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November 4, 2013

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Office of Compliance
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Food and Drug Administration
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Re: Warning Letter No. 413065 (October 11, 2013)

Dear Mr. Tien:

This letter responds to the warning letter from William A. Correll Jr. (the Correll letter) dated October 11, 2013, regarding the marketing of the Company's dietary supplements containing the dietary ingredient aegeline. The Correll letter states that (1) FDA knows of no information demonstrating that aegeline is a dietary ingredient, (2) if aegeline is a dietary ingredient, FDA believes it would be a new dietary ingredient (NDI) for which a notification has not been submitted, and (3) FDA knows of no evidence demonstrating the safety of aegeline as a dietary ingredient. This letter and its appendices demonstrate that aegeline complies with the applicable requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for a lawful dietary ingredient and does not present a significant or unreasonable risk of illness or injury to consumers under the conditions of use recommended or suggested in the labeling.

In the spirit of cooperation, the Company agreed on October 8, 2013, to stop distributing in the United States its dietary supplements that contain aegeline while the cluster of acute non-viral hepatitis cases in Hawaii are being investigated. Although the Company knows of no valid concern about the safety of aegeline or OxyElite Pro, the Company has made the business

decision, in light of the adverse publicity, to reformulate the product and to discontinue the use of aegeline in the United States. As FDA is aware, the Company has voluntarily destroyed its distribution center inventory of all dietary supplements containing aegeline. Reformulated replacement products will be marketed shortly.

I. Aegeline is a Dietary Ingredient

Section 201(ff)(1) of the FD&C Act defines a dietary supplement as:

> a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
>
> (A) a vitamin;
>
> (B) a mineral;
>
> (C) an herb or other botanical;
>
> (D) an amino acid;
>
> (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
>
> (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)...[1]

The dietary ingredient involved here, aegeline, satisfies the statutory definition of a dietary ingredient in two ways: (1) under Sections 201(ff)(1)(C) and (F), as a constituent of a botanical—bael fruit, leaves, and bark—and (2) under Section 201(ff)(1)(E), as a dietary substance for use to supplement the diet by increasing the total dietary intake.

A. The Bael Tree is a Botanical Plant

[1] FD&C Act § 201(ff)(1).

The word "botanical" is broadly defined as "Of or pertaining to plants or plant life."[2] The term "tree" is defined as "A usually tall woody plant."[3] Thus, the parts of the bael tree that are used for food, including use in dietary supplements, all fall within the definition of the word "botanical."

The bael tree is known by the Latin binomial name of *Aegle marmelos*. It is native to India, but is cultivated throughout the surrounding areas. The bael tree belongs to the family Rutaceae, which are the "citrus" plants. It is grown, and the fruit, leaves, and bark have been consumed as food, throughout much of Southeast Asia since at least 1500 BC.[4]

The famous botanist, Dr. David Fairchild, created the Office of Seed and Plant Introduction of the United States Department of Agriculture in 1897[5] and served as the USDA Agricultural Explorer in Charge for the next 27 years.[6] He introduced many important plant species as agricultural crops into the United States, including soy beans, pistachios, dates, nectarines, bamboo, avocados, and mangos.[7] Fairchild acquired a taste for bael fruit during his time in Southeast Asia, brought bael seeds back to the United States, grew the tree beginning in 1918, and consumed its fruit at his home in Coconut, Florida. He distributed the fruit, plant, and seeds to friends and colleagues in the United States, encouraging others to cultivate bael as a

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[2] The American Heritage Dictionary of the English Language 154 (1975) (Appendix 1).

[3] Id at 1367 (Appendix 1).

[4] Roy, S.K., Bael, *in* Fruits of India, Tropical and Subtropical 498 (Bose, T.K., ed., 1985) (Appendix 2); V. Singanan et al., The Hepatoprotective Effect of Bael Leaves (Aegle marmelos) in Alcohol Induced Liver Injury in Albino Rats, 2 Int'l J. Sci. Tech., No. 2, at 83 (2007) (Appendix 3).

[5] W. Shurtleff & A. Aoyagi, History of Soybeans and Soyfoods in Southeast Asia 847, 943 (2010) (Appendix 4).

[6] Id. at 224, 943 (Appendix 4).

[7] A. McClellan, The Cherry Blossom Festival 28 (2005) (Appendix 5).

potential commercial fruit. Fairchild documented importation of bael seeds into the United States and cultivation of the bael tree by the Hawaii Experiment Station beginning in 1906.[8] Other references document importation in other parts of the country in 1909[9], 1912[10], and 1918[11].

B. Aegeline is a Well-Documented Constituent of Bael Fruit, Leaves, and Bark

It appears that aegeline was first isolated from the fruit, leaves, and bark of the bael tree in 1952.[12] Since that time, the literature is replete with studies isolating aegeline using a wide variety of analytical methods and technology.[13]

C. The Fruit, Leaves, and Bark of the Bael Tree Have Been Used for Food in Southeast Asia for Centuries

There are many ways by which the bael fruit, leaves, and bark are consumed as food.[14] The fruit is eaten fresh or dried. If fresh, the juice is strained and sweetened to make a

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[8] D. Fairchild, In Defense of the Bael Fruit, Aegele Marmelos, 56 Proc. of Florida State Hort. Soc. 165 (1943) (Appendix 6).

[9] USDA Bureau of Plant Industry, Seeds and Plants Imported During the Period from July 1 to September 30, 1909, at 23 (1910) (Appendix 7).

[10] USDA Bureau of Plant Industry, Seeds and Plants Imported During the Period from January to March 31, 1912, at 282 (1913) (Appendix 8).

[11] G.L. Peltier, Relative Susceptibility to Citrus - Canker of Different Species and Hybrids of the Genus Citrus, Including the Wild Relatives, 19 J. of Agric. Res. 339, 341 (1920) (Appendix 9).

[12] A. Chatterjee & S. Bose, Studies on the Active Principles Isolated from the Leaves of *Aegle Marmelos*, Correa, 29 J. Indian Chem. Soc. 425 (1952) (Appendix 10).

[13] E.g., R.N. Chakravarti & B. Dasgupta, The Structure of Aegeline, J. Chem. Soc. 1580 (1958) (Appendix 11); B.R. Sharma et. al., Marmeline, an Alkaloid, and Other Components of Unripe Fruits of Aegle Marmelos, 20 Phytochemistry, No. 11, at 2606 (1981) (Appendix 12); T.R. Govindachari & M.S. Premila, Some Alkaloids from Aegle Marmelos, 22 Phytochemistry, No. 3, at 755 (1983) (Appendix 13); S. Riyanto et al., Alkaloids from Aegle Marmelos (Rutaceae), 7 Malaysian J. Anal. Sci., No. 2, at 463 (2001) (Appendix 14); S. Lanjhiyana et al., A Validated HPTLC Method for Simultaneous Estimation of Two Marker Compounds in Aegle Marmelos (L.) Corr., (Rutaceae) Root Bark, 4 Der Pharmacia Lettre, No. 1, at 92 (2012) (Appendix 15); A. Karmase et al., Evaluation of Anti-Obesity Effect of Aegle Marmelos Leaves, 20 Phytomedicine, No. 10, at 805 (2013) (Appendix 16).

drink similar to lemonade. Unstrained, the pulp is made into a breakfast food. If the fruit is dried, it is usually sliced, sun-dried, and simmered in water. The leaves are eaten as salad greens. The bark can be infused in water to make tea. It was the use of the pulp, combined with palm sugar, to make a breakfast food, that lead David Fairchild to grow bael fruit in Florida.

In India, by beating the seeded pulp of bael fruit, together with milk and sugar, a very popular drink is produced. The mature, but still unripe bael fruit is made into a jam with the addition of citric acid. The half-ripe bael fruit is used to make marmalade or syrup. The pulp is used to make jelly and toffee. The fruit powder is used in cold drinks. The young leaves and shoots are consumed both in salads and as a seasoning agent or condiment in food. It has documented nutritional value.[15]

D. Bael Food Products are Marketed Throughout the United States Today on the Internet

A current internet search of the term "sale of bael products" reveals 29 pages of food products made from bael. These include bael seeds, bael fruit (both fresh and dried), bael tea, and some 290 separate entries for food products containing bael ingredients.

II. Aegeline is Not a New Dietary Ingredient that Requires a New Dietary Ingredient Submission

It is unnecessary to determine whether the importation and cultivation of bael trees in the United States for food use prior to 1994 constitutes the "marketing" of aegeline that excludes it

[14] E.g., J.F. Morton, Fruits of Warm Climates: Bael Fruit (1987) (Appendix 17); A. Chevallier, The Encyclopedia of Medicinal Plants (1996) (Appendix 18); S. Facciola, Cornucopia II: A Source Book of Edible Plants (1998) (Appendix 19); A. Davidson, The Oxford Companion to Food (2d ed. 2006) (Appendix 20); P.C. Sharma et al., A Review on Bael Tree 6 Nat. Prod. Radiance, No. 2, at 171 (2007) (Appendix 21); N.P. Yadav & C.S. Chanotia, Phytochemical and Pharmacological Profile of Leaves Aegle Marmelos Linn., The Pharma Review, Nov.-Dec., at 44 (2009) (Appendix 22); S. Dhankhar et al., Aegle Marmelos (Linn.) Correa: A Potential Source of Phytomedicine, 5 J. Med. Plant Res., No. 9, at 1497 (2011) (Appendix 23).

[15] Sharma, note 14 supra, at 173-174 (Appendix 22).

from the definition of a new dietary ingredient under Section 413(c) of the FD&C Act. Section 413(a)(1) provides that, even if a dietary ingredient was not marketed in the United States prior to 1994, it is not subject to the requirement for an NDI submission under 413(a)(2) if:

> (1) The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered.

Because aegeline is unquestionably a constituent of the fruit, leaves, and bark of the bael tree, all of which have been used as food for centuries, and aegeline can be extracted from these three parts of the bael tree without any chemical alteration, an NDI submission to FDA for aegeline is not required. As is true for the vast majority of dietary ingredients, most of the aegeline used in dietary supplements is a synthetic counterpart of the natural extract.

III. Nonclinical and Clinical Test Data Demonstrate No Safety Concern About Aegeline

A. Nonclinical Toxicity Data

1. Tests on Extracts from the Fruit and Leaves

Data from studies of animals consuming various extracts from bael fruit and leaves indicate very low acute and subacute toxicity. An ethanol extract of bael fruit was reported to be non-toxic in mice given intraperitoneal doses of up to 6 g extract/kg.[16] The no observed adverse effect level (NOAEL) for clinical observations or mortality in mice observed for 14 days after a single oral gavage dose of has been determined as 1250 mg extract/kg[17]. Mice administered intraperitoneal injections of up to 50 mg/kg ethanolic extracts for 14 days did

[16] G.C. Jagetia et al., Fruit Extract of Aegle Marmelos Protects Mice Against Radiation-Induced Lethality, 3 Integrative Cancer Therap., at 323 (2009) (Appendix 24).

[17] P.V. Joshi et al., In Vitro Antidiarrheal Activity and Toxicity Profile of Aegle Marmelos Correa ex Roxb, Dried Fruit Pulp, 8 Nat. Prod. Radiance, No. 5, at 498 (2009) (Appendix 25).

not exhibit any gross or histopathological toxicity.[18] In rats, extracts of bael leaves did not result in toxicity following intraperitoneal injections of up to 100 mg/kg. [19]

2. Tests on Aegeline

Four nonclinical oral toxicity studies of aegeline have been conducted in rats and rabbits.

Groups of 10 male and female Wistar rats were given single oral gavage doses of aegeline of 0, 500, 1000, or 2000 mg/kg of aegeline and observed daily for 14 days for general health, clinical observations of CNS effects, body weight, and mortality.[20] No clinical signs were observed in the control or treated animals. No pre-terminal mortality occurred during the entire study period. Body weight gain and feed intake of all the animals was normal. Gross pathology examination revealed no abnormal changes in any of the observed tissues, including the liver. Based on the study results, the study investigators determined that the maximum tolerated dose (MTD) in Wistar rats was greater than 2000 mg/Kg.

Similarly, groups of 6 male and female New Zealand White rabbits were given single oral gavage doses of 0, 500, 1000, or 2000 mg/kg of aegeline and observed daily for 14 days for general health, clinical observations of CNS effects, body weight, and mortality.[21] No clinical signs were observed in the control or treated animals. No pre-terminal mortality occurred during the entire study period. Body weight gain and feed intake of all the animals

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[18] A. Veerappan et al., Acute and Subacute Toxicity Studies on Aegle Marmelos Corr., an Indian Medicinal Plant, 14 Phytomed Nos. 2 & 3, at 209 (2007) (Appendix 26).

[19] Id at 9 (Appendix 26).

[20] Clintox Bioservices, Report on Determination of Maximum Tolerated Dose (MTD) of Aegeline in Wistar Rats (July 10, 2012) (Appendix 27).

[21] Clintox Bioservices, Report on Determination of Maximum Tolerated Dose (MTD) of Aegeline in New Zealand White Rabbits (July 10, 2012) (Appendix 28).

were normal. Gross pathology examination revealed no abnormal changes in any of the observed tissues, including the liver. As with the rat study, the study investigators determined that the MTD in rabbits was greater than 2000 mg/Kg.

Subchronic 90-day aegeline oral toxicity studies were also performed in rats and rabbits. Groups of 20 male and female Wistar rats were given daily oral gavage doses of 0, 50, 100, or 200 mg/kg for 90 days.[22] All animals were observed daily for signs of overt toxicity, body weight, feed intake, and mortality. Clinical observations for CNS effects were performed, as well as functional observation battery tests. Urinalysis, hematology, and clinical chemistry analysis, as well as gross pathological examination of heart, lung, liver, kidneys, spleen, stomach, large intestine, small intestine, brain and skin were performed at sacrifice of the animals. In general, no significant clinical observations or abnormalities were observed in experimental groups. No pre-terminal mortality occurred. The body weight gain and feed intake of the treated animals was similar to that of controls. No abnormalities were observed during the functional observation battery tests. Most of the parameters of hematology and serum biochemistry analyses were within the normal range in the treatment groups as compared to the vehicle control group. In urinalysis, there were no treatment related changes in any of the experimental animals. There was no significant difference between groups in absolute and relative organ weights. No treatment-related differences between groups in gross pathology and histopathology examination were reported. The study authors concluded that daily oral administration of up to 200 mg/kg aegeline once per day for 90 days did not cause any adverse effects in rats.

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[22] Clintox Bioservices, Report on 90-Day Repeated Dose Toxicity Study of Orally Administered Aegelin in Wistar Rats with Recovery Period of 14 Days (Draft 2013) (Appendix 29).

Groups of 8 male and female New Zealand white rabbits were given daily oral gavage doses of 0, 50, 100, or 200 mg/kg for 90 days.[23] All animals were observed daily for signs of overt toxicity, body weight, feed intake, and mortality. Clinical observations for CNS effects were also performed, as well as ophthalmic observations. Urinalysis, hematology, and clinical chemistry analysis, as well as gross pathological examination of heart, lung, liver, kidneys, spleen, stomach, large intestine, small intestine, brain and skin were performed at sacrifice of the animals. No significant clinical abnormalities were observed in experimental groups. No pre-terminal mortality occurred. The body weight gain and feed intake of the treated animals was similar to that of the controls. No ophthalmic abnormalities were observed. Parameters of hematology and serum biochemistry analyses were within the normal range in the treatment groups as compared to the vehicle control group. In urinalysis, there were no treatment related changes in any of the experimental animals. There was no significant difference between groups in absolute and relative organ weights. No treatment-related differences between groups in gross pathology and histopathology examination were reported. The study authors concluded that daily oral administration of up to 200 mg/kg aegeline once per day for 90 days did not cause any adverse effects in rabbits.

Thus, the nonclinical studies of aegeline in two species of laboratory animals did not indicate signs of toxicity at oral doses of up to 200 mg/kg for 90-days. Scaling the subchronic NOAELs to human equivalent doses (HEDs), based on body surface area,[24] results in HED NOAELs of 32 to 64 mg/kg/day, or 2240 to 4480 mg aegeline/day, for a 70 kg

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[23] Clintox Biosciences, Report on 90-Day Repeated Dose Toxicity Study of Aegeline Administered by Oral Gavage in New Zealand White Rabbits with Recovery Period of 14 Days (Draft 2013) (Appendix 30).

[24] FDA, Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (July 2005) (Appendix 31).

adult. These HED NOAELs are 19 to 37 times higher than the maximum recommended daily intake per day for OxyElite Pro; 15 to 30 times higher than the maximum recommended intake per day for OxyElite Pro Advanced; 6 to 11 times higher than the maximum recommended intake per day for Versa-1; and 8 to 17 times higher than maximum recommended intake per day for OxyElite Pro Super Thermo Powder.

B. Clinical Data on Aegeline

Serum clinical chemistry data for adult volunteers consuming aegeline for up to 5 weeks show no acute hepatotoxic effects in humans. An in-house pilot study was performed to evaluate the effects of daily aegeline consumption in capsules on blood serum indicators of liver, kidney, sex hormone, and thyroid health.[25] The administered daily doses ranged from 200 to 800 mg aegeline for 2 to 5 weeks in a group of six adult males. No adverse effects were reported by the study subjects. Clinical chemistry tests did not indicate any adverse effects on kidney (glomerular filtration rate, glucose, BUN, creatinine, and electrolyte levels), endocrine (total and free testosterone, estradiol, sex-hormone binding globulin, LH, FSH, TSH, and total and free T3, T4 levels), or liver (protein, albumin, globulin, bilirubin, alkaline phosphatase, AST, and ALT levels) function.

If aegeline was causing acute non-viral hepatitis in Hawaii, participants in this study should have manifested acute non-viral hepatitis. The doses administered were higher than those in OxyElite Pro, and the study period of up to 5 weeks is clearly long enough to demonstrate an acute non-viral attack of hepatitis. Yet no liver toxicity of any kind occurred.

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[25] ENVIRON, Blood Test Indicators of Liver, Kidney, Sex Hormone, and Thyroid Health Following Aegeline Ingestion for 2 to 5 Weeks (January 25, 2013) (Appendix 32).

C. Historical Human Consumption

As discussed in Part I of this response, bael is a citrus fruit that, along with other parts of the bael tree, has been used as food in India dating back to 1500 B.C. Bael fruit has long been consumed throughout Southeast Asia and in the United States since the early 1900s.

Published reviews of bael and aegeline consumption and ethnobotanical compendia provide no evidence or suggestion that bael or its component alkaloids, including aegeline, increase the risk of hepatotoxic effects. In fact, aegeline-containing components of bael have been traditionally used for centuries to ameliorate jaundice and underlying hepatitis.

This history of widespread use of bael throughout Southeast Asia with no evidence of liver toxicity indicates that the aegeline contained in bael leaves, fruit, and bark has safely been used in the food supply for centuries.

D. Conclusions

Data for determining the safety of aegeline consumption in humans are available from studies describing the effects of bael extracts on animals, acute and subchronic trials of aegeline consumption in test animals, and studies in human volunteers for up to 5 weeks. None of the available data indicate that aegeline may cause adverse effects, including in the liver, in humans or animals, even at doses that are orders of magnitude higher than recommended on the labels of dietary supplements.

IV. There is No Credible Scientific or Medical Evidence that Aegeline or OxyElite Pro Has Caused the Cluster of Acute Non-Viral Hepatitis Cases in Hawaii

A. The Dietary Supplements Marketed by the Company that Contain Aegeline are Not Directly Distributed in Hawaii, and Thus the Sales of Aegeline-Containing Products are Proportionately Less in Hawaii than in the Continental United States

The Company has never distributed any of its products directly for sale in Hawaii. A person who wishes to purchase the Company's products in Hawaii must therefore buy them on

the internet (e.g., Amazon or Ebay) or from retail stores that access them from distributors located in the Continental United States. Nor does the Company advertise its products in Hawaii. Accordingly, there is proportionately less of the Company's products available for sale in Hawaii than in the Continental United States, where the Company has actively distributed and marketed its products (until October 10, 2013, when it discontinued domestic distribution of its dietary supplements containing aegeline).

One would therefore expect that, if aegeline or OxyElite Pro caused any health problems, those problems would become apparent earlier, and would be far more prevalent, in the Continental United States. In fact, however, just the opposite has occurred. As will be seen in the next section the cluster of acute non-viral hepatitis in Hawaii is proportionately far greater than in the Continental United States. This is directly inconsistent with a hypothesis that aegeline is the causative agent. Indeed, it flatly contradicts and refutes that hypothesis.

B. If Aegeline or OxyElite Pro Were the Cause of the Hawaiian Cluster, There Would be an Epidemic of Thousands of Acute Non-Viral Hepatitis Cases Throughout the Continental United States, but This Has Not Occurred

Hawaii has a population of about 1.4 million people. The United States has a population of about 314 million. Thus, Hawaii represents approximately 0.45 percent of the United States population. From these figures it is simple mathematics to calculate, on a proportionate population basis, the number of acute non-viral hepatitis cases that would occur in the Continental United States if aegeline or OxyElite Pro were the cause:

Cases in Hawaii	Proportionate Cases in the Continental United States
20	4,485
25	5,607
30	6,728
35	7,850
40	8,970

45	10,092
50	11,214

The most recent public data on the number of cases can be found in USA Today for October 25, 2013.[26] The article states that Hawaii now has 41 confirmed cases of acute non-viral hepatitis cases associated with aegeline or OxyElite Pro. That means that one would expect to find 9,195 cases on a proportionate basis in the Continental United States. But the article also reports that the Centers for Disease Control and Prevention (CDC) has found only 7 cases, and a potential of another 10, in the other 49 states, not 9,195. If aegeline or OxyElite Pro were the cause, CDC and FDA would have no difficulty in finding thousands of cases. Yet even with scouring the country for cases, they can find only 7-17, in the parts of the country where the Company concentrated its advertising and marketing. The lack of cases elsewhere conclusively shows that neither OxyElite Pro or its ingredients are causing the epidemic in Hawaii.

C. Epidemiology Can Only Raise an Hypothesis Based on an Association; It Cannot Prove Causation

It is a well-recognized and well-accepted principle that epidemiology can establish hypotheses about the causes of disease, but it cannot prove causation. As two well-known epidemiologists wrote a decade ago:

> Epidemiology uses many methods to identify the causes of disease, although it remains impossible to provide proof that any specific factor is a cause. We are only able to present supporting evidence.[27]

That is the situation here. The association between aegeline and acute non-viral hepatitis can only be shown to be a causal relationship by rigorous statistical and biological analysis. The

[26] A. Young, Firm in Outbreak Probe Has History of Run-Ins with FDA (USA Today, October 25, 2013) (Appendix 33).

[27] F. Schentz & S. Paulsen, Determining Causation in Epidemiology, 27 Comm. Dent. Oral Epidemiol., No. 3, at 161 (1992) (Appendix 34).

immediately preceding sections demonstrate that there is no statistical relationship between aegeline and acute non-viral hepatitis. The next section shows that there is also no biological relationship.

D. The Nonclinical and Clinical Tests on Aegeline Show No Liver Toxicity

Part III of this response reviews the nonclinical and clinical testing of aegeline as well as the human consumption of bael fruit, leaves, and bark containing aegeline for hundreds of years. There is no evidence of liver toxicity, or of any other form of toxicity of any kind. Thus, there is no biological evidence to support a hypothesis that aegeline causes acute non-viral hepatitis. The toxicity testing and extensive human exposure refute any such hypothesis.

E. Expert Epidemiologists Have Shown that Hasty Attempts to Blame Botanicals for Outbreaks of Human Harm Have Proven to be Wrong Upon Closer Statistical and Biological Analysis

Initial case reports of herb-induced liver injury are notoriously unreliable and are often found, on closer analysis, to be linked to other causes. For example, a 2013 analysis of 23 published series and regulatory assessments of suspected cases of herbal hepatotoxicity found that all provided evidence for alternative explanations other than the incriminated herbal product.[28] Looking at individual cases, the authors found alternative causes in approximately half of the cases (48.5% or 278/573). The most frequent alternative cause was potentially hepatotoxic co-medication. The authors also found that in another quarter (29.0% or 166/573) of the cases the presence of liver disease was questionable, a temporal association was lacking, or case data for assessment were missing. The authors thus identified diagnostic problems in more than three-quarters (77.5%) of cases. In another study of a suspected outbreak of non-viral

[28] R. Teschke et al., Herbal Hepatotoxicity: Suspected Cases Assessed for Alternative Causes, Eur. J. Gastroenterol. Hepatol. (Mar. 18, 2013 [Epub ahead of print]) (Appendix 35).

hepatitis due to the herb, *Pelargonium sidoides*, the authors evaluated 13 spontaneous cases using the updated scale of CIOMS (Council for International Organizations of Medical Sciences), the proper method for assessing causality.[29] The authors found a lack of hepatotoxicity for all 13 cases.

Similar high levels of false reporting are often seen for pharmaceuticals. In case series initially assumed to be drug-induced liver injury, alternative diagnoses are common and may account for up to 47.1% of reported cases.[30] False reports of harmful effects, even when a product is ultimately shown to be safe and effective, can often bankrupt a company or lead to the voluntary discontinuation of the distribution of a beneficial product. For example, in 1983 the morning sickness drug Bendectin was taken off the market by Merrell Dow Pharmaceuticals after the company was hounded by baseless class action lawsuits that the drug caused birth defects. The business decision to remove the product was to the dismay of doctors who realized the media reports and lawsuits were unfounded.[31] In April 2013, FDA approved the return of Bendectin to the U.S. marked under the trade name Diclegis.[32] False reporting and incorrect diagnoses is harmful to companies and to consumers, as well as to patients if the appropriate therapy is not provided.

V. Conclusion

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[29] R. Teschke et al., Initially Purported Hepatotoxicity by *Pelargonium Sidoides*: The Dilemma of Pharmacovigilance and Proposals for Improvement, 11 Ann. Hepatol. 500 (2012) (Appendix 36).

[30] R. Teschke, note 28 supra (Appendix 35).

[31] *See* L. Lasagna & S.R. Shulman, Bendectin and the Language of Causation, *in* Phantom Risk: Scientific Inference and the Law, at 101 (1993) (Appendix 37).

[32] FDA Approves Diclegis for Pregnant Women Experiencing Nausea and Vomiting (Apr. 8, 2013) (Appendix 38).

For the reasons discussed in this response, aegeline is a lawful dietary ingredient that does not require the submission of an NDI. Aegeline and OxyElite Pro do not present a significant or unreasonable risk of illness or injury to consumers under the conditions of use recommended or suggested in the labeling.

Sincerely yours,

Kenneth F. Miles

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USPlabs, LLC.
Chief Compliance Officer