DOPING AUTORITEIT

By e-mail to: violet.maziar@wada-ama.org

Regarding: Netherlands reaction to draft 2010 Prohibited List International Standard (a joint submission of four stakeholders)

Capelle aan den IJssel, July 30th 2009

Dear Mr. Howman,

Thank you for your invitation to review the draft 2010 Prohibited List International Standard. With this letter, I would like to provide you with the comments of the Netherlands, a joint submission of four stakeholders: the Ministry of Health, Welfare, and Sports, the National Olympic Committee NOC*NSF, the NOC*NSF athlete committee, and the NADO, Anti-Doping Authority the Netherlands. Please accept this as a fourfold contribution to your consultation process.

The annual process of consultation on the Prohibited List International Standard is of the utmost importance to day-to-day anti-doping work. Most questions that a NADO receives about doping and/or the existing anti-doping regulations require an answer with a reference to 'the List'. It's credibility should be beyond refute amongst athletes, coaches, doctors, pharmacists, policy makers, and the general public.

We fear that at the present this is not always the case.

In our daily work, we notice that the credibility of the Prohibited List is loosing ground. More and more, we experience that this starts to damage the credibility of our anti-doping efforts in general. A large part of our efforts, and of those who are more then willing to follow all aspects of the existing framework of anti-doping regulations, is currently focused on trying to understand the rational behind (parts of) the Prohibited List and, as related issues, looking for more harmonisation in the TUE and whereabouts regulations. At the same time, we know there are cheats around who require more attention then we can give them. In our conviction, the balance between these two groups of 'clients' is shifting towards the wrong end.

With this introduction, we would like to draw your attention to two general remarks regarding the draft 2010 Prohibited List International Standard. We will proceed to provide you with our review and comments on specific groups of substances and methods, as requested by your email from May 5th 2009. As every year, we have used our continuous relationship with athletes, physicians, pharmacists, and scientists over the previous year to collate our remarks and comments. And as always, we would like to offer our assistance if the work of the List Committee 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 do so.

General comment 1 – prioritization is needed

The World Anti-Doping Code clearly states in article 4.3 that substances that fulfil two out of the three well-known criteria shall be *considered* for inclusion on the Prohibited List. This leaves room for weighing the several aspects that play a role, as has been done in the past in the decisions not to put substances such as buproprion, thyroid hormone or nicotine on the Prohibited List.

(As a side note, we would like to explain that the status of thyroid hormones is especially puzzling to us. Many (former) athletes have admitted using thyroid hormones with success, and in the case of baseball player Barry Bonds it is even proven through his 'doping calendars' that he used them. There is also ample physiological evidence that this substance promotes weight loss, and thus will be performance enhancing in weight-bearing sports. There is no controversy on the potential health damage of it's use by non-patients, and it is our belief that the use of such a potent medical drug by otherwise healthy athletes violates the Spirit of Sport. Thus, this substance would be a logical candidate to put on the Prohibited List. But it never has been listed, when other groups of substances have been, for which the evidence of performance enhancement is much weaker.)

It is a difficult task for the List Committee, the Health, Medical and Research Committee and the Executive Committee to weigh all differing opinions and to make their decisions. In order to help them to make a balanced decision, we would like to repeat our comments that we made over the last few years, as our opinion in this regard has only been strengthened in the past year.

- There is strong evidence and overwhelming consensus that inhaled beta-2 agonists do not improve performance (see e.g. Carlsen et al., Allergy 63, 492–505, 2008);
- there is no convincing evidence that corticosteroids improve performance (see for a recent study Kuipers et al., Br J Sports Med 42, 568-571, 2008); and
- there is lack of evidence that cannabis would improve performance (since the announced publication of Ms. Marilyn Huestis on this subject has not yet materialised the best review on this matter is still Campos et al., Sports Med 33(6): 395-9, 2003). Together with the evidence put forward by Johns, Br J Psychiatry 178: 116-22, 2001 and Kumar, Anaesthesia 56(11): 1059-68, 2001 and more recently by Hunault et al., Psychopharmacology 201(2): 171-81, 2008 it must be concluded that the majority of evidence on cannabinoids is pointing to an ergolytic effect rather than an ergogenic one in almost all sports (a more extensive description of the study by Hunault, focussing especially on psychomotor effects, can be found as Mensinga et al., 2006, on the website http://www.rivm.nl/bibliotheek/rapporten/267002002.html).

We could argue that the same principle is true for the group of narcotics, but since these substances are not as often used or detected as the substances mentioned above, these do not draw heavily on the resources of anti-doping organisations. We are aware of the differing opinions on these matters all around the world, but we would like to ask the several committees involved to contemplate the following questions:

- How many of the 399 athletes who tested positive on beta-2 agonists in 2007 would be athletes who tried to cheat on their opponents, and how many would be athletes requiring medically justified medication?
- How many of the 288 athletes who had an adverse analytical finding for corticosteroids in 2007 would be athletes who tried to cheat on their opponents, and how many would be athletes requiring medically justified medication?
- How many of the 576 athletes who had an adverse analytical finding for cannabinoids in 2007 would be athletes who tried to cheat on their opponents, and how many would be athletes who developed a bad habit who got caught during an In Competition doping control while using the cannabis at least a day before their event?
  (Please note that these three groups combine for 26% of all adverse analytical findings in 2007)
- Finally: how many cheating athletes who decided to use steroids, erythropoietin, growth hormone, insulin and/or blood doping did we miss during our controls in 2007 because all anti-doping organisations, as all other agencies and companies, need to cope with less than ideal resources?

We would like to emphasise that we do not condone the non-medical use of any medicine in any way, and we emphasise strongly that non-medical use of cannabinoids should be avoided by all athletes as it is detrimental to themselves and to the image of sport. But the Prohibited List International Standard is the backbone of all anti-doping efforts and should thus focus on providing the best possible support to these efforts, without diverting attention and resources to all existing wrongdoings. Gambling, throwing matches, and violence are just some other examples of behaviour that should be eradicated from the world of sport in the strongest way possible – but not through anti-doping regulations. In our view, the abuse of beta-2 agonists, corticosteroids, and cannabinoids fall into the same category as they are unlikely to have a strong pharmacological influence on *athletic* competitions. We know we are not alone in this desire to shorten the Prohibited List and to focus more on the most relevant groups of substances and methods. In those previous instances that WADA has made all commentaries to the Prohibited List International Standard public, the percentage of stakeholders that had concerns regarding the List ranged from 30 to 45%. Not a majority, but still a very large group that should not be ignored.

Besides this fundamental point, we also envisage financial problems if the cost-effectiveness of our anti-doping efforts is not taken into account in a sufficient manner. In 2006 the report on the costs of anti-doping, presented to the Executive Committee in October of that year, showed that many stakeholders experience cost constraints in their day-to-day work, and this feeling will have increased considerably in the light of the current financial crisis. Also from a financial point of view we have to focus in order to be able to continue to do our work properly.

We kindly ask WADA to acknowledge our firm opinion in this regard, and try to come up with a solution that recognises the different views that exist on this issue rather than deciding in a manner which completely rejects the strongly held views of one group. This could be done by several measures, i.e. raising thresholds, changing the rules on sanctioning for these substances, and/or limiting their prohibited status to certain sports known to have problems regarding these substances.

General comment 2 – less influence in medical guidelines

Almost all stakeholders ask WADA to provide them with more guidelines and more harmonization in order to leave as little doubt as possible in the interpretation of the World Anti-Doping Program. It is therefore unavoidable that WADA makes use of current medical guidelines, as drafted by international bodies of medical specialists. In our view, however, WADA is sometimes taking a few too many steps in this area in the desire to clarify certain subjects. This is especially true for the current rules regarding beta2-agonists. WADA's TUE-guidelines state for example that 'The treatment should be modified or stopped if the diagnosis is revisited' (Medical Information to Support the Decisions of TUECs regarding asthma, version 1.3, 2-6-2009). It is not up to WADA or any ADO to persuade an athlete or a physician to stop a treatment. We can only explain to an athlete that we do not condone certain medication during (and surrounding) competitions. The outcome may be the same (the athlete involved will have to look for an alternative treatment), but the philosophical principle is essentially different: WADA and its stakeholders deal with doping issues in the world of sports and are not in a position to prescribe or withhold medical treatments. See also our comments on groups S3 (on the diagnosis of asthma) and M2 (on intravenous infusions).

Specific comments – per group

Introductory text
The remark "the use of any drug should be limited to medically justified indications" does not include section M (methods), which gave us some problems in a recent doping case involving illegal infusions.
➢ We ask the List Committee to change the word "drug" into "therapeutic substance or method".

S1
We have been informed by the Royal Dutch Association for the Advancement of Pharmacy that the INN-name for methyltrienolone has been changed to metribolone. This should be changed in group S1-1-a.
➢ We ask the List Committee to change the name methyltrienolone into metribolone.

The long texts explaining what happens when values are found outside the 'normal' range are still very difficult to interpret. We would like to repeat our suggestion that most of the texts explaining the courses of action after an atypical result should be moved to a technical document. The Prohibited List International Standard should list the prohibited substances and methods; the way in which evidence is gathered in order to determine whether a violation has occurred or not is more technical and distracts the attention from the List's true focus.
➢ We ask the List Committee to delete the texts explaining the courses of action after an atypical result, and move these to a technical document.

S2
The addition of mentioning several growth factors increases the clarity of this group, and we think that this new wording will make it easier to explain to physicians that the method of injecting 'Platelet Rich Plasma' (PRP) or 'Platelet Leukocyte Gel' (PLG) is indeed prohibited. On an fundamental level, we still find it puzzling that this method is also prohibited if the growth factors are of endogenous origin and are re-injected within (approximately) half an hour without making use of any activating substances. It is not more performance enhancing than other medical therapies, it is not a health hazard if performed in a clinical setting and it is becoming more and more accepted as regular therapy (see for a recent review Sánchez et al., Sports Med 39(5): 345-54, 2009) and thus it can hardly be considered to be against the spirit of sport. Although PRP/PLG involves injecting growth factors, it is not really different from the fact that traces of IGF-1 can be found in regular milk, or that octopamine can be found in chocolate: it is interesting to talk about it, but it is not a practical doping problem, and thus it should not be made an issue by banning it and requiring TUEs as a consequence (we do not require TUEs for milk or chocolate either).
➢ We ask the List Committee to allow the method of injecting 'platelet rich plasma' (PRP) or 'Platelet Leukocyte Gel' (PLG) in therapeutic settings (without requiring a TUE).

A second issue within this group, is that we would like to ask the List Committee to clarify the status of gonadorelin and gonadorelin-agonists. We have been informed by WADA's scientific department that triptorelin is prohibited for both males and females (and thus presumably is considered to be related to corticotrophins), where leuprorelin and goserelin are considered to be prohibited for males only (and thus related to LH). This is a strange dichotomy, which requires further explanation.
➢ We ask the List Committee to come up with one common rule for all gonadorelin-agonists.

Finally, the use of the term 'hormones' in the title of this group remains to be puzzling, as all anabolic steroids (in group S1) and corticosteroids (S9) are hormones as well. A more accurate term would be 'peptide hormones' as apposed to 'anabolic agents' (S1), and 'glucocorticoids' (S9).
➢ We ask the List Committee to change the name of the group S2 into 'peptide hormones'.

S3
The simplification of the text is much appreciated. But the group of beta-2 agonists still requires an enormous amount of attention, both in our informational materials, in our TUE-system, and in our result management process. In our view, their ergogenic potential is very weak (see also our general comments on prioritization), and thus these efforts are out of balance. Adding to this sense of dissatisfaction with the current rules is the fact that true asthmatics may run into trouble with the existing firm TUE-regulations. If an athlete has had an optimal medication regimen for several years, the experienced complaints may in fact diminish, leading to 'negative' test results in pulmonary function tests. Anti-doping regulators should not require that such an athlete temporarily stops his/her medication in order to 'prove' he/she is not a cheat, nor a victim of bad medical science (see also our general comments on medical guidelines).
- We ask the List Committee to change the rules regarding inhaled beta-2 agonists. This can be done in several ways, e.g. by only requiring a TUE application if certain thresholds are exceeded, but a new rule should acknowledge that this group currently requires far more attention and resources than their doping potential justifies.

Regarding this group, we would like to draw your attention to the (somewhat unclear) status of fenoterol, a beta2-agonist that is quite commonly prescribed as an inhalation treatment for Dutch asthmatics. The Prohibited List in its current form, and in the proposed text for 2010, simply states that "all beta2-agonists...are prohibited," which handles all existing beta2-agonists equally. The TUE-standard, however, still singles out four specific substances (salbutamol, formoterol, salmeterol, and terbutaline) when explaining the rules for obtaining a TUE for a beta2-agonist. This is an inconsistency in the two relevant documents, but both are binding within the framework of the World Anti-Doping Program. This inconsistency should be dealt with by either the List committee, or the TUE committee, but preferably by both. We would prefer that the text in the Prohibited List is followed, as inhaled fenoterol can be prescribed by Dutch doctors according to current good clinical practice. On our national level, it is difficult to explain why this particular beta2-agonist should deserve special treatment.
- We ask the List Committee and the TUE committee to find a solution for the status of fenoterol, preferably by changing the wording in the current TUE-standard.

As a side note, we highly appreciate WADA's recent publication of new guidelines on this subject (Medical Information to Support the Decisions of TUECs regarding asthma, version 1.3, 2-6-2009) that specifically allow histamine testing to support the diagnosis of asthma. This was an area of recent controversy and we totally agree with this clarification, which takes the various existing medical practices around the world into account.

Just before finalising this letter, we were informed that WADA is currently funding research with the aim to find ways to discriminate between inhaled and other beta2-agonist use, with the aim of allowing the inhaled route without a TUE. This would be great news, and we would like to make clear that we fully support this initiative. Perhaps, the current rules regarding salbutamol (with a threshold of 1000 ng/ml) may serve as an example for all other beta2-agonists (including fenoterol).

S4
The addition of the two examples is an improvement.

S5
The addition of glycerol and the explanations on pamabrom are understandable, but regarding glycerol we would like to draw your attention to the fact that almost all urines will contain this substance as it is endogenously produced and often consumed in a variety of products. It is likely that a threshold value will need to be determined and that studies into this subject should be carried out as soon as possible. The lab in Cologne already has a lot of experience in this area and we advise WADA to find a solution soon in close cooperation with this lab.

➢ We ask WADA to determine a practical threshold value for glycerol in close cooperation with the labs to avoid false positive findings.

M1
The introduced texts on hyperoxic conditions confirm their status, but in our view this status is not really necessary. Bottled oxygen is not likely to have a great influence on performance, and its health dangers are primarily in carrying an oxygen tank – not as much in its physiological effects. In all likelihood, any physiological effect will be transient at best. We have heard rumours that athletes are using small oxygen cans during matches/competitions, but as long as these are just rumours, together with the effects we described earlier, this is not enough to ban this method. Finally, the spirit of sport is hardly compromised by using devices that are legally sold all over the world ("pure" oxygen is increasingly being sold in the regular, non-medical, market). In our view, this is an issue of low priority. In addition, it will be interesting to learn what the exact definition of 'hyperoxic' will be; 20,98% of oxygen? 23%? 30%?
➢ We ask the List Committee not to list 'hyperoxic conditions' based on 'requests' alone. If evidence of misuse exists, we would like to be informed so we can judge the merits of such evidence ourselves.

M2
We thank you for the change in wording regarding intravenous infusions last year and we support the decision to keep it unchanged. This is a good example of making practical anti-doping rules while acknowledging the existing medical field of practice.

M3
The current (and proposed) definition of gene doping seems to be too broad. One might argue that 'the use of pharmacological or biological agents that alter gene expression' may include any intervention that stimulates protein synthesis. We are not specialised to foresee all potential problems in this change of definition, but in our view gene doping is best described as 'the non-therapeutic use of cells, genes, genetic elements, or the modulation of gene expression, having the capacity to enhance athletic performance', as it was described on the 2008 List. The current proposal seems to be not just a rewording, but a true change and changing the definition of gene doping each year does not help to increase the credibility of the Prohibited List.
➢ We ask the List Committee to leave the definition of gene doping unchanged, or preferably return to the 2008 definition.

S6
The issue of pseudoephedrine is revisited, and rightly so. Last year, the decision not to re-list this substance was made very late in the consultation process and out of the stakeholder's eye (just like the changes in corticosteroids and finasteride), which is not compatible with the regular annual process to comment and update the Prohibited List.
➢ We ask WADA to follow the agreed upon processes of consultation meticulously in every change of the Prohibited List, as per paragraph 4.1 of the World Anti-Doping Code.

We find the approach that is taken towards pseudoephedrine interesting, and in general it makes good sense. We are not totally convinced that there is a real problem with this substance, certainly not in all sports, but the scientific results of the last few years show that there is a combination of potential performance enhancing properties and potential health hazards. This sufficiently explains the prohibited status in our view, although we do fear that the over-the-counter availability of this substance in many countries of the world will lead to unintentional doping cases, as it has done in the past. In addition, we would like to emphasise that the graphs on the prevalence of its use are interesting background information, but should not be critical in the decision to prohibit the substance or not, as 'prevalence of use' is not one of the criteria mentioned in article 4.3 of the World Anti-Doping Code.

➢ We ask the List Committee to base its decision regarding pseudoephedrine on the consensus that exists among stakeholders and on the criteria that are mentioned in the World Anti-Doping Code; not on the prevalence of its use or misuse. It should also be borne in mind that it is a widely available substance in many countries, and thus we ask the List Committee to weigh the potential to catch doping cheats on one hand and the risk of inadvertent positive findings on the other (see also our first general comment).

In addition, we are still not convinced that the division of the group of stimulants into a specified part and a non-specified part can be explained clear enough in order to avoid awkward situations, such as benzylpiperazine-positives that are based on contaminated supplements, cocaine-positives because of analgesics used in nose or ear surgery, or bromantan positives because of legitimate medical use. Therefore, we would like to repeat our request to the List Committee to state clearly what arguments have been weighed more heavily than others in making this dichotomy (history of use, pharmacological potential, or other).
➢ We ask the List Committee to explain the backgrounds of the decisions to list certain stimulants under section S6a, and others under section S6b.

While looking forward to such an explanation, we would like to ask WADA to move methylhexaneamine to the 'specified' part as we envisage problems regarding this substance if it remains to be listed as 'non specified'. It is increasingly marketed as a nutritional supplement and it is available as a supplement in several countries, including the Netherlands. It would be the first substance on the Prohibited List that can be legally sold in any store in our country. The risk of an athlete testing positive for this substance inadvertently is pretty high, even with the best educational programs. There is also a more pharmacological reason to ask for this change: since the effects of methylhexaneamine are comparable to ephedrine, pseuoephedrine, cathine, etcetera, it would be far more logical to list it in section b (specified stimulants).
➢ We ask the List Committee to list methylhexaneamine under section b, if it is indeed decided to list this particular stimulant.

S8/S9
We refer to our comments made earlier regarding these groups of substances (in the section with general comments on prioritization), with the following additions.

For S8, we would like to draw your attention to a recent report by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). As with most substances on the Prohibited List, the actual effects of cannabis on athletic performance have not been studied extensively. But in the case of cannabis use, there is a similar task, especially focussing on the mental aspects of performance, that has been studied in more depth: the effects on driving a vehicle. In a recent monograph published by the EMCDDA the following conclusions were drawn: "Several comprehensive reviews of this literature have emerged, and the results appear to be very consistent. A consistent conclusion is that the acute effect of moderate or higher doses of cannabis impairs the skills related to safe driving and injury risk." And: "a meta-analysis of 60 studies … concluded that marijuana causes impairment of every performance area connected with safe driving of a vehicle, such as tracking, psychomotor skills, reaction time, visual functions, and attention. Of these performance criteria, the most deterioration from marijuana use was found for measures of attention (e.g. the continuous performance task), tracking (e.g. the pursuit rotor task) and psychomotor skills (e.g. simple reaction time)". (Reference: EMCDDA (2008), A cannabis reader: global issues and local experiences, Monograph series 8, Volume 1, European Monitoring Centre for Drugs and Drug Addiction, Lisbon, Portugal; The publication is available on the Internet at: http://www.emcdda.europa.eu/publications/monographs/cannabis)

Since reaction time, visual functions, and attention are essential tasks in almost all athletic endeavours, it can be concluded that science has clearly proven that cannabis use is detrimental to almost all athletic performances. In our view this can lead to only one conclusion: cannabis has no place in sports and since anti-doping regulations are an integral and fundamental part of sports, cannabis does not have a place in the existing anti-doping framework either. This is a fundamental principle that should be seen

separately from the fact that from a governmental level it is understandable to discourage cannabis use in any population, especially in young people.
- We ask the List Committee to acknowledge the fact that cannabis is, in all likelihood, detrimental to athletic performances and does not deserve a place on a prohibited list of doping substances.

For S9 we would like to add that the term 'glucocorticosteroids' is not correct, as all pharmacology experts that we have spoken to have explained to us. It should be 'glucocorticoids' (see also our final remark under S2).
- We ask the List Committee to change the name of group S9 into 'glucocorticoids', if this group remains to be on the Prohibited List.

P1/P2
The IPC/WBF/FITA changes make the list more understandable, and thus better.

Final comment
We recognize and understand the enormous task of the List Committee to read, weigh, and decide on all the comments they receive. These comments will all too often be incompatible as there are many different (strong) views on the Prohibited List and on the different possible ways on how to amend or change it. We would like to suggest that a special working symposium, dealing solely with the philosophy and content of the Prohibited List, might be the best way to find a common approach that would be supported by a much larger proportion of all stakeholders than in the current situation. Suggested attendants could be the current and former members of the List Committee, regular contributors to the annual review process, pharmacological experts and other medical professionals, scientists with particular knowledge on controversial subjects, and a selection of coaches/trainers/athletes who are striving daily for optimal (and legal) performance enhancement. This would be the most democratic way to address issues such as weighing the impact of the three criteria mentioned in the WADC, the difference between In Competition/Out of Competiton prohibitions, the necessity to list certain substances for certain sports only, etcetera. We would be more than happy to assist WADA in organising such a symposium.
- We propose that all fundamental issues of the Prohibited List will be discussed at a working symposium in the not too distant future, since this will be the best way to find a common approach regarding Prohibited List issues. This way, the Prohibited List International Standard could be supported by a much larger proportion of all stakeholders than in the current situation.

We hope our contributions are useful and we look forward to the final 2010 Prohibited List International Standard.

With sincere greetings and the best wishes for you and your team,

Also on behalf of the Ministry of Health, Welfare, and Sports, the National Olympic Committee NOC*NSF, and the NOC*NSF athlete committee,

Anti-Doping Authority the Netherlands

Herman Ram
CEO