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May 13, 2015

Via Email and Regular Mail

Mabel Lee
United States Food and Drug Administration
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
Office of Compliance (HFS-608)
Division of Enforcement
College Park, Maryland 20740-3835

Re: April 22, 2015 Warning Letter of William A. Correll

Dear Ms. Lee:

Please accept this letter as an initial response to the April 22, 2015 Warning Letter authored by William A. Correll (the "Correll Letter").[1] Both myself, as the Chief Executive Officer of Hi-Tech Pharmaceuticals, Inc. ("Hi-Tech"), and Stacey Alexander, Hi-Tech's Chief Scientific Officer, want to assure you and your colleagues at the FDA that Hi-Tech strives to its utmost, and expends substantial resources and manpower, to ensure that the Company's products are of the highest quality and safety and that product labeling accurately reflects the composition of and ingredients used in Hi-Tech's products. We appreciate the importance of the concerns

[1] To the extent that this letter and/or its attachments contain proprietary business information and/or trade secrets of Hi-Tech as defined by Federal Rule of Civil Procedure 26(c)(1)(G), we request that you maintain the confidentiality of the information so that it is exempt from FOIA disclosure. We further request prior notice of at least ten business days before the FDA complies with a FOIA or other request for this information from any third party. Finally, we note that public disclosure of confidential business information by FDA personnel is forbidden by 18 U.S.C. ¶ 1905 and 21 U.S.C. ¶ 331(j).

raised in the Warning Letter, welcome the opportunity to respond to those concerns, and as need be, engage in further dialogue with you and your colleagues at the Center.

In his letter, Mr. Correll concludes that BMPEA is not a "dietary ingredient." He reaches this conclusion because the agency is apparently unaware of any evidence to support the assertion that BMPEA is a constituent of the botanical *Acacia rigidula*. In this response, we discuss (and attach) evidence supporting the fact that BMPEA is indeed a naturally occurring constituent of *Acacia rigidula*. It follows that Hi-Tech's *Acacia rigidula* extract/BMPEA ingredient meets the Federal Food, Drug, and Cosmetic Act's ("FFDCA") statutory definition of "dietary ingredient." Since the remainder of the issues/requirements highlighted in FDA's Warning Letter are inapplicable to "dietary ingredients," we do not specifically address them in this initial response.

At the outset we note that the Correll Letter cites to no research, studies or other data suggesting that any Hi-Tech product containing BMPEA is unsafe or mislabeled. Nevertheless, the Correll Letter makes the following assertions: 1) that BMPEA is not a "dietary ingredient," 2) that BMPEA is not an extract of the *Acacia rigidula* plant, 3) that BMPEA is not an approved food additive, and 4) that there is an insufficient basis to conclude that BMPEA is generally recognized as safe for use in food. We will address each of these points in turn.

I. BMPEA is a Dietary Ingredient

It is notable that the Correll Letter conspicuously omits any citation or reference to pertinent sections of the Dietary Supplement Health and Education Act ("DSHEA") Pub. L. No. 103-417, 108 Stat. 4325 (1994). Pursuant to DSHEA, dietary supplements such as those marketed by Hi-Tech are presumed safe and the burden is on the FDA to establish that a dietary supplement product is "adulterated." 21 U.S.C. ¶ 342(f)(1). Simply assuming a product is not a

dietary supplement by alleging that it does not contain a "dietary ingredient" and implying that it is unsafe, without reference to any evidence to support these contentions, improperly attempts to shift the burden of proof to Hi-Tech when it is the FDA that must establish a basis to remove a product from the marketplace. Nevertheless, there is an ample basis to support BMPEA's categorization as a "dietary ingredient."

Dietary supplements/ingredients are defined at 21 U.S.C. ¶ 321(ff)(1) which provides:

> a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: 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).

Hi-Tech's BMPEA qualifies as a dietary ingredient under 21 U.S.C. § 321(ff)(1)(C) and (F) because available data support our position that it is an extract and constituent of the *Acacia rigidula* plant (which FDA expressly recognizes as a "botanical" in its Warning Letter). As explained below, BMPEA is found in various species of the *Acacia* plant and thus qualifies as a dietary ingredient because it is a botanical, an extract of which is included in various Hi-Tech products. There is a long history of the use of different portions of *Acacia* plants as food. For example "acacia gum" is derived from various *Acacia* trees and "gum Arabic" is derived from African *Acacia* trees and has been used for decades in soft drinks and candies. *Acacia* seeds have been used as a flavoring for ice cream, chocolates and desserts and have been affirmed as GRAS by the FDA for a variety of different uses. *See* 21 C.F.R. § 184.1330.

As noted in the Correll Letter, several Hi-Tech products expressly list BMPEA (derived from *Acacia rigidula*) as an ingredient. Indeed, said products are specifically marketed to increase the dietary intake of BMPEA, and therefore satisfy the requirements of 21 U.S.C. ¶ 321(ff)(1)(E). As such, BMPEA qualifies as a dietary ingredient under Section 321(ff)(1)(E).

II. BMPEA Is An Extract of *Acacia rigidula*

BMPEA is also a dietary ingredient under Sections 321(ff)(1)(C) and (F) because, in the case of Hi-Tech's products, it is an extract of the *Acacia rigidula* plant. Hi-Tech developed a proprietary process to produce an extract from the *Acacia rigidula* plant which contains BMPEA as well as other ingredients. Thus it is a dietary ingredient under both Sections 321(ff)(1)(C) and (F). If necessary, Hi-Tech is willing to meet with FDA staff to describe in further detail, in confidence, this extraction process/technology. Attached hereto as Exhibit 1, is a 2003 letter from our initial extract supplier, Auspure Biotechnology Co. LTD., regarding a study it conducted on *Acacia rigidula* that found BMPEA in quantities of 7.8 ppm (early season) and 12.4 ppm (late season).[2]

There is also existing scientific research to support the proposition that BMPEA naturally occurs in *Acacia rigidula* and related plant species. Independent researchers have published research regarding the detection of methylphenethylamines in *Acacia rigidula*. *See* Clement, *Toxic Amines And Alkaloids From Acacia Rigidula,* Vol. 49 Phytochemistry 1377-80 (1998); Camp and Norvell, *The Phenylethlamine Alkaloids of Native Range Plants,* Vol. 20 Economic Botany 274-78 (July-Sep. 1966). Other research confirms the presence of methylphenethylamines in *Acacia berlandieri,* a closely related species to *Acacia rigidula* that grows in the same region. *See* Windels, et al., *Effects of aeration on phenolic amine content of guajillo,* Vol. 56 Journal of Range Management 529-33 (2003); Forbes, et al., *Seasonal variation of two phenolic amines in Acacia berlandieri,* Vol. 30 Journal of Arid Environments

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[2] For ease of FDA review, this letter has been redacted of extraneous information to focus on the study at hand. Please also note that only some, but not all, of the constituents identified in the study are actually included in the BMPEA-containing *Acacia rigidula* extract that is supplied to Hi-Tech.

403-15 (1994); Pemberton, et al., *Technical Note: An Improved Method for Extraction and Quantification of Toxic Phenethylamines from Acacia berlandieri,* Vol. 71 Journal of Animal Science 467-70 (1993); Adams and Camp, *The Isolation And Identification Of Three Alkaloids From Acacia Berlandieri,* Vol. 4 Taxicom 85-90 (1966); Camp and Moore, *A Quantitative Method for the Alkaloid of Acacia berlandieri,* Vol. 49 J. of the Amer. Pharm. Assoc. 158-60 (1960). Copies of all of these articles are attached hereto as Exhibit 2.

Acacia plant species are found beyond the North American continent. Research dating back to the 1950s has shown the presence of methylphenethylamines in multiple varieties of Acacia other than *Acacia rigidula* and *Acacia berlandieri, See, e.g.*, Fitzgerald, *Alkaloids Of The Australian Leguminosae*, Vol. 17 Aust. J. Chem. 160-62 (1964); White, *Examination of Further Legumes, Mainly Lupinos And Acacia Species For Alkaloids*, Vol. 38B New Zealand J. of. Sci. & Tech. 718-25 (1957); and White, *Alkaloids Of The Leguminosae*, Vol. 35B New Zealand J. of Sci & Tech 451-55 (1954). Copies of these articles are attached hereto as Exhibit 3. Hi-Tech decided to use an extract of *Acacia rigidula* in its products based on cost and availability. The Company's Chinese partner extracted BMPEA and related compounds as early as 2003, using, in part, the research published in 1997 by Dr. Clement cited above.

Finally, Hi-Tech has commissioned an analysis by ChromaDex to definitively answer the question of whether or not *Acacia rigidula* contains BMPEA. ChromaDex is a publicly traded, multi-million dollar company which has particular expertise in the analytical testing of botanicals. The company counts amongst its scientists holders of doctorate degrees in chemistry from Ivy League universities as well as a holder of the Nobel Prize for chemistry. ChromaDex is in the process of gathering samples of *Acacia rigidula*, the extracts used by Hi-Tech, and

reference compounds. We expect to be able to present a report on the company's analysis by September 30, 2015.

III. Hi-Tech Has Not Classified BMPEA as a Food Additive

Hi-Tech does not challenge the contention that BMPEA is not an approved food additive. To the contrary, BMPEA is a dietary ingredient sold in a variety of dietary supplements. Pursuant to 21 U.S.C. ¶ 342(f), as noted above, the burden is on the FDA to show that a dietary ingredient is unsafe and the marketer of a dietary ingredient is given procedural protections such as a right to notice and an opportunity to be heard prior to the FDA taking action against such an ingredient. 21 U.S.C. ¶ 342(f)(2).

The FDA's attempt to characterize BMPEA as a "food additive" no doubt is an effort to circumvent its burden of proof under DSHEA and to establish that BMPEA is "adulterated" pursuant to 21 U.S.C. ¶ 342(a)(2)(C)(i) as a "food additive that is unsafe," avoiding the procedural safeguards for marketers of dietary supplements/ingredients. However, 21 U.S.C. ¶ 321(s)(6), expressly excludes dietary ingredients "intended for use in a dietary supplement" from the category of "food additives." In short describing BMPEA as a "food additive," approved or not, should not be part of the analysis of this dietary ingredient.

IV. BMPEA is Safe

Hi-Tech believes BMPEA safety should not even come into question since *Acacia rigidula* is an old dietary ingredient. Contrary to the assertion of the Correll Letter, Hi-Tech feels there is overwhelming evidence that BMPEA and *Acacia rigidula* are safe. "Nonetheless, given the recent publicity surrounding BMPEA-containing products, and the fact that FDA raised food additive status as an obvious concern should BMPEA not be a dietary ingredient, we would like to simply highlight the fact that studies show that Hi-Tech has manufactured and marketed

products containing this ingredient for more than a decade, since 2003. We conservatively estimate that more than a billion doses of Hi-Tech products containing BMPEA have been consumed by members of the public. We have searched Hi-Tech's records and have not located a single report of death or serious illness or injury from any of these products. From approximately 2006 through 2010, Hi-Tech supplied *Acacia rigidula*/BMPEA to Nutrex Research, a competing dietary supplement company, for use in Nutrex's products. We have been advised by Nutrex Research's management that their company sold approximately 200 million doses of BMPEA containing products, also without any reports of death or serious illness or injury. From approximately 2007 through 2011, Hi-Tech supplied Acacia alkaloids, including BMPEA, to VPX Sports, another competing dietary supplement company, for use in VPX's Meltdown and Redline products. We have been advised by VPX's management that their company sold in excess of 50 million doses of BMPEA containing products, also without any reports of death or serious illness or injury.

Similarly, we have reviewed the article authored by Cohen, et al., *An amphetamine isomer whose efficacy and safety in humans has never been studied, β-methylphenylethylamine(BMPEA), is found in multiple dietary supplements,* Wiley Online Library, (March 1, 2015), which is apparently the document which prompted the sending of the Correll Letter. Dr. Cohen purports to identify 11 different dietary supplement brands (including several Hi-Tech products) which contain BMPEA. FDA has not announced the receipt of adverse events associated with any of these 11 products. *See,* FDA: *Recent FDA Action on*

Dietary Supplements Labeled as Containing BMPEA (April 2015), available at http://www.fda.gov/Food/DietarySupplements/QADietarySupplements/ucm443790.htm.[3]

Finally, contrary to the very title of Dr. Cohen's article, BMPEA has been studied for efficacy and safety in humans multiple times. These studies have been performed by multiple researchers/scientists over a period of several years. The studies have been of the products of Hi-Tech and its competitors. Most of these studies have had their results reported in peer reviewed journals. None of them reported any toxicity, serious adverse events or other safety concerns for products containing BMPEA.

First, Hi-Tech sponsored several human clinical trials of both Hi-Tech products and *Acacia rigidula*. Attached hereto as Exhibit 4, are 4 reports of such research conducted by Patrick Jacobs, PhD including: *The Acute Physiological Effects of Acacia Rigidula; The Acute Metabolic, Hemodynamic, and Psychological Effects of Fastin®-XR, A Commercial Weight Loss Product; The Acute Physiological and Psychological Effects of Fastin®-RR, A Commercial Weight Loss Product; and The Effects of Fastin®-RR, A Commercial Weight Loss Product, on Body Weight and Body Composition in Persons Participating in a Weight Loss Program.* Both Fastin®-XR and Fastin®-RR contain BMPEA, as well as other phenethylamine alkaloids, extracted from *Acacia rigidula.*

As reflected in the above attached reports, there were no unexpected adverse events associated with any of the Jacobs studies. In *The Acute Physiological and Psychological Effects of Fastin®-RR, A Commercial Weight Loss Product,* Dr. Jacobs found that, in the first few hours

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[3] The FDA's initial response to the Cohen article was to release a statement on or about April 7, 2015, stating that "...our review of the available information on products containing BMPEA does not identify a specific safety concern at this time..." see Statement of FDA spokeswoman, Juli Putnam, reported by numerous media outlets. It is unfortunate that the FDA later felt compelled to yield to the publicity and apparent political pressure that accompanied the Cohen article by issuing warning letters to Hi-Tech and other dietary supplement companies.

post-ingestion, Fastin®-RR produced a moderately higher increase in heart rate and blood pressure than caffeine, none of which would be considered dangerous by medical professionals. Moreover, In *The Effects of Fastin®-RR, A Commercial Weight Loss Product, on Body Weight and Body Composition in Persons Participating in a Weight Loss Program,* Dr. Jacobs found that, over the course of several weeks, the effects of Fastin®-RR on heart rate and blood pressure was less than that of caffeine. Dr. Jacobs' *Acacia rigidula* study showed no statistically significant difference in heart rate or blood pressure changes between caffeine and *Acacia rigidula.* Finally, Dr. Jacobs' analysis of Fastin®-XR revealed results similar to his research of Fastin®-RR, a moderately higher increase in heart rate and blood pressure, several hours after ingestion, compared to caffeine.

Dr. Jacobs' work also substantiates the efficacy of Hi-Tech's products. He found a statistically significant decrease for body weight and BMI in the eight week study of Fastin®-RR. His research into Fastin®XR and *Acacia rigidula* showed that both produce a short term increase in energy expenditure and measures of metabolism.

Second, there have been several studies of the VPX dietary supplement product, Meltdown, which have been published in peer reviewed journals: Rashti, et al, *Thermogenic effect of meltdown RTD energy drink in young healthy women: a double blind, cross over design study,* Lipids in Health and Disease (December 17, 2009); Bloomer, et al., Effect *of the dietary supplement Meltdown on catecholamine secretion, markers of lipolysis, and metabolic rate in men and women: a randomized, placebo controlled, cross-over study,* Lipids in Health and Disease (August 5, 2009); Hoffman, et al., *Thermogenic effect of an acute ingestion of a weight loss supplement,* Journal of the International Society of Sports Nutrition (January 6, 2009); Bloomer, et al., *Dietary supplement increases plasma norepinephrine, lipolysis, and metabolic*

rate in resistance trained men, Journal of the International Society of Sports Nutrition (January 28, 2009); and Jitomir, et al., *The acute effects of the thermogenic supplement Meltdown on energy expenditure, fat oxidation, and hemodynamic responses in young, healthy males,* Journal of the International Society of Sports Nutrition (December 16, 2008). Copies of these articles are attached hereto as Exhibit 5. Notably, the researchers describe Meltdown as containing a "proprietary blend of B-methylphenylethylamine and methyl-B-phenylethylamine." See Hoffman's January 6, 2009 Study at page 3; Jitomir's December 16, 2008 Study at page 3.

Like Dr. Jacobs, none of the Meltdown researchers reported any significant adverse events in their studies. Jitomir's study found no statistically significant increases in either blood pressure or heart rate. Jitomir December 16, 2008 Study at 6. Rashti's study found no statistically significant increase in either heart rate or diastolic blood pressure and only a moderate increase in systolic blood pressure which "remained within the normal range." Rashti December 17, 2009 Study at 4. The other Meltdown studies, again similar to Dr. Jacobs' work, found moderate, transient increases in blood pressure and heart rate several hours after ingestion of Meltdown compared to a placebo. Additionally, all of the Meltdown studies supported its efficacy as a weight loss aide, finding statistically significant increases in energy expenditure and metabolism.

Third, still another group of researchers studied BMPEA containing products in humans. Hu Chang Chun and Amy Gao of the Center for Evidenced-Based Chinese Medicine conducted two studies of an herbal combination/"stack" which included *Acacia rigidula:* Chun and Gao, *Synergistic interactions between Acacia Rigidula, and Caffeine (A+C stack): A Multi-Purpose study,* Chemycos Technology Ltd. (June-September 2005); Chun and Gao, *An herbal combination-YCAX stack-containing Yohimbine, Citrus aurantium, Acacia rigidula, and*

Xanthines for weight loss: a randomized, double-blind trial, Chemycos Technology Ltd. (October-December 2004). Copies of the reports of these studies are attached hereto as Exhibit 6. In both studies the researches described the product being studied as containing 150 mg of phenylethylamine alkaloids. In the 2004 study of the "YCAX stack," Chun and Gao expressly noted that the *Acacia rigidula* extract at issue contained "Beta-methylphenylethylamine." Chun and Gao 2004 Study at 7.

As with the other studies described above, Chun and Gao did not report any serious adverse events. In the 2005 study of *Acacia rigidula* and caffeine, Chun and Gao found no statistically significant difference in either heart rate or blood pressure between placebo and the product under investigation. In the 2004 Study of the "YCAX Stack," the researchers noted no statistically significant difference in blood pressure between placebo and the product under investigation. While the 2004 Study did reveal a statistically significant difference in heart rate between placebo and the product under investigation, follow-up electrocardiogram testing showed no abnormalities in the study subjects. The most common adverse symptoms reported by the study subjects were dry mouth and insomnia. Chun and Gao 2004 Study at 6-7. Finally, consistent with the results of the other studies reported herein, Chun and Gao supported the efficacy of dietary supplements containing *Acacia rigidula* by finding statistically significant increases in measures of energy expenditure and metabolism.

In short, multiple studies, involving scores of individuals, by separate sets of researchers, have yielded remarkably consistent results over a period of several years regarding the safety and efficacy of BMPEA containing products. Combined with the uneventful consumption of many millions of doses of BMPEA by the general public, and the lack of any adverse event reports for BMPEA containing products of death, serious illness or injury, there is a more than ample basis

to conclude that BMPEA is safe and qualifies for GRAS for use in foods as its parent plant (*Acacia)* does.[4] Nevertheless, Hi-Tech has retained a team of highly credentialed pharmacologists and physicians to review and analyze the available information regarding the safety of BMPEA and is preparing to supplement this response with their analyses. We hope to have those ready for your consideration within 90 days.

V. The Cohen Study is Unreliable

While not expressly referenced in the Correll Letter, it appears undeniable that this correspondence was precipitated by the release of the Cohen Study mentioned above. Accordingly, we believe it is important for the FDA to take a hard look at the so-called "research" of Dr. Cohen and his team. As set forth below, the Cohen article is deeply flawed.

To begin, given that he is listed first before his co-authors, it is a reasonable assumption that Dr. Cohen is the lead author of the article and primarily responsible for its content. Far from being an unbiased scientist searching for knowledge and truth, Dr. Cohen has repeatedly and vociferously stated his disdain for the dietary supplement industry and what is, in his view, the purportedly deficient regulation of same by the FDA. *See, e.g.,* Cohen, *Hazards of Hindsight-Monitoring the Safety of Nutritional Supplements,* Vol. 370 N. Engl. J. of Med. 1277-80 (April 3, 2014); Cohen, *How America's Flawed Supplement Law Creates the Mirage of Weight Loss Cures,* Vol. 2 Harvard Public Health Review 1 (October 2014); Cohen, *The natural pill myth,* The Boston Globe (May 13, 2012); Cohen, *A False Sense of Security? The U.S. Food and Drug Administration's Framework for Evaluating New Supplement Ingredients,* Vol. 16 Antioxid Redox Signal 458-60 (March 1, 2012); Cohen, *Assessing Supplement Safety-the FDA's*

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[4] We note, in passing, that a closely related compound to BMPEA, N,N-Dimethylphenylethylamine, has been recognized as an approved food additive by the World Health Organization.

Controversial Proposal, Vol. 366 N. Engl. J. of Med. 389-91 (February 2, 2012); Cohen, *American Roulette-Contaminated Dietary Supplements,* Vol. 361 N. Eng. J. of Med. 1523-25 (October 15, 2009); Cohen, *Science, Politics and the Regulation of Dietary Supplements: It's Time to Repeal DSHEA,* Vol. 31 Am. J. Law & Med. 175-214 (2005).

Dr. Cohen's bias is reflected in the tone of his article. He cites no adverse event reports or other information about any purported danger accompanying BMPEA. Despite his own admission of a purported lack of any research on the efficacy or safety of BMPEA in humans, Cohen Study at 2, Dr. Cohen's article chastises the FDA for its failure to warn consumers or take regulatory action, and demands that the dietary supplement industry recall all products containing BMPEA. Shortly after the release of his article, Dr. Cohen embarked on an unseemly media tour during which he continued to rail against both the FDA and the dietary supplement industry regarding the "dangers" of BMPEA without any evidentiary support for his comments. See, e.g. Cohen's April 7, 2015 Interview with CBS located at http://www.cbsnews.com/news/new-study-warns-against-dietary-supplements-containing-bmpea-calls-fda-action/. This is not the conduct of a respected scientist but rather a biased seeker of media glory, regardless of the facts.

More disturbing than Dr. Cohen's bias, is the apparent abandonment by him and his team of the scientific method. A legitimate scientific researcher searches for prior work on their topic of interest and then cites to the prior research and discusses same and/or critiques it. It is apparent that either Dr. Cohen and his colleagues did not bother to conduct a literature search prior to publishing their article or, worse still, did conduct a literature search but chose to simply ignore the work of any other scientist that conflicted with their agenda and theories.

Despite Dr. Cohen's bold claim that there has been no human research regarding the efficacy and safety of BMPEA containing products, as demonstrated above, there were multiple studies, conducted well before the Cohen article. Had Dr. Cohen or any member of his team spent an hour on the internet they would have discovered not only the Meltdown studies cited above, but also Dr. Jacobs' research, the results of which have been and are publicly available. *See* Jacobs, *"Acute physiological effects of the commercially available weight-loss/energy product, Fastin-XR®, in contrast with the individual effects of caffeine and Acacia Rigidula,"* Journal of the Int'l Soc. of Sports Nutrition 2012, A/S1/P10; Jacobs, *"The acute metabolic responses to Fastin-RR®, a commercial weight loss product, on body weight and obese individuals,"* Journal of the Int'l Soc. of Sports Nutrition, 2013, 10/S1/P11; Jacobs, *"The effects of Fastin®-RR, a commercial weight loss product, on body weight and body composition, resting hemodynamics and psychological mood in overweight and obese person, participating in an eight week weight-loss program,"* Journal of the Int'l Soc. of Sports Nutrition 2014, 11/S1/P20. Copies of these articles are attached hereto as Exhibit 7.

Equally disturbing is Dr. Cohen's use of scientific research which he does cite. The Cohen Study cites to decades old animal research for the proposition that BMPEA increases blood pressure and can cross the blood-brain barrier in animals. He conspicuously omits that, the very research he cites, showed that other phenylethylamine compounds crossed the blood-brain barrier more readily than BMPEA, see Mosnaim, et al., *Rat Brain Uptake Index for Phenylethylamine and Various Monomethylated Derivatives*, Vol. 38 Neurochemistry Research 842-46 (2013), and, similarly, that the purported presser effects of BMPEA were also less. See Winder, et al., *Comparative Properties of Six Phenethylamines With Observations On the Nature of Tachyphylaxis*, Vol. 93 J. of Pharm. & Exp. Ther. 63-80 (1947).

Dr. Cohen's article falls short of what is to be expected from an unbiased scientific researcher. His conclusions and suggestions clearly demonstrate Dr. Cohen's bias and should be ignored by the FDA.

VI. The FDA's Prior Research on *Acacia rigidula* Has Issues

While not cited in the Correll Letter, we believe that, underlying the assertion that BMPEA is not an extract of *Acacia rigidula,* is the work of FDA researchers reflected in Pawar, et al., *Determination of selected biogenic amines in Acacia rigidula plant materials and dietary supplements using LC-MS/MS methods,* Vol. 88 Journal of Pharmaceutical and Biomedical Analysis 457-66 (2014). Among other findings, Pawar and his team did not detect BMPEA in the samples of *Acacia rigidula* that they analyzed. While we are not suggesting that the Pawar study is compromised by the same bias and flaws that characterize Dr. Cohen's work, there are some anomalies in the data reported and methods employed by the Pawar research team that raise questions as to the results they obtained from their analysis of *Acacia rigidula.*

Several years prior to the Pawar study, a team of researchers from Texas A & M University studied *Acacia rigidula* as well as a closely related plant species, *Acacia berlandieri*, which grows in the same region. They published their results in a peer reviewed journal. *See* Clement, et al., *Toxic Amines And Alkaloids From Acacia Rigidula,* Vol. 49 Phytochemistry 1377-80 (1998); Clement, et al., *Toxic Amines And Alkaloids From Acacia Berlandieri,* Vol. 46 Phytochemistry 249-54 (1997). Copies of these studies are attached hereto as Exhibit 8. The varieties and quantities of phenethylamine alkaloids identified by Clements, et al., differed dramatically from those found by Pawar and his team. We have spoken to researchers from Texas A&M that performed much of the work on Texas Acacia's, and they have confirmed the presence of methylphenylethylamine in various Acacia species, including *Acacia Rigidula.*

Analytical results of botanicals can vary substantially depending on how the sample is gathered. The time of year when the plant is harvested, the region from where the plant sample is gathered, the environmental and soil conditions present, the history of rainfall and other weather conditions, the part of the plant analyzed (stem, leaves, roots, etc.) all of this can drastically affect the chemical composition of the plant. *See, e.g.*, White, *Isolation of B-Phenylethylamine From Acacia Species*, Vol. 25 New Zealand J. of Sci. and Tech. 139-142 (1944) (noting that tops and flowers of *Acacia* plants have dramatically more alkaloids than pods and seeds). Indeed, this is reflected in Clements' work which found starkly different results depending on what season and drought conditions prevailed when the plant samples she later analyzed were gathered. In fact, the quantities of amines and alkaloids found in *Acacia rigidula* by Clement were many thousands of percent greater than those found by Pawar. Other than to concede that: "The origin of our plant materials and the methods of sample preparation and analysis differ from those reported by Clement et al. Hence we did not expect to quantitatively reproduce their data.," Pawar Study at 462, the Pawar Study provides virtually no information about the plant samples they analyzed or the conditions under which they were gathered. This alone raises questions about the accuracy and interpretation of the Study's findings.

As Pawar correctly noted above, sample preparation is also a crucial factor in interpreting a botanical study's analysis. Pawar and his team "processed" the plant samples including having them freeze-dried and powdered prior to use. Pawar Study at 458. By contrast, in both of their studies, Clements' team stressed that it was important "to maintain the extracts and isolates under an inert atmosphere. Left unprotected, the isolated amines and alkaloids readily decomposed." Clement 1998 Study at 250; Clement 1997 Study at 1378. In a later interview discussing her research, Clement noted the need to protect the plant extracts with an argon

blanket (thereby producing an inert atmosphere) in order to insure the chemical integrity of the samples. See, Natural Products Insider, November 26, 2013, available at http://www.naturalproductsinsider.com/articles/2013/11/blackbrush-scapegoats-or-shaky-goats.aspx.

Without more information as to Pawar's "processing," a thorough analysis of his team's research results would be needed to conduct a thorough analysis of his team's research results. Finally, the results of Pawar's analysis raise significant issues. While, as noted above, significant variances can be expected depending on how, when and where a botanical sample is gathered, as well as how the sample is later prepared, the differences between the work of the Pawar and Clement research teams are simply astonishing. As noted at page 462 of the Pawar Study, the quantities of amines and alkaloids found in *Acacia rigidula* by Clements were many thousands of percent greater than those found by Pawar. Rather than question their own research methods or findings, Pawar simply brushes this aside by stating: "We do not have an explanation for the large quantitative difference between our findings and those of Clement at al." *Id.*

Finally, one Pawar finding in particular stands out. The Pawar team tested for the presence in *Acacia rigidula* of N-methyl B-phenethylamine or "NMPEA" an isomer and closely related compound to BMPEA. Pawar's team found no NMPEA in two *Acacia rigidula* samples and less than the limit of quantification ("LOQ") in two others. Putting aside the dramatic contrast between Pawar's and Clement's findings as to the presence of NMPEA, the Pawar results for this compound also stand in sharp contrast to the findings of other researchers going back decades. *See, e.g.,* Camp and Norvell, *The Phenylethylamine Alkaloids of Native Range Plants,* Vol. 20 Economic Botany 274-78 (1966) (finding BMPEA in *Acacia rigidula*, .025% total weight of phenylethlamine alkaloids in plant).

In short, the Pawar Study may have flaws in its methodology that resulted in the failure of the researchers to detect BMPEA in *Acacia rigidula.* If these FDA researchers are willing to share their underlying data and work papers, Hi-Tech would have them analyzed by the experts at ChromaDex.

VII. Expert Review and Report on BMPEA by Marvin A. Heuer, M.D.

There are a wide range of native plants that have amines as well known components. Phenylethylamine and beta hydroxyl phenylethylamines and the related hydroxyl amines are ubiquitous in the plant kingdom. These amines and their derivatives may occur at significantly high levels in certain species. They are found in over 30 species of plants including multiple varieties of acacia, geraniacea, leguminosae and even various forms of algae. Remember, the hormone adrenalin (epinephrine) and the neurotransmitters of the sympathetic nervous system (noradrenalin, dopamine) are hydroxylated phenylethylamines known as catecholeamines.

Although Hi-Tech believes BMPEA safety should not even come into question since *Acacia rigidula* is an old dietary ingredient. "Nonetheless, given the recent publicity surrounding BMPEA-containing products, and the fact that FDA raised food additive status as an obvious concern should BMPEA not be a dietary ingredient, Therefore, Dr. Heuer briefly highlighted a portion of the multitude of animal data and human data covering pharmacology and toxicology of BMPEA and related structures as well. Some of the very first research into the safety and pharmacology of the amines like BMPEA was done in the early 1940's by Upjohn Company. They also studied the safety and toxicology of many of these items and noted very low toxicity in many of them. The data on BMPEA shows marked safety and huge tolerability and safety at extremely high test doses.

Conclusion

For the reasons stated above, and the evidence attached, we submit that BMPEA is a "dietary ingredient" under the FFDCA, and that Hi-Tech products labeled to contain BMPEA are therefore not misbranded under the FFDCA. We look forward to the opportunity to provide you with the additional information described herein, and we welcome questions from the Center. We respectfully request that if the agency, upon consideration of this response, has additional questions or is of the view that further regulatory or enforcement action may be warranted in this matter, that we be granted the opportunity to meet with the Center to address any concerns.

We thank you in advance for your consideration of this initial response. It is the FDA's burden to establish that a dietary ingredient is unsafe and needs to be removed from the marketplace. The regulatory standard for food additives does not apply in these circumstances. Ample evidence exists that BMPEA is both an extract of the plant *Acacia rigidula* and safe for use in food.

If any follow up to our response is required, please contact Jared Wheat at Hi-Tech or any of Hi-Tech's outside regulatory counsel. Smitha G. Stansbury or Mark Brown at King & Spalding LLP 1700 Pennsylvania Avenue, NW, Washington, D.C. 20006, Tel# 202-626-2902 sstansbury@kslaw.com and mbrown@kslaw.com Hi-Tech also had help in preparation of this memo by Jack Wenik, 973-639-5221, jwenik@ebglaw.com and James Boiani, 202-861-1891 JBoiani@ebglaw.com Epstein, Becker & Green P.C.,1227 25th Street, NW. Washington, DC 20037.

Respectfully submitted,

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s/ Stacey Alexander

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To the extent that this letter and/or its attachments contain proprietary business information and/or trade secrets of Hi-Tech as defined by Federal Rule of Civil Procedure 26(c)(1)(G), we request that you maintain the confidentiality of the information so that it is exempt from FOIA disclosure. We further request prior notice of at least ten business days before the FDA complies with a FOIA or other request for this information from any third party. Finally, we note that public disclosure of confidential business information by FDA personnel is forbidden by 18 U.S.C. ¶ 1905 and 21 U.S.C. ¶ 331(j).