that a remark could be made that the use of narcotics is allowed during surgical interventions, much like the remark on intravenous infusions in section M2-2, or that this section can be deleted altogether.

Monitoring Program
In the 'Summary of Modifications and Explanatory Notes' it is mentioned that the previous collection of data on pseudo-ephedrine below 150 mcg/ml has led to sufficient data "leading to clear conclusions".

- Could you please be transparent about rationale of this decision and share your conclusions with the anti-doping community?

S0 / S6 / S9 / M1 / P1 / P2
No comments.