Submission 1 of 3.

[redacted]

To <SMP@health.gov.au>,
cc
bcc
Subject Further Submissions [SEC=No Protective Marking]

DOCUMENT NOT YET CLASSIFIED

Hi,

I was making a final submission regarding DMAA and it usage in sports supplements. [redacted] Never in my time have I heard anything negative from [redacted] regarding health effects, this is in spite of daily use by most of them. Now, if one was to believe that DMAA was that dangerous and bad for your health wouldn't we have heard negative reports? This supplement has now been used for over 6 years almost daily and we have not heard ANY negative reports. If DMAA was deserved of being scheduled into schedule 9, higher then ephedrine etc, then shouldn't there be evidence of harsh health effects?

I truly believe the better option would be to regulate the ingredient and ensure it is not abused. I also think making supplement sellers/retailers earn a diploma or degree would be a great benefit for the industry.

[redacted]

Submission 2 of 3.

Re-Submission Regarding DMAA

Firstly, thank you for the opportunity to submit a further submission. I received notification that the TGA has made an interim decision to schedule DMAA into S9 of the SUSMP.

Although my position and recommendations have remained substantially unchanged, I will summarise them again for your perusal, and also include a number of new points that are very important and relate to the submission process.

The main argument of this submission is that S9 is completely over-restrictive for DMAA. Schedule 9 is reserved for drugs or poisons with no therapeutic potential, as well as being potentially dangerous or addictive.

This interim decision does not seem to have been made via an evidence-based process or with the public interest at heart. I strongly recommend treating DMAA similarly to synephrine, by scheduling it into S4 over a certain dosage limit. We believe the TGA has acted without regard for the public interest in this matter for the following reasons:

- Only people who submitted originally have the right to submit again. Why? Surely most people's submissions change very little from number one to number two. It is only after the initial interim decision has been made that the public tends to become aware of the issue. I know a number of people who were about to submit until they realised they were not allowed to, and were outraged at their impotence to comment on a public issue. **This impediment to public comment is highly undemocratic**, and seems to be specifically designed to prevent the public from getting involved in an issue that affects us. I would appreciate an explanation of this procedure.
- Automatic scheduling of these kinds of substances into S9 without a rigorous scientific enquiry into the real harms, risks and benefits has **the potential to deny the public substances that can assist them in their health aims.** In this case, many people use DMAA to achieve their fitness aims or weightloss aims. Surely adults in a democracy have the right to make choices about what they ingest to achieve their aims, as long as appropriate health warnings and information is provided.
- Automatic scheduling also **limits the scope for scientific research** to be conducted, and thereby limits future medical breakthroughs.
- **The two-week period provided between interim decision and implementation of the ban is outrageous. This shows no concern for the hundreds of legitimate small businesses that will be adversely affected by these bans.** Not only will a number of top-selling items be made unavailable, the stocks of many of these products will suddenly become highly illegal, making these businesses unable to recoup losses for these products. I have never seen such a quick implementation of a scheduling decision. When pseudo-ephedrine was scheduled, the pharmaceutical company involved received *years* to take these products off the shelf, despite the high risk these products have for affecting public health by being turned into amphetamines. I strongly suggest that you extend your grace-period in this case. These are difficult economic times, and you will cripple many Australian families with this tiny window of opportunity to recover losses on these products. Even if you don't approve of the vitamin shops, health food shops, sports supplement businesses, and the legal highs businesses, they are still run as legitimate small businesses by genuine Australian families trying to make ends meet. These people are also part of the public, whose interests you are supposed to represent.

I propose that in making this decision, you have not followed due process. Under s52E, certain matters must be taken into account when scheduling a substance, especially the risks and benefits of the use of a substance. Furthermore, the extent of use of a substance and the potential for abuse of a substance should be taken into account. None of these important points seem to have been taken into account:

- **DMAA is known to be an effective weight-loss and fitness aid**, which, although this may not be considered a health outcome in and of itself, has **wide-reaching positive health effects** due to the numerous chronic health problems associated with obesity in Australia today.
- What is more, **DMAA has a similar risk and safety profile to synephrine,** which is derived from *Citrus aurantium* immature fruit, and is commonly used in Traditional Chinese Medicine to increase metabolism and boost a sluggish digestion. Despite both synephrine and DMAA displaying similar risks and potentials for harm when used incorrectly, the TGA advisory committee decided to impose a maximum dosage limit, which has effectively mitigated adverse effects from this substance**. Above the 100mg cut off limit, synephrine is S4 (pharmacist prescription only),** which allows those who can benefit from this substance, and are not at risk of developing negative side effects, access via the carefully-controlled prescription process.
- Users report significant increases in energy and endurance, along with a feeling of wellbeing, without the energy crash associated with high caffeine intake. Considering the wide-spread use and availability of this substance, it seems highly likely that any potential for abuse would have already been exploited, and be obvious by now. Therefore, one can conclude that **DMAA's potential for abuse is low**.
- Your very own advisory committee advised Schedule C, not Schedule 9. I am curious to know why you would diverge from the advice provided by the expert advisory committee.
- In your interim decision, you mentioned that the potential for illicit use is high. This statement makes little sense, as there is zero potential for illicit use unless it becomes an illegal substance, which as it currently stands it is not. This is a skewed kind of reasoning, where the reason for the decision is only true because of the decision. What's more, **outright banning these products will drive a number of people who currently use these legally to continue their use illegally,** increasing the problem with illegal drugs, rather than addressing it!

It is my sincere suggestion that DMAA be treated the same way as synephrine: imposed a maximum dosage of 100mg, and above this level being scheduled in S4. I also suggest that you review the process you currently apply to these issues, to increase public involvement. Whatever the scheduling decision , it is only fair to allow a period of 6 months for the numerous small businesses to adapt to the scheduling decisions.

Furthermore I suggest that outside this issue you consider adopting a rational approach to new substances similar to that New Zealand has taken, where manufacturers must (within reason) prove that their products are safe, rather than outright banning. This will do much more to tackle the problems authorities are having with the increase in unknown highs and supplements that the current approach.

Thank you for your careful consideration of my arguments.

[redacted]

Submission 3 of 3.

July 25, 2012

Medicines and Poisons Scheduling Secretariat (MDP88)
GPO Box 9848
CANBERRA ACT 2601

Response to the Interim Decision of the Medicines Scheduling Delegate of the Secretary on Including 1,3-Dimethylamylamine (1,3-DMAA) in Schedule 9 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)

This submission is made on behalf of USPlabs, LLC (the Company), which markets dietary supplement products in Australia and throughout the world containing 1,3-DMAA. The Company was the party on behalf of whom a full submission (the Original Submission) was made on 1,3-DMAA by [redacted] on 25 May 2012 to the Secretary to the Department of Health and Ageing for consideration by the Advisory Committee on Medicines Scheduling (ACMS) with respect to the scheduling of 1,3-DMAA.

I. Confidentiality

The Company requested that the Original Submission to the ACMS remain confidential, because it contains extensive information on the safety of 1,3-DMAA that is proprietary to the Company. In light of the Interim Decision of the medicines scheduling delegate (the Delegate) of the Secretary on this matter, however, the Company now withdraws its request for confidentiality. All of the information in the Original Submission of 25 May 2012 and this submission may now be made available to the public. In this way, interested scientists and members of the public will have available the full range of safety information that the Company has commissioned on the safety of this dietary supplement when used in accordance with the label directions for use and warnings. The Company reiterates the information contained in the Original Submission to the ACMS in support of this response to the Interim Decision of the Delegate.

II. The History of this Proceeding

As a result of New Zealand's temporary prohibition of 1,3-DMAA effective for one year as of 9 April 2012, the Delegate initiated a proposal to include this dietary ingredient in Schedule 9 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). In accordance with the Scheduling Policy Framework for Medicines and Chemicals (the Framework), the matter was referred to the ACMS for expert scientific advice on the matter.

After a thorough review of the submissions made on this matter, the ACMS recommended against scheduling 1,3-DMAA in Schedule 9 and instead recommended that this dietary substance be placed in Appendix C. In his decision on 10 July 2012, however, the Delegate rejected the expert scientific advice of the ACMS and issued an interim decision to include 1,3-DMAA in Schedule 9, effective as of 1 August 2012. The Delegate provided no

evidence or explanation for why he overruled the ACMS. The Delegate allowed additional submissions by 25 July 2012.

III. The Position of the Company

The Company believes that the scientific evidence contained in the Original Submission demonstrates that 1,3-DMAA is safe for use as a dietary supplement in accordance with the directions for use and warnings contained in the labeling. More than a billion servings of dietary supplements containing 1,3-DMAA have been consumed worldwide, without a single documented instance of a serious adverse event when used in accordance with the labeling.

Nonetheless, the Company recognizes that the ACMS and the Delegate have both recommended action that precludes continued marketing of 1,3-DMAA in Australia. The Company has already stopped importation of 1,3-DMAA into Australia and has ceased distribution within the country. This was necessitated by the 1 August 2012 implementation date established by the Delegate. Accordingly, for business reasons, the Company has concluded not to oppose the inclusion of 1,3-DMAA in Appendix C, as recommended by the expert scientific committee established to consider these issues, the ACMS. But the Company strongly opposes inclusion of 1,3-DMAA in Schedule 9, for the same reasons that the ACMS opposed such an approach.

IV. 1,3-DMAA is Labeled and Marketed as a Dietary Supplement, Not a Drug

Throughout the world, 1,3-DMAA is uniformly labeled and marketed for use as an ingredient in a pre-workout dietary supplement taken as part of an exercise fitness program. It is one of the most popular dietary supplement ingredients marketed for this purpose. As already noted, more than a billion servings of dietary supplements containing 1,3-DMAA have been safely consumed for this purpose.

Products containing 1,3-DMAA are not labeled or marketed as a drug. Although the ingredient has well established dietary supplement value, it has no approved therapeutic use in any country in the world. Thus, provisions that govern the use of drugs in general, and Section 52E of the Therapeutic Goods Act 1989 in particular, are not applicable to these products. That is undoubtedly why the ACMS did not refer to Section 52E in its evaluation of 1,3-DMAA.

Even if Section 52E were applicable, it would not justify the Interim Decision of the Delegate. The dietary supplement benefits of 1,3-DMAA outweigh the rare instances of harm caused by misuse of this dietary ingredient. More than a billion servings have been safely consumed as a dietary supplement. Its toxicity is very low, as demonstrated by seven clinical studies and 30 years of safe use under an NDA as a nonprescription drug in the United States. It is labeled and marketed solely for use as a pre-market dietary supplement. It is not abused in the way that narcotics are abused, and instances of misuse are rare.

Accordingly, the appropriate regulatory framework for 1,3-DMAA in Australia is the Framework. The Framework covers all chemicals, whether they are used as food, dietary

supplements, drugs, cosmetics, paint, household cleansers, industrial products, or any other product.

V. The Recommendation of the ACMS Must Be Given Great Weight by the Delegate

The Framework was developed by the National Coordinating Committee on Therapeutic Goods in order to establish a uniform and consistent national approach to scheduling decisions in Australia. Under Section 5 of Chapter 1, the ACMS is established as an "expert advisory committee." Section 5.3.4 requires that the ACMS have expertise in such relevant scientific disciplines as toxicology, pharmacology, and clinical pharmacology. Accordingly, the recommendations of this expert scientific advisory committee must be given great weight, in order to promote the reliability and the consistent national approach that is the objective of the Framework. The Delegate has not given a full explanation and adequate reasons in the Interim Decision for rejecting the ACMS recommendations. The failure to follow the expert scientific advice of the ACMS, or to provide evidence or a rationale for overruling the ACMS, undermines the credibility of the Framework, the Interim Decision of the Delegate, and the entire Australian scheduling process.

VI. As the ACMS Determined, 1,3-DMAA Does Not Meet the Criteria for Schedule 9 of SUSMP

As Section 1.2 of Chapter 3 of the Framework states on page 16 with respect to Schedule 9:

> "…the highly restricted criteria for this schedule mean that very few substances are likely to be considered for, or included in this schedule."

Consistent with the intent of the Framework, the ACMS concluded that 1,3-DMAA does not meet the criteria for Schedule 9 set forth in the factors established on page 26 of the Framework. Those three factors are as follows:

1. "**The substance is included in either Schedule IV to the United Nations Single Convention on Narcotic Drugs, 1961 or in Schedule I to the United Nations Convention on Psychotropic Substances 1971."**

As the ACMS pointed out, 1,3-DMAA is not a narcotic and is not psychoactive. It is not related to, and does not have the same physiological or psychological effects as, other controlled substances, such as amphetamine. It is not addictive and it does not cause withdrawal. Thus, the primary purpose of Schedule 9 -- to ban narcotic and other psychoactive substances in accordance with international treaties on these types of substances -- is not met.

Instead, 1,3-DMAA is a stimulant. As the ACMS concluded, it does not have the substantial toxicological and pharmacological properties that would warrant a Schedule 9 listing. The amount of 1,3-DMAA in the Company's dietary supplements has the same stimulant effect as the caffeine contained in 2-3 cups of coffee. Indeed, as the report by Dr. Rodricks and his

colleagues[1] included in the Original Submission points out, there is a very close relationship between 1,3-DMAA and caffeine. In this respect, dietary supplements that contain the amount of 1,3-DMAA that are marketed in Australia today cannot be distinguished from widely marketed caffeinated energy beverages and other common sources of caffeine. There is far greater evidence of the use of caffeinated beverages, in particular, as a party drug when combined with alcohol, than there is with respect to 1,3-DMAA. We are submitting a separate report by Dr. Rodricks and his colleagues that was not available at the time the Original Submission was made on the close relationship between caffeine and 1,3-DMAA.[2] Dr. Rodricks is among the most highly respected toxicologists in the world. He is a member of the Institute of Medicine of the United States National Academy of Sciences and has served as Associate Commissioner of the United States Food and Drug Administration.

In a newspaper article published in "The Age" on July 8, 2012, an equally highly respected Australian scientist, Dr. Ian Musgrave, was quoted as making the following comments:

> The Chair of Toxicology at the Australasian Society for Pharmacology and Toxicology, Dr. Ian Musgrave, said he was "baffled" as to why DMAA was being considered for such a serious ban. "Even amphetamine is schedule 8," he said. "Unless the Department has information I haven't seen, it's unclear why they want to make it a Schedule 9 drug."

In short, 1,3-DMAA does not meet the primary criterion for Schedule 9.

2. "The substance has either no currently established therapeutic value, or taking into consideration the danger to the health of individuals and of the community (both immediate and imminent) associated with the use of the substance as compared to the therapeutic advantages of the substance, the benefits are substantially outweighed by the risks."

As already noted, 1,3-DMAA has no approved therapeutic value. Nor does any other dietary supplement or any food, cosmetic, or industrial chemical. But this is not a ground to include all these chemicals in Schedule 9. This simply underscores that 1,3-DMAA is being considered under the wrong provisions. It should be considered under Appendix C, where other non-therapeutic products such as cosmetics, household cleansers, and paints are included.

Although 1,3-DMAA is not a therapeutic product, it does have established dietary supplement value, as demonstrated by its substantial popularity as a fitness supplement throughout the world. When used as directed in the labeling, it has never been shown to be toxic. Like all consumer products, if it is misused it can be harmful. Evidence of misuse of 1,3-DMAA is very rare.

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[1] Joseph V. Rodricks et al., Safety Evaluation of 1,3 Dimethylamylamine (DMAA) in Dietary Supplement Products (May 2012).

[2] Environ International Corporation, A Comparison of the Physiological Effects of Caffeine and Dimethylamylamine (DMAA) (May 8, 2012).

3. "The substance has no currently established therapeutic value and is likely to present a high risk of dependency, abuse, misuse or illicit use."

Again, as noted above, 1,3-DMAA has established dietary supplement value, but no approved therapeutic value. The dietary ingredient has no risk of dependency, abuse, or illicit use, as the ACMS found. As explained above, the instances of misuse have been relatively few in light of its widespread use as a fitness supplement. Indeed, when used as directed and in accordance with label warnings, there is no scientific evidence of any serious adverse event anywhere in the world. In comparison with the much greater abuse of caffeine dietary supplement products with alcohol, 1,3-DMAA is far safer.

VII. The Determination of the ACMS

The ACMS -- the expert scientific committee established under the Framework to assure the reliability and consistency of scheduling decisions under the SUSMP -- similarly concluded that 1,3-DMAA should not be included in Schedule 9 for the following reasons:

> First, the toxicological and pharmacological properties of 1,3-DMAA -- which are discussed in detail in the Original Submission, together with the attachments to that Submission -- show that there is inadequate evidence to suggest that the toxicological and pharmacological properties of the dietary ingredient warrant a Schedule 9 listing.
>
> Second, 1,3-DMAA is not listed in any of the international conventions on narcotic and psychotropic substances.
>
> Third, there is a lack of supporting evidence to reach the conclusion that 1,3-DMAA needs the same level of control as amphetamine (which is a Schedule 8 drug).
>
> Fourth, the toxicological properties of 1,3-DMAA are properly considered under the Appendix C scheduling criteria rather than the Schedule 9 criteria.

The ACMS goes on to conclude that 1,3-DMAA does meet the criteria for inclusion in Appendix C. As noted above, although the Company does not agree with this conclusion, for business reasons we have concluded not to oppose it.

VIII. The Seven Factors Briefly Listed in the Interim Decision as Considered by the Delegate With Regard to the Proposal Weigh Heavily in Favor of Including 1,3-DMAA in Appendix C Rather Than in Schedule 9

"New Zealand's temporary Class Notice."

Only the New Zealand temporary one-year class drug notice is consistent with the inclusion of 1,3-DMAA in Schedule 9. All of the other six factors support consideration of 1,3-DMAA in Appendix C.

Like the Delegate's Interim Decision for Australia, the New Zealand notice provides no evidence or reasons for its action. Accordingly, it is entitled to little or no weight.

"International scheduling decisions, including the United States FDA, Canada and United Kingdom."

International scheduling decisions that are ongoing in the United States, Canada, and the United Kingdom are not based upon concern about the safety of 1,3-DMAA. All three raise and focus on the question whether, under the different statutory provisions that apply in each of the three countries, 1,3-DMAA is properly classified as a drug rather than as a dietary supplement or otherwise violates the statutory requirements to be classified as a dietary supplement. In the United States and the United Kingdom, the matter has not yet been resolved. In the United States an FDA spokesperson stated to the press that the warning letters were sent because the companies "had not submitted NDI [new dietary ingredient] notifications for their DMAA supplements."[3] In Canada, the decision was made that 1,3-DMAA is properly classified as a drug under Canadian law. None of these proceedings is based upon, or relates to, the safety of the ingredient when used in accordance with labeled directions and warnings.

"public submissions received."

Five of the six public submissions received by the ACMS support the safety of 1,3-DMAA. Only one opposes safety, on the ground that the ingredient is "addictive." As the ACMS immediately pointed out, however, there is no scientific basis for concluding that 1,3-DMAA is addictive.

"ACMS advice."

The ACMS advice that 1,3-DMAA should properly be considered under Appendix C and not Schedule 9 was ignored in the Interim Decision of the Delegate, without explanation. For the reasons we discuss above, we believe that the delegate should follow the ACMS advice.

[3] Nutraingredients (April 30, 2012).

"section 52E of the Therapeutic Goods Act 1989."

Section 52E of the Therapeutic Goods Act 1989 applies to drugs. 1,3-DMAA is not labeled or marketed as a drug, and dietary supplements containing 1,3-DMAA have no approved therapeutic value. This may be a factor in scheduling it in Appendix C, but it is clearly not a reason by itself for including it in Schedule 9. Schedule 9 was not intended to become a list of non-therapeutic consumer products and household substances.

"scheduling factors."

As we noted above, the Framework regards Schedule 9 as "highly restrictive" and states that it should be used for "very few substances." Schedule 9 is intended to encompass narcotics and other psychoactive drugs that present serious problems of addiction, dependence, and social disruption.

"other relevant information"

We are unaware of what other information the Delegate considered "relevant." None of the other relevant information in the Original Submission supports scheduling 1,3-DMAA in Schedule 9. The Delegate should identify and discuss the relevance of any other information he considers.

IX. The Seven Reasons Briefly Listed by the Delegate for the Interim Decision to Include 1,3-DMAA in Schedule 9 Do Not Support That Decision

The Delegate cites seven very brief "reasons" for the Interim Decision to schedule 1,3-DMAA in Schedule 9 of the SUSMP. An analysis of these reasons demonstrates that they do not support inclusion in Schedule 9.

"there are no current approved therapeutic uses for DMAA"

This is a criterion for Appendix C, not for Schedule 9. If all substances that have no current approved therapeutic use were put in Schedule 9, it would result in a ban of all dietary supplements, all cosmetics, all paints, and all other household chemicals and products. This criterion, by itself, is not enough for Schedule 9.

"there are no benefits but there are significant risks"

Neither the ACMS nor the Delegate have considered the dietary supplement benefits of 1,3-DMAA. Rather, they have considered only the therapeutic benefits. The Company agrees, of course, that there are no approved therapeutic uses of 1,3-DMAA or, indeed, any other dietary supplement, cosmetic, or other non-drug consumer product. This does not mean that they should be listed in Schedule 9.

There has been no showing of a significant risk other than a modest amount of misuse. Any substance can, of course, be dangerous if misused. Again, rare instances of misuse -- which

occur with every consumer product -- is not a criterion for Schedule 9, which is intended to be used for dangerous narcotics and related controlled substances.

"there are risks due to DMAA's toxicity"

1,3-DMAA was used as a nonprescription drug in the United States from 1948 until 1978 -- a full 30 years -- under a new drug application (NDA). It was withdrawn by the manufacturer for business reasons, and FDA therefore withdrew approval of the NDA, not because of any concern by FDA or the company about safety. There are seven recently-published clinical studies showing the safety of 1,3-DMAA under conditions established in the labeling, all of which are in the Original Submission. Although misuse of 1,3-DMAA -- like misuse of any substance -- can on rare occasions result in significant risk, that is not a basis for Schedule 9 classification.

"DMAA presents a high risk of abuse, misuse and illicit use"

There have been rare instances of misuse and, as noted immediately above, this can result in a significant risk. The same is true of all substances and consumer products, and is not a criterion for inclusion in Schedule 9. These rare instances do not demonstrate a high risk of misuse. 1,3-DMAA is not a highly toxic substance.

The kind of abuse and illicit use to which reference is made in Schedule 9 is not simple misuse. In the context of Schedule 9, abuse and illicit use contemplate illegal use of dangerous narcotics and other illicit controlled substances that result in major social harm. That, of course, is not an issue here.

"reports of adverse events including high blood pressure, psychiatric disorders, cerebral hemorrhage and stroke"

The Company is unaware of any substantial reports of such adverse events caused by 1,3-DMAA. The Delegate provides no evidence to support this statement. Certainly, such adverse events have not occurred in the United States. The Company has reviewed all adverse events relating to 1,3-DMAA that have been reported either to FDA or to the Company. There is not a single corroborated serious adverse event that has been reported when the products containing 1,3-DMAA were used in accordance with the labeled directions and warnings. The seven clinical trials, including trials under stressful athletic performance conditions, have not reported a significant issue of high blood pressure, much less other serious adverse events. The Delegate's allegation must either be documented by sound science or withdrawn.

"an absence of studies demonstrating the long-term safety of DMAA"

As noted above, 1,3-DMAA was used in the United States for 30 years as the active ingredient in a nonprescription drug under a new drug application (NDA) with no identified safety problems. There is substantial evidence of both short-term and long-term safety of the ingredient in the Original Submission.

"the wide variability in the potency of the different doses of DMAA"

One purpose of Appendix C is to provide the opportunity to establish limits on potency in order to assure the safety of an ingredient. Variations in potency present an issue more appropriate for Appendix C than for Schedule 9. If potency alone were a criterion for Schedule 9, all of the current Appendix C substances would instead belong in Schedule 9.

X. Conclusion

Although the Company does not agree that 1,3-DMAA is unsafe when used in a dietary supplement under appropriate labeled directions for use and warnings, for business reasons the Company has concluded not to oppose inclusion of this ingredient in Appendix C. We oppose its inclusion in Schedule 9 because that schedule is intended for narcotics and other very serious illicit controlled substances that have major law enforcement and other adverse social consequences. Quite simply, Schedule 9 is intended for narcotics and related substances of a type that are completely different from 1,3-DMAA.

Respectfully submitted,

A Comparison of the Physiological Effects of Caffeine and Dimethylamylamine (DMAA)

The compound, 1,3-dimethylamylamine (DMAA) is a central nervous system stimulant added to some dietary supplements. It shares similar pharmacological effects in humans with caffeine (1,3,7-trimethylxanthine), a central nervous system stimulant consumed worldwide in the diet.

Both DMAA and caffeine are amine, or alkaloid-type, compounds occurring naturally in plants. Caffeine is found in coffee, tea, cacao beans (source for chocolate and cocoa) guarana, mate, bissy nuts and kola nuts, though the compound has been identified in more than 60 plant species (Frary et al. 2005, Barone et al. 1996). DMAA has been found in parts-per-billion to parts-per-million concentration levels in both geranium (*Pelargonium graveolens*) plant tissue (stems and leaves) and distilled plant oil (Li et al. 2012, Ping et al. 1992, USPlabs 2012).

Caffeine is consumed by more than 80% of the world's population each day and 82-87% of the U.S. population (Frary et al. 2005, Heckman et al. 2012). Published values of average daily caffeine intake from beverage consumption in the U.S. range from 106-170 mg/day for adults and 120 mg/day for all ages (Knight et al. 2004). Total average daily caffeine intake in the U.S. from food and beverages is 227-300 mg/day for adults and 193 mg/day for all consumers (Frary et al. 2005, Knight et al. 2004). Caffeine consumption by U.S. adults, expressed on a per body weight basis, was reported to be approximately 4 mg/kg/day (Knight et al. 2004), which can be attained by consuming 2-4 cups of coffee or 2-6 cups of brewed tea. Outside of the U.S., daily average caffeine intake of 400 mg/day (or 6 mg/kg/day for a 70 kg adult) has been reported (Biaggioni and Davis 2002), with average intake in Denmark reported to be 7 mg/kg/day (Barone et al. 1996).

Nawrot et al. (2003), in their comprehensive review of the literature, estimated a safe level of daily caffeine consumption of 400 mg/day, which was not associated with adverse health effects for healthy adults. However, doses as high as 750 mg/day have also been shown to be well tolerated in normal subjects (Biaggioni and Davis 2002), while patients with cardiovascular disease exhibited favorable tolerance for doses of up to a 250 mg dose (Hirsch et al. 1989).

The similarities between caffeine and DMAA for physiological changes in hemodynamic effects were reported in adults in a randomized, double-blinded, crossover clinical study (Bloomer et al. 2011). Ten healthy men and women were given 250 mg caffeine or 50 mg DMAA while at a rest. Caffeine ingestion resulted in an average maximum increase in systolic (SBP) and diastolic blood pressure (DBP) of 6 mm Hg and a decrease in heart rate of 5 beats per minute (bpm) over a 120 minute period after administration. A 50 mg dose DMAA resulted in an average maximum increase in SBP and DBP of 7 and 8 mm Hg, respectively, while heart rate decreased by 4 bpm. The changes in blood pressure and heart rate following doses of 250 mg caffeine or 50 mg DMAA were not statistically different.

In this same study, Bloomer et al. (2011a) reported that doses of 75 mg DMAA (which is 25% to 275% greater than in a labeled single serving of the USPlabs products OxyElite Pro™ or Jack3d™) resulted in average maximum increases in SBP and DBP of 16 and 9 mm Hg, respectively, along with a decrease in heart rate of 3 bpm. The increases in SBP and DBP from 75 mg DMAA doses are not significantly different from those reported in other clinical studies involving similar subject populations. Robertson et al. (1978), in a double-blind crossover clinical study, gave 250 mg caffeine to nine young, healthy men and women at rest. The average maximum increase in SBP and DBP was 14 mm Hg and 10 mm Hg, respectively, while heart rate decreased initially and then increased slightly. Nurminen et al. (1999) reported that a 250 mg caffeine dose in adults produced an average maximum increase in SBP and DBP of 12 mm Hg and 13 mm Hg, respectively. In a single-dose study evaluating the hemodynamic effects of Jack3d™, Farney et al. (2012) reported that a double serving of the product, providing 40 mg of DMAA and 250 mg of caffeine, resulted in an average maximum increase in SBP and DBP of 13 and 8 mm Hg. DMAA and caffeine also share similar hemodynamic effect profiles over time; peak magnitude of effects appear within 30-60 minutes post-administration, followed by a gradual decline to baseline (Hirsch et al. 1989, Robertson et al. 1978, Farney et al. 2012, Marsh et al. 1951, Mort and Kruse 2008). Thus, the effects of DMAA consumed in labeled servings of Jack3d™ and OxyElite Pro™ upon blood pressure are quite similar to those seen with a 250 mg dose of caffeine, the amount found in 2-3 cups of coffee or 2-6 cups of brewed tea.

For caffeine, the transient reduction in heart rate concomitant with the increase in blood pressure is thought to arise from the baroreceptor reflex, in which an increase in blood pressure results in

a decrease in heart rate (Lane and Manus 1989). This homeostatic mechanism aids in maintaining a steady total cardiac workload. It is only when the baroreceptor reflex is overcome that this does not occur. The initiation of the baroreceptor reflex was indicated in clinical studies of resting adults who consumed DMAA (Bloomer et al. 2011a, Farney et al. 2012, Whitehead et al. 2012, Marsh et al. 1951). Additionally, strenuously exercising adults who consumed DMAA or placebo exhibited no difference in heart rate, indicating that labeled DMAA use does not increase cardiac workload (Bloomer et al. 2011b). Tachyphylaxis, the partial tolerance to changes in blood pressure after an initial administration, appears to occur for both caffeine and DMAA (25, 26).

Both caffeine and DMAA have both exhibited very good tolerance by adults. Caffeine consumption levels substantially higher (400-500 mg/day) than those typically (275-300 mg/day) consumed are considered well tolerated (Kivity et al. 1990). Similarly, DMAA was shown to be well tolerated alone or in finished dietary supplement formulations (Bloomer et al. 2011a, Farney et al. 2012, Bloomer 2012, Whitehead et al. 2012, Bloomer et al. 2011b, McCarthy et al 2012a, McCarthy et al. 2012b) with no adverse health impacts reported. Furthermore, a dose 3 mg/kg DMAA dose (3.5 to 10.5 times greater than DMAA in labeled servings of OxyElite Pro or Jack3d for a 70 kg adult) has also been explored in a small group of individuals and also was shown to be well tolerated, with no serious adverse events. Recent clinical trials of DMAA and caffeine consumed in combination provide hemodynamic data for subjects that ingested both compounds just prior to exercise (Farney et al. 2012, Whitehead et al. 2012, Bloomer et al. 2011b), post exercise (Bloomer et al. 2011b), and over the course of time in which regular exercise was performed (Farney et al. 2012, Whitehead et al. 2012, McCarthy et al. 2012b). The available data for DMAA and caffeine do not indicate that consumption of both compounds in the dietary supplements OxyElite Pro™ or Jack3d™ would increase the susceptibility of adults to adverse cardiovascular events while exercising.

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[redacted]

Friday, 25 May 2012

The Secretary
Scheduling Assistant
GPO Box 9848
Canberra ACT 2601

Re: Response to Advisory Committee on Medicines Scheduling (ACMS) - Proposal to include DMAA in Schedule 9

This submission is made at the request of a client whose formulated (oral sports dietary supplement powder) product contains, as one of its ingredients, an amount of DMAA.

This submission is relevant to the scheduling proposal for 1,3-dimethylamylamine (DMAA) to include DMAA in Schedule 9, where the delegate has requested advice from the ACMS in regarding to this scheduling proposal under section 5.2 of the SPF (page 6).

In relation to this submission, we would request that the following matters in accordance with the Scheduling Policy framework be treated as confidential information:

[redacted]

2. The Cantox Health Sciences International - safety of DMAA - February 2012 report.
3. Rodricks, J.V., Turnbull, D. & Lumpkin, M. 1,3 Dimethylamylamine (DMAA) is not an Amphetamine-like Compound: Comparison of Chemical and Pharmacological Differences. Environ International 2012.
4. Rodricks, J.V., Turnbull, D. & Lumpkin, M. Safety Evaluation of 1,3 Dimethylamylamine (DMAA) in Dietary Supplement Products. Environ International 2012.

Items 2, 3 and 4 in the above list, are reports commissioned by our client, and represent its confidential and proprietary information. Our client considers that this information is pertinent to matters to be considered by the Committee, and if such matter was to be subject to public release, it would not submit the same as part of the scheduling review process.

If the Secretary has any issues in respect of the above claims to confidential treatment we would request that such matters be discussed with us.

This document may contain privileged or confidential information intended only for the addressee. If you are not the intended recipient, you are advised that any distribution, publication or copying of this communication is strictly prohibited.

In accordance with Section 52E of the Therapeutic Goods Act, we have addressed the following matters:

a) The risks and benefits of the use of DMAA
b) The purposes for which DMAA is to be used and the extent of use of DMAA
c) The toxicity of DMAA
d) The dosage, formulation, labelling, packaging and presentation of DMAA
e) The potential for abuse of DMAA

Risks and benefits of the use of DMAA

There are a variety of formulated products for sale as dietary supplements (globally) which are also in regular use in Australia, which contain, as one of their ingredients, DMAA.

Formulated products containing DMAA have been associated with a low incidence of adverse events, when compared to their extensive use worldwide. For example, from the estimated one billion servings (10-20mg DMAA per serving) of dietary supplements containing DMAA sold by the dietary supplement industry in the United States during between 2009 and 2012, there were 21 adverse reaction reports in that 3 year period (some voluntary, anonymous, online).

Further, 12 of those 21 adverse reaction reports reported use in violation of its labelled Directions for Use and Warnings, including dosages greater or more frequent than those in the labelled dosage instructions and uses in conjunction with other supplements, stimulants, medications, alcohol. Nine of the incidents didn't meet the statutory definition of a "serious adverse event" (results in death, life-threatening experience, inpatient hospitalisation, disability or incapacity, congenital abnormality or birth defect).

Studies have been undertaken with reference to both DMAA in isolation and formulated products containing DMAA.

Peer reviewed clinical studies at the University of Memphis involving formulated product containing DMAA did not show a statistically significant increase in blood pressure in an acute and chronic setting.[1,2]

Another study which administered DMAA and caffeine prior to exercise, found the combination of DMAA and caffeine resulted in no statistically significant difference in blood pressure or heart rate compared to placebo. The authors of the study stated, “Interestingly, the combination of caffeine + 1,3-D did not result in a higher SBP compared with placebo. In fact, the response was nearly identical to that of placebo—for both SBP and HR.”[3]

Additional studies indicate blood pressure changes are offset by reduced heart rate to maintain consistent cardiovascular load.[2,3]

Thus, there is no scientific evidence that labelled use of formulated products by healthy adults will compromise individual health or increase susceptibility to heart-related injuries.[4] It is not warranted to prohibit use of suitably labelled, formulated products containing DMAA, through inclusion of DMAA in Schedule 9.

Purposes for which DMAA is to be used and the extent of use of DMAA

The use of DMAA in humans is not new and has been documented since the 1940s. It is a naturally occurring aliphatic amine that has sympathomimetic properties. It was marketed as an FDA-approved OTC nasal decongestant for 30 years, and is currently used as a stimulant in formulated products.[4]

DMAA is a constituent of the geranium plant (ppb levels). It has never been introduced in any market as a "steroid".[5] To the extent that DMAA is sold in pure form into the open market in various parts of the world, such sales of the pure compound have no connection to its inclusion in appropriate proportions in formulated products. It is not a steroid and has no chemical or physiological relation to a steroid.[4,6]

Recently, media reports have included remarks by 2 scientists that DMAA is a stimulant similar to amphetamine and is an amphetamine derivative.[7] This is not the case. DMAA is an aliphatic amine with sympathomimetic activity. It lacks the phenyl or benzene ring that all amphetamines and its derivatives have.[6] Therefore, it is not an amphetamine and is in no way related to being an amphetamine, and should not be in the same company as amphetamines, or the other substances included in Schedule 9.[6]

A comprehensive report is provided, which details the dissimilarities between DMAA and amphetamines.[6] Aside from the significant structural differences between these distinctly different chemical classes, the absence of a benzene ring in DMAA significantly differentiates it from amphetamines in terms of the way DMAA interacts with proteins (i.e. receptors) in neurons.[6] As a nervous system stimulant and toxicant, amphetamine is far more potent than DMAA, while the psycho-stimulatory effects of amphetamine are not observed at all with DMAA.[6]

Further, the compound does not have norepinephrinergic effects, as demonstrated by Bloomer et al. (2011) which showed no effect by DMAA or caffeine and DMAA combined, upon circulating norepinephrine levels.[8]

Toxicity of DMAA

One study has indicated that DMAA has the same effects on the body as caffeine. The stimulatory haemodynamic effects, including short-term increases in blood pressure, of DMAA in formulated products at labelled usage rates are statistically identical to those from the amount of caffeine in 2-3 cups of coffee.[4] The clinical data indicate lack of changes in clinical markers that would be exhibited as precursors or manifestations of clinically adverse outcomes.[4]

Further, the Cantox report states "it is unlikely that DMAA consumption from [formulated products] would cause adverse effects when used as directed by the appropriate population."[5]

Over the past few years years, 6 published clinical studies related to DMAA, have provided data on the haemodynamic, haematological, liver and renal safety of formulated products containing DMAA in healthy adults consuming labelled doses for up to 10 weeks.[1-3,8-10] Clinical studies are in progress, aiming to provide further details regarding the pharmacokinetics of DMAA and to add additional clinical observations throughout 12-weeks of DMAA use by larger groups of volunteers than previously tested.

Dosage, formulation, labelling, packaging and presentation of DMAA

A serving size of DMAA from formulated product is between 10mg and 20mg, and that 2 to 3 servings per day are recommended (based on two products currently marketed overseas).

The labels of formulated products sold overseas specify that use of these products should be limited to healthy adults, in consultation with a physician. The product labels also recommend a limit on the consumption, with one product indicating it should be used no more than 5 days during any 7-day period, and the other stating that it should be used continuously for no more than 8 weeks, followed by a 4 week cessation of dosing. The product labels also state that no additional caffeine should be used, nor should the products be combined with alcohol.

Potential for abuse of DMAA

DMAA has not exhibited characteristics of an addictive substance.[4,6] The potential for dependency, and subsequent abuse, of DMAA is very unlikely.

Based on leading "dietary supplement" products overseas containing DMAA, formulated product will not contain more than 20mg per serve DMAA in powder, capsule or tablet form, with a recommendation daily intake of 3 servings (ie. 60mg DMAA per day).[5] Abuse of formulated product containing such low concentrations of DMAA is unlikely.

The report of abuse of pure DMAA appearing in the New Zealand Press in 2010 were related to cerebral haemorrhage in a 21-year-old male who took a bolus dose of DMAA (approximately 600 mg), caffeine (150 mg) – a dosage that would not be achieved from a formulated sports product. The amount consumed was 30 - 60 times the amount from formulated sports products. It is also noted that the substance was ingested in combination with unknown quantities of alcohol and other substances.[11] Such co-exposures are explicitly contraindicated on labelling of formulated product labels.

There has been a published report from New Zealand concerning 3 cases of cerebral haemorrhage after the use of "legal party pills" containing DMAA, where the subjects also consumed an unpublished quantity of alcohol. It should be noted that labelling of formulated sports product advises against the use of the product in the presence of alcohol.[12]

In the cases reported by Gee et al. (2012), the quality of manufacture is unknown in relation to the "party pills" consumed.

Formulated sports dietary supplements containing DMAA as a minor ingredient are considered by sports enthusiasts to have a place in exercise regimes. The use of unregulated, non-manufacture- or formulation-controlled "party pills", used by people to substitute for illicit substances, should not result in the prohibition of the legitimate use of DMAA in, for example GMP-manufactured medicines for stamina and endurance.

Conclusion

It is our client's contention the "factors for prohibited substances" required to be met for inclusion in Schedule 9 of the Poisons Standard are not met by DMAA in the context of formulated sports dietary supplement. Therefore DMAA should not be included in Schedule 9 of the Poisons Standard.

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