DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
College Park, MD 20740

April 18, 2013

Mr. Jonathan W. Doyle
President
USPlabs, LLC
10761 King William Dr.
Dallas, TX 75220

Re: Warning Letter 285519

Dear Mr. Doyle:

We acknowledge receipt of your letters dated May 15 and 17, 2012, September 28, 2012, and January 14, 2013, which respond to the April 24, 2012, FDA Warning Letter issued to your firm. In the Warning Letter, FDA advised you that your products Oxy Elite Pro and Jack3D, which are labeled and/or promoted as dietary supplements and contain 1, 3-dimethylamylamine HCl (DMAA), are adulterated. We have reviewed the response letters and the studies you presented in those letters, as discussed below.

DMAA is declared as a dietary ingredient in the labeling of Oxy Elite Pro and Jack3D. You assert that DMAA is a dietary ingredient under section 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 321(ff)(1)) in two ways: (1) it is a constituent of a botanical, namely the geranium *Pelargonium graveolens*, under section 201(ff)(1)(C) and (F); and (2) it is a dietary substance for use by man to supplement the diet under section 201(ff)(1)(E). FDA disagrees with both of these assertions. DMAA does not qualify as a dietary ingredient under section 201(ff)(1)(C) or 201(ff)(1)(F) because DMAA is not an herb or other botanical, nor is it a constituent of a botanical. Although you claim that DMAA is present as a constituent of the geranium *P. graveolens*, the totality of the science available on the subject does not credibly support this claim, as explained below. [1,2,3,4,5,6,7] Additionally,

[1] Ping et al. A study on the chemical constituents of geranium oil. Journal of Guizhou Institute of Technology. 1996. 25(1):82-85.
[2] Li et al. Identification and quantification of dimethylamylamine in geranium by liquid chromatography tandem mass spectrometry. Analytical Chemistry Insights. 2012:7:47-58.
[3] Fleming et al. Analysis and confirmation of 1,3-DMAA and 1,4-DMAA in geranium plants using high performance liquid chromatography with tandem mass spectrometry at ng/g concentrations. Analytical Chemistry Insights. 2012:7:59-78.
[4] Zhang et al. 1,3-dimethylamylamine (DMAA) in supplements and geranium products: natural or synthetic? Drug Testing Analysis. 2012:4(12):986-990.
[5] El Sohly et al. Pelargonium oil and methyl hexaneamine (MHA): analytical approaches supporting the absence of MHA in authenticated Pelargonium graveolens plant material and oil. Journal of Analytical Toxicology. 2012:00:1-15.
[6] Di Lorenzo et al. Could 1,3 dimethylamylamine (DMAA) in food supplements have a natural origin? Drug Test Anal. 2012 Sep 3.

FDA disagrees with your assertion that DMAA qualifies as a dietary ingredient under section 201(ff)(1)(E), because you have not presented evidence that DMAA is a dietary substance for use by man to supplement the diet by increasing total dietary intake and, to the best of FDA's knowledge, no such evidence exists.

We reviewed the scientific information you provided, as well as other studies not funded by USPlabs, regarding the presence of DMAA in *P. graveolens*. The Ping et al., Li et al., and Fleming et al. studies that you provided reported finding DMAA as a constituent of geranium oil. However, these studies are contradicted by other studies and cannot be relied on because of the deficiencies and inconsistencies discussed below.

In the Ping et al. study, the plant material described as *P. graveolens* was reportedly collected from the Guizhou province in China. However, the description of the authentication methods used in the study suggests that the plant material was not properly authenticated. A study cannot be considered scientifically valid if the material tested has not been authenticated and characterized such that the material can be reproduced.[8, 9] To properly authenticate a sample of plant material, collection and identification information needs to be compiled and documented, including the proper Latin binomial name of the plant material; the name of the collector or collectors of the sample; the date and location of collection; a description of the geography and habitat of the place where the sample was collected; a unique collection number or code; a description of the plant part(s) collected; organoleptic characteristics[10] of the plant material (e.g., smell, taste, touch, color); processing steps (e.g., drying method, time, and temperature); and representative images (e.g., digital pictures or sketches) of the plant in its growing habitat and as a post-harvest mounted specimen.[11] Additionally, a representative sample of the collected material in the form of a voucher specimen (i.e., a representative specimen used to confirm the identity of the plant species referred to in the study) containing an accurate description of the plant needs to be stored in either a registered public herbarium, certified research institute, or, in the case of commercial materials, an on-site herbarium repository.[12, 13] In the Ping et al. study, these authentication procedures necessary to ensure the validity of study results were not documented.

The Ping et al. study states that the dried plant material was subjected to steam distillation to obtain the essential oil. During gas chromatography (GC)–mass spectrometry (MS) analysis

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[7] Lisi et al. Studies of methylhexaneamine in supplements and geranium oil. Drug Test Anal. 2011 Nov-Dec;3(11-12):873-6.

[8] Smillie and Khan, A Comprehensive Approach to Identifying and Authenticating Botanical Products. Clin Pharmacol Ther. 2010 Feb;87(2):175-86. doi: 10.1038/clpt.2009.287. Epub 2009 Dec 23.

[9] Wolsko et al., Lack of Herbal Supplement Characterization in Published Randomized Controlled trials. Am. J. Med. 118, 1087–1093 (2005).

[10] Organoleptic characteristics are those that can be evaluated through the senses (i.e., sight, smell, taste, touch, and hearing). Houghton P., ESTABLISHING IDENTIFICATION CRITERIA FOR BOTANICALS Drug Information Journal, Vol. 32, pp. 461–469, 1998.

[11] Khan and Smilie, Implementing a "Quality by Design" Approach to Assure the Safety and Integrity of Botanical Dietary Supplements. J. Nat. Prod., 2012, 75 (9), pp 1665–1673.

[12] Van Breemen et al., The Role of Quality Assurance and Standardization in the Safety of Botanical Dietary Supplements. Chem Res Toxicol. 2007 April; 20(4): 577–582.

[13] American Herbal Products Association and American Herbal Pharmacopeia, Good Agricultural And Collection Practice For Herbal Raw Materials. December 2006 (http://www.ahpa.org/portals/0/pdfs/06_1208_AHPA-AHP_GACP.pdf).

of the steam distillate, Ping et al. separated 40 peaks and claimed to identify 31 components. However, the identifications were based solely on the matching of mass spectra with those in a mass spectral library and did not include reports of the quality of the matches. If the method of identifying a component is to compare its spectrum to those of all the candidates in the spectral library and determine which candidate provides the best fit (the highest spectral similarity), the accuracy of the identification should be documented with a report showing the percentage match between the component and each candidate from the library.[14] Without a report showing the quality of the matches, there is no way to determine whether the study authors in fact chose the best match or whether better fits may have been available -- in which case it is likely that the component was misidentified. Further, no reference standards (samples of synthetic DMAA used to check whether the analytical method is capable of finding DMAA) were analyzed to confirm the identifications by using the retention time of the compound or by using the fragmentation pattern.[15] Other studies that have analyzed the chromatogram peaks suggested that the detection of 4-methyl-2-hexanamine and 5-methyl-2-hexanamine in the Ping et al. study was due to a mistranslation or misidentification, and that what was found was instead 2-hexanamide, 4-methyl and 2-hexanamide, 5-methyl, different molecules altogether.[16] The chromatographic trace from the Ping et al. study also has the compounds eluting late in the chromatogram, whereas methylhexaneamine is very volatile and elutes very early, requiring low GC starting temperatures.[17]

In the Li et al. study, the authors reported that they found the presence of DMAA and 1, 2-dimethylamylamine in an analysis of *P. graveolens* plant materials. These plant materials were reportedly collected from three geographical locations in China: Yunnan, Jiangsu, and Guizhou provinces. According to the paper, geranium plants from these three areas in China were provided by Yi Jin of Yunnan University and were authenticated by Professor Xu Youkai, PhD, of the Xishuangbanna Tropical Botanical Garden-Chinese Academy of Sciences. However, the study does not provide all of the information necessary to demonstrate proper authentication. These omissions raise questions about the identity and quality of the plant materials tested. For example, the study did not document the date of collection or provide a description of the geography and habitat where the plant materials were collected. Geranium oil samples were reportedly acquired from Jiangxi Ji'an Hengcheng Flavor Oil Factory, but no additional information on authentication methods was provided. Further, the methodology of the study was flawed in that samples were analyzed for DMAA and 1,4-dimethylamylamine by an LC–MS/MS method without the derivatization technique[18] that would be necessary to make detection of a compound possible at the low concentration reported in this study.[19]

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[14] Ausloos, et al., The critical evaluation of a comprehensive mass spectral library. J.Am. Soc. Mass Spectrom. 1999, 10, 287–299.

[15] Pawar et al., Updates on chemical and biological research on botanical ingredients in dietary supplements. Anal Bioanal Chem online publication DOI 10.1007/s00216-012-6691-2.

[16] *See supra* notes 5 and 15. *See infra* note 17.

[17] Health Canada, Health Products and Food Branch, Classification of 1,3-Dimethlyamylamine (DMAA) (2011).

[18] Derivatization is a technique used in chemistry which transforms a chemical compound into a product (the reaction's derivate) of similar chemical structure, called a derivative. When small amounts of an analyte are believed to be present, derivatives are made so that certain detection techniques can be taken advantage of (like fluorescence). Chiral derivatizing agents react with enantiomers to give diastereomers. Since diastereomers have different physical properties, they may be further analyzed by high-performance liquid chromatography (HPLC). At a low concentration of DMAA, such as was found in the study by Li et al., one would need to derive to make detection of DMAA possible. *See* Chandrul and Srivastava, Enantiomeric separation in pharmaceutical analysis:

After analyzing the *P. graveolens* plant materials, Li et al. reported that isomers of DMAA were present in equal ratio to the synthetic DMAA used as a reference material. Detection methods reportedly revealed the presence of 1,3-DMAA in all tested plant and oil samples, with quantities ranging from 13.6 ng/g to 13271 ng/g. 1,4-DMAA was also reportedly detected in some plant and oil samples, but not all. Li et al. therefore concluded that DMAA is naturally occurring in geranium plants of the *P. graveolens* species. However, the levels reported by Ping et al. were considerably higher than those reported by Li et al. The large variations in DMAA content -- up to three orders of magnitude -- reported in these studies (both sponsored by USPlabs) raises serious questions about the validity of the findings when the studies are evaluated for consistency, reproducibility, and robustness.[20] However, despite the large variance in the total reported concentration of DMAA in the findings of these studies, there is no reported finding of variance in the proportion of optical isomers of DMAA. Variation in the proportion of optical isomers would be expected with seasonal or geographic variations in the total concentration of DMAA. Unprecedented findings of this nature usually require a more in depth scientific study and additional scientific tools to confirm the accuracy of the findings. USPlabs has provided no such follow-up studies.

The Li et al. study touched on the issue of stereochemistry, specifically the ratio of stereoisomers.[21] The similarity of stereoisomer ratios between the DMAA reportedly found in the plant material and the synthetic DMAA standard used as a reference material in the study suggests that the DMAA found in the plant was in fact synthetically produced, as nature usually favors one stereochemical confirmation over another due to biosynthetic and enzymatic pathways in botanicals. The chromatograms in the study showed that the isomeric ratio Li et al. purported to find in the plant was identical to that of the synthetic standards used in the study. This finding that the chirality[22]of DMAA found in botanicals is indistinguishable from that of synthetically produced standards was not satisfactorily explained in Li et al. and would require a demonstration of the biosynthetic pathway by which the geranium plant produces the racemic compound[23] to have any scientific credibility in the face of the growing evidence from other studies that DMAA does not exist in the plant.[24]

A chromatographic approach, J. Chem. Pharm. Res. 2010: 2(4):923-934, http://jocpr.com/vol2-iss4-2010/JCPR-2-4-923-934.pdf

[19] *See supra* note 15.

[20] *See supra* notes 8 and 9.

[21] A stereoisomer is any of a group of isomers in which atoms are linked in the same order but differ in their spatial arrangement. stereoisomer. 2013. In Merriam-Webster.com. Retrieved April 17, 2013, from http://www.merriam-webster.com/dictionary/stereoisomer.

[22] Chirality is or relates to a molecule that is not superimposable on its mirror image. chirality. 2013. In Merriam-Webster.com. Retrieved April 17, 2013, from http://www.merriam-webster.com/dictionary/chirality.

[23] Racemic is, relates to, or constitutes a compound or mixture that is composed of equal amounts of dextrorotatory and levorotatory forms of the same compound and is not optically active. recemic. 2013. In Merriam-Webster.com. Retrieved April 17, 2013, from http://www.merriam-webster.com/dictionary/racemic.

[24] *See* Zhang et al. 1,3-dimethylamylamine (DMAA) in supplements and geranium products: natural or synthetic? Drug Testing Analysis. 2012:4(12):986-990; El Sohly et al. Pelargonium oil and methyl hexaneamine (MHA): analytical approaches supporting the absence of MHA in authenticated Pelargonium graveolens plant material and oil. Journal of Analytical Toxicology. 2012:00:1-15; Di Lorenzo et al. Could 1,3 dimethylamylamine (DMAA) in food supplements have a natural origin? Drug Test Anal. 2012 Sep 3; Lisi et al. Studies of methylhexaneamine in supplements and geranium oil. Drug Test Anal. 2011 Nov-Dec;3(11-12):873-6.

The authors of the Fleming et al. study claimed to confirm the presence of DMAA and 1,4-dimethylamylamine in geranium plant material using HPLC–MS. Fleming et al. analyzed three *P. graveolens* samples reportedly collected from Changzhou, Guiyang, and Kunming in China. However, as with the Ping et al. and Li et al. studies, vital collection and identification information (e.g., organoleptic characteristics, information on the place where the samples were collected, a description of how the samples were processed, and details on voucher specimens) was not provided in the study to demonstrate proper authentication. These omissions raise questions about the identity and quality of the samples. Further, although samples from three different areas were tested, only the plant material obtained from Changzhou was reported to contain dimethylamylamine isomers (DMAA, 97– 499 ng/g and 1,4-dimethylamylamine, 68–162 ng/g). It is important to note that Guizhou province samples were reported by Li et al. to contain 365 ng/ml DMAA, but the Guiyang (also belonging to Guizhou province) sample of Fleming et al. did not detect DMAA.

Fleming et al. claimed that one of the Changzhou samples was also analyzed by Li et al., and both sets of investigators confirmed the presence of DMAA. Thus, Fleming et al. concluded that their data provide an inter-laboratory confirmation of the presence of DMAA. However, the samples and instrumental conditions in the two analytical studies reported by Li et al. and Fleming et al. were identical. Therefore, there was no verification of the finding using a different analytical technique, which would be essential for meaningful inter-laboratory confirmation of the presence of DMAA in *P. graveolens*.[25]

The three studies you provided that reported the presence of DMAA in *P. graveolens*, which are the only three peer reviewed studies reporting the presence of DMAA in this plant species, are all confounded by the lack of adequate information regarding sample origins and handling. In other words, no scientific conclusions about the presence of DMAA in *P. graveolens* can be drawn from these studies because of this critical missing information. Without evidence of authenticated botanicals and a documented chain of custody to ensure the samples analyzed weren't misidentified or contaminated, it is virtually impossible to confirm the presence of any constituent of *P. graveolens*. The failure by Ping et al. to use a standard to confirm the retention time and mass spectrum of DMAA when it was first reported in geranium plant material also casts significant doubt on the accuracy of the initial identification. It is important to note that the subsequent studies by Li et al. and Fleming et al. failed to fully isolate and characterize DMAA as occurring in a botanical, which is significant in light of four studies not funded by USPlabs (Zhang et al., El Sohly et al. Di Lorenzo et al., and Lisi et al.) that found no DMAA in *P. graveolens*. Also significant are the reported amounts of DMAA in the Li et al., Ping et al., and Fleming et al. studies, given that the studies showing no natural occurrence of DMAA (e.g., Zhang et al.) used analytical methods that were in the appropriate range to detect and quantitate DMAA. These unlikely findings from Li et al., Ping et al., and Fleming et al. would require significant scientific evidence of how these reported amounts of DMAA came to be, yet USPlabs presented no such evidence in any of its responses to the Warning Letter.

Finally, USPlabs' studies and supporting documents do not credibly refute the studies reporting that DMAA does not occur in *P. graveolens*. These studies (Zhang et al., El Sohly et al., Di Lorenzo et al., and Lisi et al.) were conducted to develop a chemical profile of

[25] *See supra* note 15.

geranium oils. While the fact that these four studies did not report finding DMAA does not provide conclusive proof of its absence from *P. graveolens*, the studies identified and reported constituents at concentrations as low as 0.1 % of the oil composition, indicating the greater sensitivity of these methods compared to the methods used in Ping et al., Li et al., and Fleming et al. Given the concentrations of DMAA in the Ping et al., Li et al., and Fleming et al. studies, the methods used in the studies by Zhang et al., El Sohly et al., Di Lorenzo et al., and Lisi et al. would be able to detect DMAA, if it existed.

In conclusion, FDA disagrees with your contention that DMAA is a dietary ingredient under section 201(ff)(1) of the Act. The totality of the scientific evidence discussed above does not demonstrate the presence of DMAA in *P. graveolens*. Therefore, DMAA is not a constituent of *P. graveolens* that could qualify as a dietary ingredient under section 201(ff)(1)(F). Additionally, although you assert in the May 17, 2012 letter that DMAA is a dietary ingredient under section 201(ff)(1)(E) because *P. graveolens* is a dietary substance for use by man to supplement the diet by increasing total dietary intake, the possibility that geraniums may have been consumed as a food or drink by humans does not demonstrate that DMAA is a dietary substance because, as explained above, the totality of the scientific evidence does not demonstrate the presence of DMAA as a constituent of geraniums. Further, to the best of FDA's knowledge, DMAA is not commonly used as a food or drink by humans. Finally, DMAA does not qualify as a dietary ingredient under any other prong of section 201(ff)(1) of the Act.[26] Because DMAA does not qualify as a dietary ingredient, your Oxy Elite Pro and Jack3D products are adulterated under section 402(a)(2)(C) of the Act (21 U.S.C. 342(a)(2)(C)) because the products contain an unsafe food additive (i.e., DMAA).

The introduction or delivery for introduction into interstate commerce of any food that is adulterated is a prohibited act under section 301(a) of the Act (21 U.S.C. 331(a)). Further, it is a prohibited act under section 301(ll) of the Act (21 U.S.C. 331(ll)) to introduce or deliver for introduction into interstate commerce any food to which a drug approved under section 505 of the Act (21 U.S.C. 355) has been added, unless the added drug was marketed in food before being approved under section 505.[27] DMAA was approved as a drug in 1948 under section 505 of the Act and, to the best of FDA's knowledge, was not marketed in food prior to such approval, either on its own or based on its alleged presence as a component of *P. graveolens*. You have not presented any evidence of such marketing. In the absence of such evidence, your Oxy Elite Pro and Jack3D products are in violation of section 301(ll) of the Act.

We note that your response letters also addressed several other aspects of the Warning Letter, such as safety data for DMAA. Since we disagree with your conclusion that DMAA is a dietary ingredient for the reasons outlined above, this letter does not comment on the other arguments made in your submissions.

Please respond to this letter within 15 days with your plans for taking corrective actions with regard to Oxy Elite Pro, Jack3D, and any other DMAA-containing products you market. Your response should be sent to Quyen Tien, Compliance Officer, at this address: U.S. Food

[26] DMAA is not a vitamin, amino acid, herb, or other botanical. Also, to the best of FDA's knowledge, DMAA is not a concentrate, metabolite, constituent, extract, or combination of any dietary ingredient.
[27] Section 301(ll) also contains other exceptions not relevant here. See 21 U.S.C. 331(ll)(2)-(4).

and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Compliance, 5100 Paint Branch Parkway, College Park, MD, 20742. You may also contact Quyen Tien by email at Quyen.Tien@fda.hhs.gov.

Sincerely,

Jennifer A. Thomas

Jennifer A. Thomas
Director
Division of Enforcement
Office of Compliance
Center for Food Safety
And Applied Nutrition

cc: FDA Dallas District