DOPING AUTORITEIT

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Regarding: Netherlands reaction to draft 2011 Prohibited List International Standard (a shared submission of four stakeholders)

Capelle aan den IJssel, 22 July 2010

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

Thank you very much for the invitation to review the draft 2011 Prohibited List International Standard. With this letter, I would like to provide you with the comments of the Netherlands, a shared submission of four 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 always, we have used our continuous relationship with athletes, physicians, pharmacists, and scientists over the previous year to collate our remarks and comments. We thank you for discussing the comments we made last year and to follow up on some of our recommendations. We would be more than happy to assist if the work of the Expert Group can be helped by explaining our proposals in more depth or by providing alternative proposals or more data.

In the Netherlands, we share a firm anti-doping stance and fully acknowledge the fact that anti-doping measures sometimes are a burden to athletes (for example filing whereabouts information, allowing out-of-competition controls, urinating under supervision – to name just a few) and that behaviour that seems "normal" to non-athletes requires some extra attention for those who are submitted to doping controls (show consideration for the strict-liability principle when taking medicines or eating food, following the lengthy administrative procedures when requesting Therapeutic Use Exemptions - etcetera).

In the fight against doping, we ask a lot from our athletes, and mostly justifiably so, but it is our duty as anti-doping professionals to minimise the impact of anti-doping measures on the daily lives of these athletes and their direct environment. All measures must be supported by those who are involved, especially the athletes themselves. This is our basic belief in our daily work, and it holds especially true in the process of commenting on the proposed Prohibited List.

As in previous years, we strive for a Prohibited List that carries the following characteristics:

- it is as short as possible, but as long as necessary;
- it minimises the impact on good-willing athletes;
- it minimises the requirements for good-willing physicians and other support personnel;
- it optimises the possibility to catch cheating athletes and their supporting personnel;
- it is easily explainable to athletes, their support personnel and the general public.

With these characteristics in mind, it is our opinion that the List can still be improved. Before proceeding to give some specific comments on the different groups of substances and methods, we would like to emphasise three general comments that may help to understand our line of thinking and might guide yours:

1. **More prioritisation in choices to list certain substances.**
   Given their pharmacological effects, it is unclear why substances such as thyroid hormones and nicotine are not yet listed whereas substances with limited effects on athletic performance such as inhaled beta2-agonists, inhaled corticosteroids, cannabinoids, narcotics, and alcohol are. It would help to explain the rationale of the Prohibited List to either insiders or outsiders of the sports medicine community when the reasoning behind the choices is clearly stated. Article 4.3 of the World Anti-Doping Code clearly gives WADA the opportunity to weigh the three well-known criteria, and in our minds the performance enhancing characteristics of a particular substance should have the most impact in this weighing process.
   This does not just mean that certain substances or groups of substances should be added or removed from the Prohibited List. There are several other possible solutions to make the List more focussed on improving athletic performance, such as raising reporting thresholds, changing the rules on sanctioning for these substances, and/or limiting their prohibited status to certain sports known to have problems regarding this particular group of substances. We kindly ask WADA to acknowledge our firm opinion in this regard, and to choose a solution that recognises the different views that exist rather than deciding in a manner which completely rejects the strongly held views of one group. We have made some specific recommendations in the particular groups where this rationale applies.

2. **Less influence on medical decisions.**
   Anti-doping regulations most often involve pharmaceutical drugs or medical methods, which makes it unavoidable that doping-related decisions have a medical impact. But we should be very hesitant as to recommend a certain therapy or approach. This enters into the domain of the physicians of the athletes and in principle this should not be the domain of anti-doping policy makers. Allow us to give three examples: In the discussions on histamine challenge tests to confirm an asthma diagnosis, WADA has successfully chosen a position not to decide on which challenge tests are medically justified, leaving the decision to choose a certain provocation test to the physicians involved. In other cases, such as the approach towards Platelet-

derived preparations or the artificial dichotomy in the group of β2-agonists (salbutamol & salmeterol versus others), it is our view that WADA has stepped over the threshold of interfering with the physician-patient relationship. As anti-doping professionals we should always keep in mind that we can prohibit certain substances and methods as they might be abused as doping, but that it is not our position to fight (perceived) medical malpractice in all of its forms.

3. **More transparency in (suggested) changes to the Prohibited List.**
   Last year, the change in the status of pseudo-ephedrine was supported by an elaborate and clarifying document that explained the rationale of its re-introduction. This year, the most important changes (in sections S5, M2, and S9) are not accompanied by an explanation or reference. We would really appreciate an explanatory document as was provided in other years. Such a document strengthens any discussions by openness and transparency, and this holds especially true for issues regarding the Prohibited List, which need to be explained to athletes, medical support personnel, and other groups.
   In addition, the process of drafting the Prohibited List and collating comments from stakeholders would benefit from more transparency. We favour a process where both all stakeholder's comments and WADA's reaction to the proposals are made public. This way, it would also be better known publicly what the reactions of the different athlete's committees are, especially WADA's own athlete committee. We do our work to aid the athletes of the world, and it is especially their opinion that matters.

In addition to these three general principles, we would like to provide you with some specific comments, listed per group of substances or methods:

S0
The idea of banning non-approved medicines is fully supported, but we foresee three possible problems in the current wording:

1 - The "approval by appropriate official authorities" does not say anything about the current status of such approval, and in our view this is not valid anymore if it has been present only in the past.

➢ We suggest the addition of the word "current" before "approval".

2 – The current wording includes harmless substances such as supplements or even regular food, which can enter the market without official "approval" (and rightly so, in most instances).

➢ We suggest the addition of the word "pharmaceutical" or "clinical" before "authorities" to underline that we are talking about substances or methods that are being studied in clinical trials. This new section should not ban regular nutritional supplements or even regular food.

3 – Discussions may arise around the issue whether one single official approval somewhere in the world (even in a small country) might be enough or whether several approvals are necessary.

➢ We suggest that in the Summary of Modifications it is explained that this new prohibition is intended to prohibit the use of non-approved medicines (or methods) still under development and that an approval by one single official pharmaceutical authority makes such a medicine (or method) "approved" as far as section S0 of the Prohibited List International Standard is concerned.

S1
No comments.

S2
With an extra year of experience in explaining the anti-doping regulations regarding Platelet-derived preparations (e.g. Platelet Rich Plasma or Platelet Leukocyte Gel) to various (sports) physicians, which sometimes led to lengthy discussions, we are more convinced than ever that the prohibition of this experimental technique is not necessary. PRP is highly unlikely to enhance the performance of a healthy athlete as the amount of growth factors injected is very small and purely of endogenous origin – it is a mere redistribution of endogenous materials and not in a "blood doping kind of way". If given under medical supervision the possible side effects are minimal and the ethical discussions focus on the medical legality, not on athletic related issues. In summary, this is a method that should not be misinterpreted as a doping practice.
In addition, we have been explained by WADA staff that the rationale of requesting full TUEs for intramuscular applications of platelet-derived preparations is that this route of administration is not yet fully accepted as an effective therapeutic method. This is a good example of a choice that should be made by physicians, not by anti-doping policy makers.
Finally, it is a strange situation that the current Prohibited List provides in fact a double ban, as platelet-derived preparations (gels or plasma) contain growth factors IGF-1, VEGF, and FGF – all growth factors that are explicitly mentioned as examples under section S2-5. So even under the current text, where non-muscular applications "only" require a Declaration of Use under section S2-6, they are still prohibited under the previous section.

- We ask the Prohibited List Expert Group to allow the method of injecting "platelet rich plasma" (PRP) or "Platelet Leukocyte Gel" (PLG) in therapeutic settings (without requiring a TUE or Declaration of Use).

On a less important note, we wonder why virtually all examples of substances within the various groups of prohibited substances are listed in alphabetical order, except in (sub) groups S2-1 and S2-5.

- For consistency reasons, we ask to list all substances within a certain group in alphabetical order.

S3
In an accepted meta-analysis (soon to be published in Sports Medicine) Pluim et al. conclude that "No significant effects were detected for inhaled β2-agonists on endurance, strength and sprint performance in healthy athletes. There is some evidence indicating that systemic β2-agonists may have a positive effect on physical performance in healthy subjects, but the evidence base is weak." This means that even the requirement of a Declaration of Use (DoU) for inhaled β2-agonists is not necessary: as long as they are inhaled, they are not relevant from an anti-doping perspective.
In addition, there is no reason to assume that different β2-agonists have different effects, and thus the current rule of requiring a DoU for inhaled salbutamol and salmeterol but a full TUE for other β2-agonists is artificial and difficult to explain. This special rule for salbutamol and salmeterol is directly interfering in the physician's decision to prescribe certain medication as well; we have had several cases already where an athlete has been using another β2-agonist (e.g. formoterol, often prescribed in combination with budesonide) for years, and partly because of this optimal medication the required drop in lung function parameters during a provocation test is not reached. In these cases, the athlete is caught between the doping rules and their personal optimal medication regimen, but because of the current rules they often opt to switch their

medication to salbutamol. This is a real-life example where anti-doping rules interfere too much in the physician-patient relationship.
We have been informed by WADA staff members that research is being conducted to establish threshold values for other β2-agonists as well, and we strongly urge WADA to implement the results of such studies as soon as possible, preferably before January 1st 2011.

- We strongly urge WADA to allow the use of all inhaled β2-agonists.

We also ask WADA to be perfectly clear about the status of substances that require a DoU (which is obviously an issue that not only relates to group S3). The wording in the Prohibited List ("All β2-agonists […] are prohibited except salbutamol […] by inhalation which [requires] a Declaration of Use) suggests that inhaled salbutamol is not prohibited, and thus permitted. But it still *requires* a DoU which makes it unclear what the exact status is.

- We ask WADA to clarify the exact legal status of a "Declaration of Use".

S4
No comments.

S5
Desmopressin is listed as a masking agent, without explaining the reasons for this change in status of this particular drug. Presumably, the reason lies in the findings of Sanchis-Gomar et al. (Int J Sports Med 2010; 31:5–9) but such considerations should be made public by WADA. As the experiences with finasteride have shown (it disappeared from the Prohibited List as its masking potential was a lot weaker than anticipated by WADA) the Prohibited List benefits from open discussions with clear arguments.

- We ask WADA to provide documented reasons for all changes in the Prohibited List to all stakeholders, and especially on the new status for desmopressin. The discussions on the possible change in the status of pseudoephedrine in the last couple of years may serve as an example.

Another issue in this group is that the text on the requirement of a specific TUE in cases of substances with threshold limits is still very difficult to interpret. The way we understand it, it is necessary to have a TUE for a threshold substance if that substance is detected in conjunction with a masking agent, even in Out-of-Competition tests. If our interpretation is correct, we fundamentally disagree with this text as a substance that is only prohibited In-Competition can never be regarded as prohibited in an Out-of-Competition test, regardless of the circumstances.

- We ask WADA to clarify the text about TUE-requirements of masking agents, and if our above interpretation is correct we ask to delete these texts altogether or change them to follow the established rules on In- and Out-of-Competition tests.

M1
No comments.

M2
The new prohibition of "withdrawing, manipulating and reinfusing whole blood" leaves some questions unanswered:

1 - Does this prohibition include the act of plasmapheresis? This form of blood donation is performed by some athletes, including elite athletes, as a purely altruistic gesture and it will be difficult to explain if this act is banned by WADA.
2 – A more linguistic question: is it solely prohibited to perform all three acts sequentially or are all three acts (withdrawing, manipulating and reinfusing) prohibited by itself? If the latter explanation is true, this would mean that donating blood would be prohibited in

itself, even if not performed as part of a blood doping scheme (which would raise the same ethical problems as mentioned under 1).

➢ We ask WADA to address the two issues we mentioned above, either in the List itself or in a "Summary of Modifications" or an "Explanatory Note". Please bear in mind that many sports do not have an endurance component and as such these athletes should feel free to donate blood (or parts thereof) as a purely altruistic gesture.

M3

The definition of gene doping is changed every year, which is not preferable from an educational point of view. Moreover, questions remain whether the current wording is clear enough. AICAR, for example, is a substance in itself and one might argue that it is not a form of gene doping (which, by definition, is a prohibited method).

➢ We ask the Prohibited List Expert Group to leave the definition of gene doping unchanged for a few years, unless new insights or experiences require otherwise. Preferably, we should return to a definition that does not specifically mention certain substances in this group of prohibited methods.

S6

The inclusion of methylhexaneamine in the (closed) list of non-specified stimulants is highly disturbing. There are various reasons for this.
First, as we explained last year, it is the only substance on the Prohibited List that can be legally sold in any store in our country, and most likely in other countries as well. In the Explanatory Note to the Prohibited List of 2009, "legitimate market availability" is literally mentioned as a reason to list a certain stimulant as "specified". Since WADA has chosen to never disclose the reasons for a particular substance to be classified as "specified" or "non-specified", despite various requests from several stakeholders to do this, there is a possibility that this characteristic is simply overlooked so we would like to point out this strange anomaly.
Second, in the minutes of the Health, Medical & Research Committee meeting of September last year, the choice of listing this substance in section S6-a is justified with the words "as it is a non-therapeutic substance". In our view, this is precisely the reason why it should be a *specified* substance: because of its non-therapeutic nature it is easily available as an ingredient of perfectly legal nutritional supplements, yielding a great risk of unintentional doping use. This risk is even augmented as methylhexaneamine is often simply labelled as "geranium oil" or "geranium root extract" and such a wording does not give a clue about the possibility that this ingredient refers to a prohibited substance.
We have had several positive cases of methylhexaneamine-positives in the last year and we fear that this will not stop, even with the best educational efforts. In cases where an athlete can establish 1) how this substance entered his or her body and 2) that this substance was not intended to enhance the athlete's sport performance (or mask the use of a performance-enhancing substance), we feel it is justified that methylhexaneamine positives have the possibility to receive a reduced sentence according to article 10.4 of the World Anti-Doping Code.
Finally, there is also a pharmacological reason to ask for this change in the status of methylhexaneamine. Even though little is known about the precise effects of methylhexaneamine, it can be expected, based on its structure and the limited data on its pharmacology, that such effects are comparable to ephedrine, pseudoephedrine, cathine, etcetera. Thus, it would be far more logical to list methylhexaneamine in section S6-b (specified stimulants) where these other stimulants are listed as well.

➢ We urge the Prohibited List Expert Group to list methylhexaneamine under section S6-b, since its non-therapeutic nature yields a high risk of unintentional doping.

Maybe it is just a typographical error, but the text right under "S5. Stimulants" mentions the 2010 Monitoring Program. In 2011, this program will no longer be relevant.

➢ We suggest to change this reference into a new (2011) Monitoring Program, and we are looking forward to hear what substances and/or ratios are included in this program.

It is not part of the draft 2011 Prohibited List International Standard, but in various press reports out of Australia we have learned that WADA's president Mr. Fahey has personal concerns with the fact that caffeine is not listed anymore, and has asked WADA staff to consider reintroducing this substance on the Prohibited List. We would like to remind WADA's Prohibited List Expert Group of the reasons why caffeine was taken of the list back in 2003, and in our view these facts have not changed in the last seven years. It may be true that certain individual athletes seem to experience problems with their caffeine intake, but this does not change the fact that a weighted and balanced decision on this substance, based on the vastly available scientific literature, in our opinion will undoubtedly lead to the conclusion that caffeine intake is a personal decision and not a doping offence.

➢ In case the Expert Group is considering to reintroduce caffeine on the Prohibited List, we would like to stress that the available scientific literature does not lead to different conclusions than back in 2003. Thus, caffeine should not be considered a doping substance.

S7
No comments.

S8
As mentioned in our first general comment, and as explained in our comments in the previous years, we do not think that cannabis use has a place in sports but at the same time we strongly oppose to regulate this issue through doping rules and regulations. Cannabis has a severe negative effect on most cognitive and motor functions, and thus it has a severe negative effect on almost all athletic performances. Athletes who choose to use cannabis may be setting a poor example to others, but so do athletes who speed on the highway, launder money, or perform other acts that society in general denounces. Such acts should not invoke doping related sanctions either. The presence of cannabinoids on the Prohibited List is a fundamental flaw that has a negative effect on the credibility of all other substances and methods that are on this List.

➢ We repeat our request to try and find a solution that recognises our view (which we know is shared by many other stakeholders) as well as other views that exist in the world regarding the issue of "cannabinoids and doping" in a more balanced way. This might be arranged by changes in the Prohibited List or in other WADA documents (e.g. raising the reporting threshold or changing the sanction regimen in case of a first cannabis offence).

S9
The change in this group, to require a regular TUE for intraarticular injections but not for periarticular injections, does not make sense to us and is devoid of any practical understanding. Even the best physicians will agree that they will never be sure if an injection will indeed be performed inside the articular cleft or just outside this area. And as a separate yet very important issue: the nature of the injuries that require injections of corticosteroids is such that a regular TUE request (which often takes several weeks to complete) is highly unpractical. A ban of intraarticular injections might even have a health endangering effect: athletes may feel forced to enter a race or match without a treatment that general medical practice would recommend.
Moreover, we do not agree with two points that are made in the Summary of Major Modifications. The first is that this decision is based on "ongoing studies"; again, we stress that such study results should be shared with all stakeholders because without such information we cannot weigh all relevant pieces of information on this issue. Secondly, it is stated that "this route of administration results in systemic availability of glucocorticosteroids". This is a strange remark as *any* route of administration may result

in systemic effects, as this is largely dependent on the dose that is used. But, just like the group of β2-agonists, one can make a judgement call whether a certain application method can be expected to have systemic effects or not. In our view, based on the literature we know, these effects cannot be expected from intraarticular injections.
A separate issue in this particular group is that their abuse seems to be present only in a limited number of sports modalities, but they are still prohibited in all sports that follow the World Anti-Doping Program.
It can be concluded that the current set over rules regarding glucocorticosteroids, or glucocorticoids as they are more commonly referred to, is quite controversial, as is the case with cannabinoids. Here, too, the answer may be to introduce clear reporting levels for the glucocorticoids that exist. Like with the case of salbutamol, the athlete may always show retrospectively that an abnormal result may have been caused by a therapeutic dose.

- We ask the Prohibited List Expert Group to choose a practical approach in the rules regarding glucocorticoids. In our view, the proposed change makes a problematical set of rules even more complicated, and could lead to a PR-disaster. The road to a solution for this group lies either in prohibiting these substances in certain sports only (as with alcohol and β-blockers) or in introducing specific threshold limits (presumably in a technical document to the International Standard for Laboratories rather than in the Prohibited List International Standard). Otherwise, the rules are better left unchanged.

P1/P2
No comments.

These were our comments; we hope they will be of use to you. As a final remark, we would like to repeat the proposal we made last year to have a working symposium on the contents of the Prohibited List in the not too distant future. This would be the best way to find a common approach regarding Prohibited List issues, especially the most controversial ones. This way, the Prohibited List International Standard could be supported by a much larger proportion of all stakeholders than in the current situation, which would seriously strengthen the World Anti-Doping Program.

With sincere greetings and the best wishes in your efforts to compile the 2011 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
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