CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
founded 1881

November 7, 2016

VIA ELECTRONIC SUBMISSION

Division of Dockets Managements
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2016-N-2523; Request for Comment on the Status of Vinpocetine

Dear Sir or Madam:

These comments are submitted on behalf of the Consumer Healthcare Products Association[1] ("CHPA") in response to the September 7, 2016 Federal Register notice entitled "Request for Comment on the Status of Vinpocetine".[2] CHPA appreciates the opportunity to provide comments on this matter. While none of our dietary supplement member companies currently market products containing vinpocetine, we have an interest in the subject matter and wish to provide our comments.

Vinpocetine[3] is a synthetic compound closely related to vincamine, an alkaloid found in the leaves of the lesser periwinkle plant (*Vinca minor L.*). Dietary supplements containing vinpocetine have been marketed for uses including improvement of brain function, weight loss, increases in energy, and improvement in visual acuity, memory, and focus. Vinpocetine is also a prescription drug in several countries used to treat acute stroke and cognitive impairment.[4,5]

On September 7, 2016 the FDA announced its tentative conclusion that vinpocetine (1) does not meet the definition of a dietary ingredient, and (2) is excluded from the definition of a dietary supplement in the Federal Food, Drug, and Cosmetic Act (FD&C Act). As support for this

[1] CHPA, founded in 1881, is the 135-year-old national trade association representing the leading manufacturers and marketers of over-the-counter medicines and dietary supplements. CHPA is committed to empowering consumer self-care by preserving and expanding choice and availability of consumer healthcare products. chpa.org

[2] Federal Register Vol. 81 No. 173, pp. 61700-3 September 7, 2016

[3] Also known as ethyl apovincaminate, common periwinkle vinpocetine, lesser periwinkle extract or Vinca minor extract

[4] D. Bereczki, I. Fekete. Vinpocetine for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD000480.

[5] B. Avula, AG Chittiboyina, S Sagi et al., Identification and quantification of Vinpocetine and picamilon in dietary supplements sold in the United States. Drug Test & Anal 2015

position, the agency has noted that, as a synthetic compound, vinpocetine does not qualify as a dietary ingredient under 201(ff)(1)(C) of the FD&C Act. In addition, FDA notes that under Section 201(ff)(3)(B)(ii) of the FD&C Act, a dietary supplement cannot include "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" unless the article was marketed as a dietary supplement or as a food before such authorization. We respond to each of these positions below.

Vinpocetine has been the subject of five separate new dietary ingredient notification during the 1997-1999 period and has been sold as a dietary supplement in the intervening period.[6] It is unclear why FDA has only now chosen to object to the status of vinpocetine as a dietary ingredient. FDA did not originally publicly disclose the existence of an investigational new drug application (IND) in this particular case.[7] In the Federal Register notice, FDA retroactively cites examples of "substantial clinical investigations" that were "made public" demonstrating that vinpocetine was authorized for investigation as a new drug, including an article in a "major newspaper" (LA Times)[8]; an article published in a medical journal (Current Therapeutic Research)[9]; and a trade press articles (Pink Sheet, 1988).[10]

While we do not disagree that these examples may constitute examples demonstrating sufficient proof that the ingredient was authorized under an IND, this situation is somewhat concerning given that widespread distribution of neither a Los Angeles newspaper nor the Pink Sheet would be expected and the cited literature article does not appear in a search of the National Institutes of Health PubMed database. Thus, in this case, manufacturers were not provided with a reasonable opportunity to know what constitutes a legally marketed dietary supplement.

The agency has also tentatively concluded that vinpocetine does not qualify as a dietary ingredient under Section 201(ff)(1)(E) of the FD& C Act due to it being a synthetic ingredient.

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[6] October 20, 1998; March 24, 1999; April 16, 1999; May 12, 1999

[7] Vinpocetine was authorized for investigation as a new drug in 1981

[8] Maugh II, T. H., "Firm Hopes to Market New 'Memory' Drug," *The Los Angeles Times,* April 15, 1986.

[9] Manconi E, F Binaghi, and F Pitzus, "A Double-Blind Clinical Trial of Vinpocetine in the Treatment of Cerebral Insufficiency of Vascular and Degenerative Origin," *Current Therapeutic Research,* Vol. 40, No. 4, 1986.

[10] The Pink Sheet, "American Home Products' 'Third Generation' TPA Entering Clinicals," March 21, 1988.

This is despite the fact that for many years, FDA has maintained that there is no basis for treating synthetically-derived ingredients as any different from naturally-sourced versions.

FDA has accepted synthetic versions of vitamins, minerals, and amino acids as dietary ingredients under the respective dietary ingredient definitions at FDCA Section 201(ff)(1) and the FD& C Act does not restrict the use of synthetic botanical ingredients while allowing other types of dietary ingredients to be natural or synthetic. Further, when writing the act, Congress made no reference to the dietary ingredient source as being either natural or synthetic, nor did they specify that only certain categories of dietary ingredients could be produced synthetically. As such, we object to FDA using the synthetic status of vinpocetine as support for its tentative conclusion that vinpocetine does not qualify as a dietary ingredient.

As an example, in the nutrition labeling regulations, FDA states a food would be misbranded if the labeling states or implies that a natural vitamin is superior to an added or synthetic vitamin".[11] This position was reaffirmed in a 1997 Federal Register notice where the agency noted that it "is aware of nothing that establishes that a claim of difference between the natural and synthetic version of the same form of a nutrient is not misleading".[12]

FDA has also acknowledged NDI notifications for synthetic botanicals[13] and has affirmed as GRAS both natural and synthetic riboflavin,[14] vitamin A,[15] and vitamin D.[16] FDA has also approved natural as well as synthetic Vitamin D_3 as a food additive.[17] Botanical constituents, including cinnamaldehyde and vanillin,[18] have also been synthesized for many years and were ultimately recognized as safe (GRAS).

Thus, any action the agency takes in regards to concluding that vinpocetine does not qualify as a dietary ingredient should be based solely on the finding that an IND was active prior to receipt of a New Dietary Ingredient Notification. In the future, FDA should seek to apply consistent

[11] 21 CFR § 101.9(k)(4)
[12] 62 Fed. Reg. 49826, 49841 (Sept 23, 1997)
[13] zeaxanthin; March 22, 2001; FDA Report No. 96
[14] 21 CFR §184.1695(a)
[15] 21 CFR §184.1930(a)
[16] 21 CFR §184.1950
[17] 21 CFR §172.380(a)
[18] 21 CFR 182.60

standards in any similar situations where the existence of previous "substantial clinical investigations" (under an IND) for a legally marketed dietary ingredient is made public causing a change in the regulatory status of an ingredient subsequently proposed as an NDI.

We appreciate the opportunity to submit these comments. Please feel free to contact us should you have any questions or require additional information.

Sincerely,

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