Expert Review & Report

"Clarification on the regulatory status of β-Methylphenethylamine: A scientific interpretation."

Marvin A. Heuer, M.D.

May 11, 2015

Expert review and report BMPEA

Marvin A. Heuer, M.D.

I have been retained by Hi-Tech Pharmaceuticals, Inc. to act as an expert consultant in reference to the FDA warning letter of April 22, 2015. I have been retained as an expert and testified in numerous prior litigation matters, including in depositions, hearings and at trials. I have never been rejected as an expert in any matter.

I am currently the Chief Executive Officer of Heuer M.D. Research, Inc. Prior to becoming the Chief Executive Officer of Heuer M.D. Research, Inc., I served as Chief Science Officer for Iovate Health Sciences, VP of Clinical Research, IntegraMed America, VP & Director Worldwide, SmithKline Beecham Pharmaceuticals (now GlaxoSmithKline), VP of R&D, Wallace Laboratories (now Meda AB), and VP & Medical Director Worldwide, Ayerst Laboratories (now Pfizer). Furthermore, I have practiced as a family care doctor over the past 35 years. I am also currently an adjunct professor at the University of Central Florida.

I received my M.D. Degree from the University of Minnesota Medical School and my Bachelor of Science in Biology and Chemistry from Mankato State University (cum laude). I have been awarded medical licenses from California, Arizona, Florida, and Minnesota.

I have applied for and/or obtained seventy (70) patents in the supplement and medical fields. This includes substantial work in the sports nutrition field, including working in the areas of amino acids and vasodilation, human physiology, hydration, human and animal pathology, metabolism, cardiovascular health, rheumatic diseases, and immunology. I am an Associate Physician Member of the International Olympic Committee, Federation International Gymnastics for the Bahamas delegation. I have attended the Olympic Physicians committee on safety and drugs and doping at several Gymnastic Worlds competitions. I am a member of NPA (Natural

Products Association), GLG Council (Gehrson Leherman Group, Professional Consultants), ASCRP (Amerian Society of Clinical Research Professionals) and a Fellow of the American Academy of Family Physicians.
My curriculum vitae is attached hereto as **Exhibit A**.

For this report I have reviewed the FDA Warning Letter issued to Hi-Tech Pharmaceuticals April 22, 2015, CV and publications of Dr. Pieter Cohen, clinical studies on BMPEA by Hi-Tech, VPX and others, Canada NHPD summary report on p-syneprine, octopamine and related natural compounds, CFR 21, Dietary Supplement Health and Education Act of 1994, draft response to FDA by Hi-Tech, various articles through Medscape/ Medline regarding β-Methylphenethylamine, Phenylethylamine, p-synephrine, octopamine, references furnished by Hi-Tech, the Claude Winder et al paper 1947 on the properties of phenylethylamines, Boyd Graham et al publication 1944 covering comparative pharmacology of beta hydroxyl and methyoxy phenylpropylamines, Terence A. Smith 1976 publication Phenyllamine and related compounds in plants, publications of Dr. Pieter Cohen and other miscellaneous CRN, NPA, Law Digest, etc. summaries and opinions.

The DSHEA act is a very clear reference for us in cases like this. The definition in the act specifically describes what is included and what should be excluded under the actual intent of the law. By Definition, Beta-Methylphenethylamines, obviously falls into the allowed dietary supplement category. By Definition:

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) 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), (E) or (F).

It is impossible to refute the fact that β-Methylphenethylamine and related compounds are found in Acacia rigidula and other plants in this species. 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. The paper by Terence A. Smith (1976) gives a fairly comprehensive list of such plant derived amines[1]. It is also known that the chemical Methylphenylethylamine is a "body own" chemical in humans.

It is obvious that BMPEA is not a food additive. This contention is unfounded and illogical. This issue has never arisen in discussion.

It is very obvious and evident that the compound BMPEA is safe. This chemical and multiple PEA analogs are found in multiple simple everyday foods and drinks. Methylphenylethylamine can be found in many drinks and in foods such as chocolates and candies. The base gum in some foods comes from A. rigidula. The compound p-synephrine is very close to BMPEA. There is barely one carbon atom different. Diagrams showing the similarity between the two elements is attached hereto as **Exhibit B**. For example, p-synephrine is evident in human blood after ingestion of a simple glass of orange juice. There are a 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 these amines was done in the early 1940's by Upjohn Company.[2] They also studied the safety and toxicology of many of these items and noted very low toxicity in many of them. The data show marked safety and huge tolerability and safety at extremely high test doses. Another paper by Claude Winder et al in the late 1940's also helped to establish the pharmacologic mechanism of

[1] Smith, Terence A. "Phenethylamine and Related Compounds in Plants." Phytochemistry 16.1 (1976): 9-18. Print.

[2] Graham, Boyd E., and George F. Cartland. "Some Comparative Pharmacological Actions of Beta-hydroxy and Methoxy Phenyl-n-propylamines." Research Laboratories, The Upjohn Company (1944): 360-67. Print.

these amines and early on demonstrated their safety profile[3]. The safety of BMPEA is attested by the lack of safety issues after a demonstrated exposure orally in humans to over a billion doses. Hi-Tech and other companies have an excellent safety profile in products with this ingredient.

Hi-Tech has also commissioned several studies on BMPEA containing supplements. They have done studies using the compound singly and have also done studies looking at safety and efficacy of their final product[4][5][6]. 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 at Texas A&M[7]. I also reviewed the information supplied by Hi-Tech's overseas supplier on levels of β-Methylphenethylamines in A. rigidula, and found it to be consistent with the work performed by Clement et al.[8]; Camp and Norvell[9].

I also found Hi-Tech's overseas suppliers explanation of their research not finding α-methylation (amphetamine family). It is my opinion that the Texas A&M study finding amphetamine is likely *β*-methylphenethylamine as on LC-MS/MS as fragmentation and co-elution are the same. *β*-methylphenethylamine and Amphetamine have the same molecular weight – 135.21 and formula $C_9H_{13}N$ is the same for both compounds.

---

[3] Winder, Claude V., Mona M. Anderson, and Hervey C. Parke. "Comparative Properties of Six Phenethylamines, with Observations on the Nature of Tachyphylaxis." The Journal of Pharmacology and Experimental Therapeutics (1947): 66-80. Web. 12 Apr. 2015.

[4] Jacobs, Patrick L. "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 International Society of Sports Nutrition 9.Suppl 1 (2012): P10. Web.

[5] Jacobs, Patrick L. "The Acute Metabolic Responses to Fastin-RR®, a Commercial Weight Loss/energy Product, in Overweight and Obese Individuals." Journal of the International Society of Sports Nutrition 10.Suppl 1 (2013): P11. Web.

[6] Jacobs, Patrick L. "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 Persons Participating in an Eight Week Weight Loss Program." Journal of the International Society of Sports Nutrition (2014): 20. Web.

[7] Clement, Beverly A., Christina M. Goff, and T. David A. Forbes. "Toxic Amines and Alkaloids from Acacia Berlandieri." Phytochemistry 46.2 (1997): 249-54. Web.

[8] Clement, Beverly A., Christina M. Goff, and T.david A. Forbes. "Toxic Amines and Alkaloids from Acacia Rigidula." Phytochemistry 49.5 (1998): 1377-380. Web.

[9] Camp, Bennie J., and Michael J. Norvell. "The Phenylethylamine Alkaloids of Native Range Plants." Economic Botany 20.3 (1966): 274-78. Web.

FDA databases and databases of other regulators such as Health Canada reveal no evidence of a short term or a long term safety issues. Incidence and prevalence analyses of reports available reveal no point of concern. Hi-Tech continues to monitor safety of all of its ingredients and products through continue vigilance.

I find the FDA data and research trying to identify BMPEA in the patent plant as unsatisfactory. The conclusions reached are difficult to understand knowing the huge amount of data available that refutes the FDA scientists' findings. I would like an opportunity to review the FDA data. The Pawar team data offered by the FDA is at odds with scientific data recorded for decades. Because these data are so far from the norm I don't feel the need to rebut them at this time.

Finally, a brief statement regarding my analysis of the Dr. Pieter Cohen report[10]. Dr. Cohen is a long time commentator on social/false flag issues. His obvious intention is to gain visibility. I think as a junior assistant professor Dr. Cohen needs some limelight. Thus, he likes to use his pseudo scientific methods and verbal hype to get press visibility. He publishes mainly in journals with weak peer review. His publications are heavily opinion-based, non scientific, no data type pieces. Take a simple look at his recent ditty on amphetamine like BMPEA. A broad conclusion that consumers MAY be exposed to pharmacologic doses of an amphetamine like isomer is thrown out to agitate. The preponderance of data scientifically shows that BMPEA is not dangerous and a simple Internet search will show a large amount of safety data available on this subject. A chart showing a large disparity between the structure of Amphetamine and Phenylethylamine compounds such as: β-Methylphenethylamine, p-synephrine, and octopamine is attached hereto as **Exhibit B**

[10] Cohen, Pieter A., Clayton Bloszies, Caleb Yee, and Roy Gerona. "An Amphetamine Isomer Whose Efficacy and Safety in Humans Has Never Been Studied, β-methylphenylethylamine (BMPEA), Is Found in Multiple Dietary Supplements." Drug Testing and Analysis (2015): Web.

There are many relevant safety assessments on phenylethylamine compounds. A submission to Health Canada that reviews the safety of these amines and specifically p-synephrine, hordinine, octopamine, etc. completely demonstrates safety. In fact, the Canadian data demonstrate the safety of these compounds even with added high doses of other stimulants like caffeine. The NHPD has gone on record allowing use of a combination of Caffeine up to 275 mg with up to 50 mg of p-synephrine. Canada openly allows this dose without need of further review in its "Natural Health Products". Actually the FDA in its comments earlier noted that the agency did not see any safety issues with BMPEA. The full Health Canada report and conclusion (NHPD Health Canada file number (HC 172091) is attached hereto as **Exhibit C**.

In conclusion, it is my opinion that BMPEA as referred to in the Agency letter is obviously a dietary supplement and falls under the DSHEA definition. The data available to the FDA readily confirms that the products marketed by Hi-Tech are not adulterated and in my opinion these products and any Hi-Tech product containing BMPEA comply with all aspects of federal law and FDA regulations. I believe the company, Hi-Tech, has documented compliance and clearly shows no evidence of violation. It appears that Hi-Tech has procedures in place that actively and proactively monitor ingredients and products ensuring compliance with regulations and prevention of violations. I believe the safety data of BMPEA is well documented. Overall, I concur with the science and conclusions presented by Hi-Tech in their FDA response letter.

Sincerely,

Marvin A. Heuer, M.D.