NATURAL PRODUCTS ASSOCIATION

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May 1, 2019

Dr. Norman E. Sharpless, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Building 32, Room 2346
Silver Spring, MD 20993

Dear Commissioner Sharpless,

The Natural Products Association would like to ask for withdrawal of the U.S. Food and Drug Administration's (FDA's) recent use of an administrative proceeding and comment period with regard to a five-time acknowledged New Dietary Ingredient (NDI). The FDA published "Request for Comment on the Status of Vinpocetine," in the Federal Register (Docket FDA-2016-N-2523) on September 7, 2016.

After more than two decades since FDA received the first vinpocetine NDI filing, FDA decided to reevaluate vinpocetine's regulator status in 2016 after the ingredient moved through the proper NDI process and federal regulatory gates. FDA's preliminary basis in publishing the administrative proceeding for vinpocetine was that it did not appear to fit under the statutory definition of a dietary ingredient. NPA has provided evidence in FDA stakeholder comments FDA to counter that assumption. Additionally, vinpocetine has no fewer than five NDI notifications to U.S. FDA, beginning in 1997. Furthermore, FDA failed to submit an economic impact analysis to OMB regarding the cost to industry on removing vinpocetine from the marketplace.

Vinpocetine is a Five-Time Acknowledged New Dietary Ingredient

FDA gave vinpocetine the highest NDI rating, an "acknowledgement without comment" letter, in response to each filing. Each filing offered FDA the chance to evaluate the regulatory status of the ingredient through their internal databases as well as the identity and safety of the ingredient submitted as part of the notification. Part of FDA's review of a submitted NDI is to investigate its current regulatory status as a drug. During that regulatory status review process, NDI team members query FDA's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) and report back as to whether an Investigation New Drug (IND), New Drug Application (NDA), or orphan drug has ever been filed for the ingredient and whether it is still active or inactive. Because FDA classified its first vinpocetine NDI submission in 1997 as "filed without comment", any positive IND/NDA DARRTS queries on vinpocetine would most likely

have returned back as "inactive," otherwise FDA would have issued a "not a dietary ingredient" letter or NDL letter to any notifiers of vinpocetine. In fact, the Agency has filed NDL letters as early as 1999.[1] This was the same year FDA received three NDI notifications for vinpocetine.

Vinpocetine Fits Under 201(ff)(1)(E) and (F) as a Dietary Ingredient for Use in Dietary Supplements

NPA submitted comments to FDA as part of the notice and comment process on November 7, 2016. In those comments, NPA pointed out that vinpocetine, also known as ethyl apovincaminate), an ethyl ester of apovincamine, fits under 201(ff)(1)(E) and (F) of the Federal Food, Drug, and Cosmetic Act (FFDCA). The active moiety apovincamine in vinpocetine is the same active moiety (apovincamine) found as a constituent in the botanicals *Tabernaemontana rigida*, *Tabernaemontana riedelii*, *Vinca erecta*, and *Vinca minor*. In other words, apovincamine, the botanical constituent, is the methyl ester of (3α, 16α)-eburnamenine-14-carboxylic acid, while vinpocetine is the ethyl ester of (3α, 16α)-eburnamenine-14-carboxylic acid. Both ester bonds in vinpocetine and apovincamine would be cleaved by esterases in the human body, resulting in (3α, 16α)-eburnamenine-14-carboxylic acid as the active moiety or relevant article. In FDA's own NDI draft guidance,[2] FDA stated that under 21 CFR 316.3(b)(2),[3] "active moiety"

[1] See NDI #050 (report 43) for acetyl-homotaurine (acamprosate), filed on March 11, 1999.
In FDA's response letter to Chemtech Pharmics, Inc. regarding acamprosate, FDA wrote the following:

> "*The definition (of a dietary ingredient) excludes an article that is approved as a new drug under section 505 of the Act or an article authorized for investigation as a new drug, for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval or authorization, marketed as a dietary supplement or as a food (21 U.S.C. 321(ff)(3)(B)).*
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> *Acamprosate is the subject of substantial clinical studies being conducted in the United States to determine if it is a safe and effective drug treatment for alcohol dependence. The existence of these substantial clinical studies has been made public. Therefore, acetyl-homotaurine, or acamprosate, is excluded from being a dietary supplement under 21 U.S.C. 321(ff)(3)(B).*
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> *A product containing acetyl-homotaurine that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease or is intended to affect the structure or function of the body is a drug as described in 21 U.S.C. 321(g)(1). Such a product is also a new drug, as defined in 21 U.S.C. 321(p), which requires FDA approval under 21 U.S.C. 355(a) prior to marketing. The marketing of new drugs without an approved new drug application is prohibited under 21 U.S.C. 331(d).*"

[2] 81 Federal Register 53486 (Aug 12, 2016); Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; Revised Draft Guidance for Industry; Availability; [Docket No. FDA-2011-D-0376] ("NDI guidance"). p. 43.
[3] See also 21 CFR 314.108(a).

means "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other

noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

FDA Failed to Submit an Economic Impact Analysis to OMB Regarding the Cost to the Industry and Regulatory Alternatives

NPA questions FDA's authority to attempt to remove a dietary ingredient from the marketplace using an administrative proceeding. FDA's use of an administrative proceedings through 21 CFR 10.25(b) to ban a five-time acknowledged dietary ingredient is unprecedented and has no grounding in public safety. FDA has to date cited no safety concerns regarding the use of vinpocetine as a dietary ingredient for use in dietary supplements. There is no authority to ban vinpocetine after it has been an acknowledged NDI without first identifying a safety concern. FDA must follow the rules of "reg flex" as outlined in the Regulatory Flexibility Act, which would require an economic analysis of removing this ingredient as well as the Agency's basis for removal. FDA must analyze the cost impact to the industry over implementing a ban as well as providing any regulatory alternatives. Executive Order 13771 directs agencies to assess and quantify all costs and benefits of available regulatory alternatives, reduce costs, harmonize rules, promote flexibility and, if regulation is necessary, to select regulatory approaches that maximize net benefits.

The Process to Implement Dietary Ingredient Bans Should Follow Section 4 of DSHEA

It is clear from FDA's intent that it currently concludes that the dietary ingredient, in the absence of any additional information provided to them, is not a dietary ingredient for use in dietary supplements. However, it is unclear how FDA can ban an ingredient AFTER it cleared FDA's regulatory, identity, and safety hurdles. FDA wrote in their administrative proceedings notice that "we request comments on our tentative conclusion that vinpocetine is not a dietary ingredient and is excluded from the definition of dietary supplement in the Federal Food, Drug, and Cosmetic Act (FD&C Act)." Section 4 of the Dietary Supplement Health and Education Act of 1994 (DSHEA), cosponsored by nearly two-thirds of Congress and passed unanimously, provides pathways for withdrawing dietary ingredients based on safety concerns. However, FDA cites no unreasonable risk of illness or injury to public health in the administrative proceeding. In order to ensure consumer safety, FDA has the authority under DSHEA to conduct product reviews and post-marketing assessment when safety concerns arise. FDA has access to adverse events submitted through Medwatch to either the Adverse Events Reporting System (AERS) of at the Center for Drug Evaluation and Research (CDER) or the CFSAN Adverse Events Reporting System (CAERS). If there is a safety signal that warrants enforcement of this acknowledged dietary ingredient, NPA supports this activity as per FDA's regulatory authority. NPA is unaware of any adverse event to warrant any enforcement action on vinpocetine.

Conclusion

In the Federal Register notice "Request for Comment on the Status of Vinpocetine," FDA has altered its conclusion that vinpocetine is a dietary ingredient, and that it should no longer be a covered substance under the FFDCA. While there is no current ban on vinpocetine by the federal government, the administrative proceeding is causing confusion in the marketplace where some retailers are no longer willing to sell it, and as a result some firms have abandoned the manufacture of vinpocetine-containing products. While FDA has the right to inspect firms manufacturing products with vinpocetine under part 111 of the dietary supplement GMP final rule, NPA is not aware of any GMP manufacturing concerns related to vinpocetine at this time. In the absence of any misbranding or technical GMP adulteration on vinpocetine products, NPA supports the use of vinpocetine in dietary supplements. The active moiety of vinpocetine is a metabolite of the botanical constituent apovincamine, and therefore vinpocetine fits under the definition of a dietary ingredient in 201(ff) of the FFDCA. Banning the sale of vinpocetine when used as a dietary ingredient for use in a dietary supplement in the absence of any safety concern is unprecedented. DSHEA provides a regulatory framework for banning and withdrawing dietary ingredients from the market based upon safety concerns. In the absence of any risk of illness or hazard to public health, this administrative proceeding creates a new pathway to place a ban on acknowledged ingredients and introduces considerable uncertainty and confusion regarding the steps that manufacturers must comply with in order to sell safe products. NPA hopes the Agency will perform a fair and accurate economic impact analysis, and NPA also requests FDA immediately withdraw their administrative proceedings on vinpocetine from the record by issuing a notice in the Federal Register. Thanks for your consideration of this matter.

Sincerely,

Daniel Fabricant, Ph.D.
CEO and President

c: Frank Yiannas, Deputy Commissioner for Food Policy and Response