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November 7, 2016
By electronic submission

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Response to FDA Request for Comment on the Status of Vinpocetine
81 Fed. Reg. 61700 (Sept. 7, 2016); FDA Docket No. 2016-N-2523

Gentlemen:

These comments are filed jointly on behalf of our clients, the Center for Medical Freedom, United States Justice Foundation, The Senior Citizens League, DownsizeDC.org, and Downsize DC Foundation.

Identity of Commenters

The Center for Medical Freedom ("CMF") (www.centerformedicalfreedom.org) is a project of the Conservative Legal Defense and Education Fund, which was founded three decades ago in 1985 as a nonprofit, non-partisan educational organization, incorporated under the laws of Virginia. CMF is tax-exempt under Section 501(c)(3) of the Internal Revenue Code ("IRC"). CMF's mission is to educate members of the public about their right to make their own personal medical and healthcare choices, and their inherent right of self-defense to resist efforts by government at all levels to restrict and control those choices.

The United States Justice Foundation ("USJF"), located in Ramona, California, is a legal defense and educational organization, founded in 1979, and also tax-exempt under IRC Section 501(c)(3). More information about USJF can be found at www.usjf.net.

The Senior Citizens League ("TSCL") (www.tscl.org) is a nonprofit, non-partisan social welfare organization incorporated under the laws of Colorado, and is tax-exempt under Section 501(c)(4) of the Internal Revenue Code of 1986. TSCL, headquarted in Alexandria, Virginia, is known as one of the largest U.S. nonprofit and nonpartisan organizations engaging in education and advocacy on behalf of senior citizens. Its mission is to educate the public and alert senior citizens about their rights and freedoms as U.S. citizens, to assist members and

supporters regarding those rights, and to protect and defend the benefits senior citizens have earned.

TSCL has nearly one million senior citizen members and supporters. Its activities include monitoring developments in the United States with respect to the interests of senior citizens and defending those interests before government, developing educational materials designed to explain to senior citizens their various rights as U.S. citizens, raising the level of public awareness of senior citizens' rights by conducting surveys and polls, and publishing and distributing informational newsletters to members, supporters, and the public.

DownsizeDC.org ("DDC") (www.downsizedc.org) and Downsize DC Foundation ("DDCF") (www.zeroaggressionproject.org) are nonprofit organizations, tax-exempt under Sections 501(c)(4) and 501(c)(3) respectively. DDC, founded in 2004, educates both the public and the powerful on the benefits of small government. DDCF launched its Zero Aggression Project in 2015, promoting the principle that it is wrong to initiate force to achieve social or political goals.

Comments

On September 7, 2016, the Food and Drug Administration ("FDA") published in the *Federal Register* a request for public comment on the FDA's "tentative conclusion that vinpocetine is not a dietary ingredient and is excluded from the definition of dietary supplement…."[1] FDA gave two reasons for this conclusion:

- **First**, the FDA claims that vinpocetine does not qualify under the statutory definition of a "dietary supplement" (21 U.S.C. Section 321(ff)(1)).

- **Second**, the FDA claims that vinpocetine can no longer be marketed as a dietary supplement because of an alleged 1981 Investigational New Drug Application ("IND") whose filing precludes vinpocetine from later being sold as a dietary supplement.

Both of FDA's positions are incorrect as a matter of law.

I. Contrary to FDA's Assertion, Vinpocetine Is a Dietary Supplement Because It Is Clearly a "Constituent" of a "Botanical."

Vincamine is a naturally occurring chemical compound found in the leaves of a certain type of periwinkle plant. Through a chemical reaction (dehydration) involving ethyl alcohol

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[1] https://www.federalregister.gov/documents/2016/09/07/2016-21350/request-for-comment-on-the-status-of-vinpocetine

and a catalyst, vinpocetine is derived from vincamine. This is a "semisynthetic"[2] process, because the originating material for vinpocetine is a natural source, and inorganic chemicals are then used to extract a substance that does not exist in nature in that form. This semisynthetic process is to be distinguished from a totally synthetic process where a synthetic substance is created entirely from inorganic ingredients.

21 U.S.C. Sections 321(ff)(1)(C) and (F) define the term "**dietary supplement**" to include, among other things, "a concentrate, metabolite, **constituent**, extract, or combination **of any** … herb or other **botanical**…." (Emphasis added.) Applying this test to vinpocetine and the periwinkle plant, however, the FDA claims that "vinpocetine is not a **constituent** of these plants, or of any other plants. Instead, it is synthetically produced."

Another way of stating FDA's conclusion is that "vinpocetine is not a constituent of a plant **because** it is synthetically produced." Indeed, it would appear that if vinpocetine were naturally (as opposed to semisynthetically) derived from vincamine, then the FDA **would consider it a constituent** of vincamine. The FDA bases its entire decision on the fact that vinpocetine is "semisynthetically produced" rather than being derived in some other manner.

Although the term "constituent" is not defined in Section 32, it is commonly defined as "a part of a whole." In a similar context, 21 U.S.C. Section 802(41)(C)(II)(ii) uses the word "constituent" in its definition of "anabolic steroid," where the statute exempts from "anabolic steroid" any substance that "is … a concentrate, metabolite, or extract of, or **a constituent isolated directly from**, an herb or other botanical…."

Thus, properly understood, a "constituent" is a "**part of a whole isolated directly from the whole**." Under that standard, it seems clear that vinpocetine is a constituent (a part of) vincamine, which is a constituent (a part of) a perrywinkle plant (a botanical).

According to the FDA, two chemicals are used to dehydrate vincamine and isolate vinpocetine — ethyl alcohol and ferric (iron) chloride. However, these chemicals are not contained in vinpocetine. Thus, vinpocetine is "isolated directly from" vincamine, regardless of how it was obtained, either naturally or semisynthetically.

Section 321(ff)(1)(A) lists **vitamins** are an explicit category of dietary supplements. However, if being "semisynthetically produced" is enough to keep a substance from being a botanical constituent under subsections (C) and (F), then that also should be enough to prevent a substance from being considered a vitamin under subsection (A). Yet just the opposite is

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[2] Semisynthetic is defined as "produced by chemical alteration of a natural starting material." http://www.merriam-webster.com/dictionary/semisynthetic

true. Indeed, almost all vitamins are synthetic — 90 percent, according to one estimate.[3] And, according to the FDA's logic, were it not for their express inclusion in the statute, no vitamins would qualify as dietary supplements because even "natural" or "plant-based" vitamins use some sort of semisynthetic (non-natural) processes to extract the vitamins from the food, such as heating, dehydrating, vacuum, liquefaction, drying, etc.

Synthetic Vitamin B3 (Niacin), for example, is derived "using coal tar, ammonia, acids, 3-cyanopyridine, and formaldehyde."[4] Despite its fully synthetic (and highly toxic) origin, the FDA considers synthetic Vitamin B3 to be marketable as a dietary supplement utterly indistinguishable from natural sources of Vitamin B3 such as yeast, bran, and liver. Yet natural but semisynthetically derived vinpocetine is considered not to be a botanical constituent even though it comes directly from a plant.

For these reasons, clearly, vinpocetine is a constituent of a botanical and thus qualifies as a dietary supplement.

II. Vinpocetine Can Be Marketed As A Dietary Supplement Because The Statutory Requirements Have Not Been Met for the FDA to Remove it From the Dietary Supplement Market.

A. Four Statutory Requirements Must Be Satisfied to Remove Vinpocetine From the Market As a Dietary Supplement.

According to 21 USC Section 321(ff)(3)(B)(ii), a substance may no longer be marketed as a dietary supplement if all of the following four requirements are met:

(1) the substance is "**authorized for investigation as a new drug**, antibiotic, or biological;"
(2) "**substantial clinical investigations** have been instituted;"[5]
(3) "the existence of such investigations has been **made public**;"[6] and

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[3] https://liveto110.com/90-of-vitamins-are-synthetic/.

[4] https://sunwarrior.com/healthhub/natural-vs-synthetic-vitamins

[5] For **Requirement #2**, FDA claims that "articles published between 1985 and 1988 … mention or report on phase 3 clinical trials for vinpocetine…." Since phase 3 clinical trials are the final stage of testing for a new drug, the FDA claims that such trials count as "substantial clinical investigations."

[6] For **Requirement #3**, FDA claims that the existence of that investigational new drug application ("IND") was made public after it went into effect, no later than 1986.

(4) the substance "was **not before such approval**, certification, licensing, or authorization **marketed as a dietary supplement** or as a food."[7] [Emphasis added.]

This section is designed strike a balance between dietary supplements and pharmaceuticals. On the one hand, it protects a new drug, once testing is begun, so that no one may claim it is a "dietary supplement" and sell it without obtaining approval as a drug. On the other hand, the section also protects an existing dietary supplement, so that no one may claim an existing dietary supplement suddenly to be a "new drug" and thus gain monopoly power over its sale.

B. At Least Two of the Statutory Requirements Are Not Met.

1. Requirement #1 has not been met.

For **Requirement #1**, the FDA states that an investigational new drug application ("IND") "goes into effect … thirty days after FDA receives the IND, unless FDA" objects. 21 CFR Section 312.40(b). FDA claims that an IND for vinpocetine was filed in 1981, and automatically went into effect 30 days thereafter, since the FDA did not object. FDA claims that this inaction allowing the IND to proceed is equivalent to being "authorized for investigation."

However, inaction does not constitute authorization. The FDA's inaction on an IND cannot meet the statutory requirement that it be "authorized" for investigation as a new drug. The statutory requirement that FDA "authorize" an IND clearly anticipates some sort of affirmative action on the part of the agency. The fact that the FDA simply failed to object to an IND does not mean the FDA authorized the IND. FDA's regulation (allowing inaction) does not meet the requirement ("authorization") in the statute.

2. Requirement #4 has not been met.

For **Requirement #4**, FDA claims that vinpocetine was not marketed as a dietary supplement before the vinpocetine IND went into effect. FDA's evidence for this claim is that "the first new dietary ingredient notification for vinpocetine was filed in 1997…" The FDA claims that "**therefore**, [this was] also long before vinpocetine was marketed as a dietary supplement…." (Emphasis added.)

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[7] Separately from meeting this four-part test, a substance can be marketed as a dietary supplement if "the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter…."

However, the fact that it was not until 1997 that the FDA was notified that vinpocetine would be sold as a dietary supplement does not establish that vinpocetine was not marketed as a dietary supplement prior to 1997.

The statute which requires new dietary ingredient notification — 21 USC 350b — was enacted in 1994, as Section 8 of the Dietary Supplement Health and Education Act of 1994. P.L. 103-417, 108 Stat. 4331. Moreover, the regulatory "requirement for premarket notification" (21 CFR 910.6) was promulgated by FDA three years later — in 1997 — the very same year as the first vinpocetine notifications. FDA publications confirm this analysis.[8]

Before 1994, there was no reporting requirement for new dietary ingredients. Thus, FDA clearly would never have been notified that vinpocetine was to be marketed as a dietary ingredient prior to 1994. Indeed, FDA explains that "Dietary ingredients marketed prior to October 15, 1994 … are not INDs and, therefore, **do not require an IND notification**." *Id.* at 14 (emphasis added). Indeed, according to FDA's list, there were no reports whatsoever for new dietary supplements until July of 1995.[9]

The FDA presents no evidence that vinpocetine was not "marketed as a dietary supplement" from the time of its discovery in 1975, up until regulations requiring notification were effective in 1997. Specifically, the FDA does not demonstrate that vinpocetine was not sold as a dietary supplement before the IND drug application in 1981. Yet FDA would penalize vinpocetine for failing to meet a requirement that did not exist until 1997.

The FDA provides no concrete information about the existence (or lack thereof) of vinpocetine in the dietary supplement market from 1975-1981. Without doing so, the FDA cannot reasonably claim that the vinpocetine IND came first into the marketplace, and thus has no statutory authority to exclude vinpocetine from the dietary supplements market.

III. The FDA Must Consider the Adverse Affect on Seniors and Others Benefitting from Use of Vinpocetine

For the past 20 years, vinpocetine has been, and is being, used by many Americans who have a family history of Alzheimer's disease to help prevent the onset of symptoms. Moreover, those with memory issues (often the elderly) have seen significant symptom

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[8] "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry," Center for Food Safety and Applied Nutrition, Food and Drug Administration, August 2016, p.10, http://www.fda.gov/downloads/Food/GuidanceRegulation/ GuidanceDocumentsRegulatoryInformation/UCM515733.pdf.

[9] http://www.fda.gov/Food/DietarySupplements/NewDietaryIngredientsNotificationProcess/ucm109764.htm

abatement. Others have seen improvements with a variety of other health problems. Without ready and access to inexpensive vinpocetine, Americans will be confronted with sharp increases in the price that they must pay for the same substance offered as a pharmaceutical drug. This important dietary supplement should continue to be made available at current reasonable prices as a dietary supplement to the nation's seniors, in particular, who often operate on strict budgets.

At least two commenters have suggested that the FDA consider the economic impact of its extraordinary decision to rescind approval of an ingredient as a dietary supplement. Daniel Fabricant, Ph.D., CEO and Executive Director of National Products Association asked in a letter dated September 7, 2016, whether the FDA was "planning to conduct an economic impact analysis on both large and small businesses" as the result of the FDA's proposed action on vinpocetine. He noted that the proposed action "would bear little incremental public health effect … but [have] a significant incremental cost associated with the change." Similarly, a comment by Steve Lucchino noted that the proposed action "would impose significant economic costs [and] negatively effect tens of thousands of small business owners." These commenters agree that it is only reasonable for the FDA to give serious consideration to the adverse affect of its decision on businesses and consumers. Although the FDA operates under a different statutory structure than the Environmental Protection Agency, it is worth noting that the U.S. Supreme Court decided last year that the EPA must consider the economic cost of a regulation when determining whether a particular action was "appropriate and necessary." *See* Michigan v. EPA, 135 S.Ct. 2699, 2707 (2015) ("EPA strayed far beyond those bounds when it read [its relevant statute] to mean that it could ignore cost when deciding whether to regulate power plants.").

Too often the FDA appears wholly insensitive to the fact that its decisions can cause seniors and others on limited budgets to often do without. In other cases, more dangerous substitutes — ones with harsh side effects absent with vinpocetine — may be chosen. Furthermore, to the extent vinpocetine helps prevent or delay the onset of Alzheimer's symptoms, the FDA's action in this docket will cause higher nursing home care costs and untold pain for seniors and their families. The FDA must stop working against the interests of the American people.

Conclusion

For the reasons set out above, vinpocetine should continue to be available as a dietary supplement.

Sincerely yours,

/s/
Robert J. Olson

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