Regarding: Netherlands reaction to draft 2016 Prohibited List International Standard (a shared submission of four stakeholders)

Capelle aan den IJssel, 22-07-2015

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 2016 Prohibited List,

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

Anti-Doping Authority the Netherlands

Herman Ram
CEO

1. Introduction

We would like to thank WADA for giving us the opportunity to share our thoughts on the Draft 2016 Prohibited List International Standard. We feel the consultation process is a very important step in clarifying the viewpoints of the anti-doping community. The annual input from all stakeholders increases the strength of the Prohibited List and fortifies its worldwide support.

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 three separate paragraphs:

- major points of consideration;
- stance on tramadol prohibition;
- other points of consideration.

2. 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.

3. Major points of consideration

We have four major points of consideration: provide more background information, add thyroid hormones, remove cannabinoids, and split up section S2.

Provide more background information

It would be helpful if WADA would share the grounds on which a substance or method is added to the Prohibited List (or not). This primarily applies for newly suggested amendments, but could also be applicable for all other items on the Prohibited List. It will increase the worldwide support for the Prohibited List and will improve the discussions introduced by the stakeholders during the consultation process. We do not foresee any legal problems with such transparency, as article 4.3 of the World Anti-Doping Code specifically states that WADA’s decisions in these matters are final.

> Advised action
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> We would like to ask WADA and the Prohibited List Expert Group to publish the backgrounds of their decisions to place (a certain group of) substances or methods on the Prohibited List.

Add thyroid hormones (section S2)
We would like to stress the importance of adding thyroxine (T4), triiodothyronine (T3), Thyroid Stimulating Hormone (TSH) and Thyrotropin-Releasing Hormone (TRH) to the 2016 Prohibited List.

There are persistent rumours of competitive athletes using thyroid hormones to increase their performance. With (1) the theoretical power to cause weight loss, (2) the concomitant power to release energy substrates, and (3) the well-known and longstanding abuse 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 are currently being misused to enhance athletic performance in elite sports. Also, it is clear that the abuse of thyroid hormones leads to potential health risks for heart, skeletal muscle, bones, and metabolic pathways. For recent reviews on all of these effects please see *Senese et al. (Frontiers in Physiology, doi: 10.3389/fphys.2014.00475)* or *Coppola et al. (World J Hepatol 2014 March 27; 6(3): 114-129).*

> Advised action
> We strongly suggest to add thyroxine (T4), triiodothyronine (T3), Thyroid Stimulating Hormone (TSH) and Thyrotropin-Releasing Hormone (TRH) to the 2016 Prohibited List, with the most appropriate section in the current draft version being S2.

Remove cannabinoids (section S8)
Substances (such as cannabinoids) that most likely have a negative impact on athletic performance - and only theoretically might be able to have a very marginal potency to increase performance - should not be part of the anti-doping program.

Athletes - being role models - should not be using cannabinoids. Nor should they engage themselves in other morally objectionable activities (e.g. drinking & driving, adultery, speeding, using psychedelic drugs). All these activities (1) can represent an actual or potential health risk for the athlete and (2) can be considered to be against the spirit of sport, but do not have (3) the potency to increase sport performance. And obviously, none of them are considered doping, except cannabinoids. We cannot help but feel that the listing of cannabinoids is predominantly a political statement, rather than a logical outcome of weighing the code criteria. In our view, the inclusion of cannabinoids does not add value the Prohibited List.

> Advised action
> We are aware of the various views that exist on this issue, but we would like to repeat our request from previous years and ask WADA to remove cannabinoids from the 2016 Prohibited List.

In addition, if WADA decides to uphold the prohibition of cannabinoids, we feel it is unfair to sanction athletes on the basis of presence of the long-lasting metabolite 11-nor-9-carboxy-delta9-tetrahydrocannabinol. 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 testing alternatives, using multiple analytes.

> Advised action
> If WADA decides to uphold the in-competition prohibition of cannabinoids, we plead for a more sophisticated detection using the alternatives presented by the studies of Brenneissen and Mareck.

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 2015 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, we feel some of the different subsections are weakly related to each other and are better suited in other sections.

> Advised action
> 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. *Glucocorticoids*. This would be more consistent from a physiological, pharmacological and chemical point of view.

4. Stance on tramadol prohibition (section S7)

At this point in time, we believe tramadol should not be added to Prohibited List for the following reasons:

- Adding tramadol to the Prohibited List will not resolve the issue of pain killer abuse in sports. It will merely lead the athletes who contemplate taking tramadol at the moment to shift their pain killer usage to 'the next still permitted medication in line'.
- The figures of the 2014 Monitoring Program only show clear 'above average' use of tramadol in cycling, but not in other sports. It would be disproportional to ban tramadol in all sports with such a skewed distribution of use.
- The Monitoring Program also shows that the use of tramadol has decreased in the last year (for all sports, as well as specifically for cycling). Perhaps the extra attention to this substance is already working in the way that its use in sports is declining.
- There are no severe adverse side effects related to the use of tramadol for sports in general. The side effect mentioned in cycling that slower reaction times might cause more peloton collisions, is indirect.
- As mentioned in chapter 2, our review criteria state we want to minimise the impact on good-willing athletes, good-willing physicians and other support personnel. We want to make to Prohibited List as long as necessary, but also as short as possible. Following this line of thinking, we do not think listing tramadol is necessary.

All in all, we do not think adding tramadol will be an improvement of the Prohibited List. Instead we feel that the misuse of tramadol is primarily an issue of cycling, and thus should merely be addressed by the cycling community (e.g. as UCI did with their ban on injections).

5. 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)*.

<u>Advised action</u>
We suggest that both nandrolone and 19-norandrostenedione are moved to section b of S1-1.

S2
The *2015 Prohibited List - Summary of Major Modifications and Explanatory Notes* made clear that the use of cyanocobalamin (vitamin B12) and Platelet Derived Plasma preparations are not prohibited. However, over the years these remarks will no longer be easily available.

<u>Advised action</u>
To avoid confusion, we feel it is necessary to explain the permitted status of cyanocobalamin (vitamin B12) and Platelet Derived Plasma preparations in the Prohibited List itself. This could for example be done in a similar way to the remark regarding the permitted status of clonidine (in section S6).

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.

<u>Advised action</u>
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
Meldonium (Mildronate) is added to the Prohibited List based on the so far undisclosed figures of the 2015 Monitoring Program. In order to form a clear opinion in this matter, the stakeholders need to be informed of these unrevealed statistics. Furthermore, misuse alone is not enough to label a substance as doping. That is why we would like to receive more background information that led to the inclusion.

<u>Advised action</u>
Please provide the related figures of the 2015 Monitoring Program and provide us with a more elaborated rationale on why meldonium (Mildronate) should be added to the Prohibited List.

A few remarks for editorial purposes

- Subparagraph 5.3 of section S4 has no interpunction at the end.
- The number of subparagraph 5.4 of section S4 is the only subparagraph that is printed in bold.
- Following logical alphabetical enumeration Meldonium (the new subparagraph 5.4 of section S4) should be switched with Trimetazidine (subparagraph 5.3) .

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 the 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 unclarity is not advisable.

Advised action
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
See comments on the prohibition of tramadol in chapter 4.

Furthermore, no new changes have been proposed. However, our comment from last years is still valid: to our knowledge, the abuse of this category of substances is very, very limited and if these substances 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.

Advised action
We suggest to (1) make a remark that the use of narcotics is allowed during surgical interventions, much like the remark on intravenous infusions in section M2-2, or (2) delete this section altogether.

S8
See comments on the prohibited status of cannabinoids in chapter 3 (major points of consideration).

S0 / S5/ S6 / S9 / M1 / M2 / P1 / P2
No comments.

General, for editorial reasons

- There is no consistency in the current List whether a paragraph/subparagraph/enumeration should be concluded with a period (.) or a semicolon (;).