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November 7, 2016

VIA ELECTRONIC SUBMISSION

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

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

Dear Sir or Madam:

The Council for Responsible Nutrition (CRN), the leading trade association for makers and marketers of dietary supplements and dietary ingredients,[1] respectfully submits the following comments on the September 7, 2016 *Federal Register* notice (hereinafter "the notice") concerning vinpocetine.[2] In that notice, FDA announced its tentative decision to reverse its longstanding position that vinpocetine is a legal dietary ingredient—one that has been the subject of five successful new dietary ingredient (NDI) notifications and has been on the market for nearly 20 years.[3]

Such a reversal on the status of a dietary ingredient is inappropriate when, as here, there are no safety concerns. Further, it is an unprecedented move by FDA that threatens to undermine the dietary supplement industry's confidence in the NDI notification process. The

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[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing more than 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control, and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

[2] Notice, 81 Fed. Reg. 61,700 (Sept. 7, 2016).

[3] FDA acknowledged without objection the following five NDI notifications: Amrion, Inc. (July 8, 1997); Leiner Health Products (Oct. 20, 1998 and Mar. 24, 1999); General Nutrition Corporation (Apr. 16, 1999); and Pharmavite Corporation (May 12, 1999).

notice is also legally deficient because it fails to acknowledge FDA's prior position on vinpocetine, to explain adequately its new position, or to assess the economic impact of its new position on companies that have invested in the market development of vinpocetine over the past 19 years.

CRN appreciates that FDA has provided an opportunity for comment on its tentative decision. Our comments do not address the substance of the agency's claims about the manufacture of vinpocetine or the previous investigational study of this ingredient.[4] We have explained elsewhere and often our disagreement with the agency's interpretation of certain statutory categories of dietary ingredients (e.g., regarding synthetic versions of botanical constituents), and we shall soon do so again in our comments on the revised NDI draft guidance.[5] Here, we focus instead on the process FDA has set in motion for vinpocetine, and the dangerous precedent it would set. We urge FDA to withdraw its notice or otherwise refrain from revisiting the status of vinpocetine or any other dietary ingredient for which it has no safety concerns.

I. It is bad policy for the agency to revisit the status of a dietary ingredient when it has no safety concerns.

While a formal notice and comment period—like this one for vinpocetine—might be an appropriate process for determining the status of a dietary ingredient, this process should be invoked in the first instance FDA has the opportunity to evaluate an ingredient, not after an ingredient has been safely marketed for 19 years. Once FDA has concluded that an ingredient is a lawful dietary ingredient by acknowledging an NDI notification,[6] the agency should not revisit

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[4] In the notice, FDA gives two reasons for its tentative conclusion vinpocetine cannot be used in dietary supplements: (1) the agency alleges that vinpocetine does not qualify as a dietary ingredient, and (2) the agency claims the ingredient was investigated as a drug before it was used in dietary supplements. 81 Fed. Reg. 61700.

[5] *See* FDA Revised Draft Guidance, "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" (Aug. 2016) [hereinafter Revised NDI Draft Guidance]. On several other occasions, we have addressed our disagreements with the agency over the appropriate statutory interpretation of the categories of dietary ingredients in 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act. 21 U.S.C. § 321(ff)(1). Our comments on the revised NDI draft guidance will cover several critical issues, including the lawful use of synthetic constituents of botanicals. We will submit our comments on the revised draft guidance before the end of the comment period, which is now December 12, 2016.

[6] When it receives an NDI notification, the agency not only assesses whether an ingredient is safe but also whether it qualifies as a dietary ingredient under one of the statutory categories in of dietary ingredients in 201(ff)(1), 21 U.S.C. § 321(ff)(1). *See, e.g.*, Revised NDI Draft Guidance, at 54 (within 75 days of receiving a notification, FDA will respond

the ingredient's status unless it has safety concerns. The agency has not alleged any safety concern with vinpocetine, nor has it offered any new information about the ingredient that was not available when it received the first NDI notification for vinpocetine nearly 20 years ago.

Although FDA has not said why it is revisiting the status of vinpocetine, Senator Claire McCaskill (D-MO) sent a letter to the agency about picamilon and vinpocetine in October 2015, claiming that these ingredients were "synthetic or semi-synthetic" and requesting more information about them.[7] In line with its mission to protect public health, the agency should focus on ingredients that pose clear safety risks and the integrity of the NDI notification process, rather than turning its attention to ingredients that are in the news for political reasons.

Further, FDA's unprecedented step comes at an inopportune time for the industry. CRN has been working with FDA in good faith on the policies and interpretations the agency announced in the original NDI draft guidance and its recent revision.[8] Threatening products that have been on the market for nearly 20 years after five NDI notifications, the agency's notice on vinpocetine is not in the same spirit of cooperation. It also undermines the agency's goals. For example, in the revised NDI draft guidance, the agency encourages companies to submit NDI notifications even when the statute does not require them to do so.[9] Companies now may be less inclined to participate voluntarily in the NDI notification process if the agency may simply reverse an acknowledgement at any time—for example, when it receives pressure from a member of Congress. Such action by FDA also creates unpredictability in the marketplace, thereby discouraging innovation and new product development.

CRN and its members rely upon the agency's determination during the NDI notification process. Indeed, armed with successful NDI notifications for vinpocetine, companies invested

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with a "[l]etter of acknowledgment without objection" or it will raise an objection such as "safety concerns," "gaps" in information, or that "the NDI is not a dietary ingredient under 21 U.S.C. 321(ff)(1)").

[7] Letter from Sen. Claire McCaskill to Stephen Ostroff, FDA (Oct. 6, 2015).

[8] Published in August 2016, the revised draft guidance is an update of the original NDI draft guidance from 2011.

[9] *See* Revised NDI Draft Guidance, at 25 ("[I]t may be advisable to submit a NDI notification voluntarily when a dietary supplement contains a significantly higher level of an NDI than is used in conventional foods. FDA has reviewed and intends to continue reviewing voluntarily submitted notifications for NDIs that are exempt from the notification requirement under 21 U.S.C. 350b(a)(1) because they have been present in the food supply as articles used for food in a form in which the food has not been chemically altered.").

substantial sums—assuring the safety and quality of its manufacturing, and building brands around it. According to a database maintained by the National Institutes of Health, more than 300 dietary supplements contain vinpocetine, although this number is likely an underestimate.[10] Before changing its position on vinpocetine for reasons unrelated to safety, FDA should assess the number of products its decision would affect and the economic costs to industry, including possible reformulations or recalls of products.

II. The notice about vinpocetine is legally deficient.

In addition to being bad policy, the notice is legally deficient in several respects. Most critically, with this notice FDA has departed from past agency practice without adequate explanation.[11] One of the basic principles of administrative law is that the "agency must give adequate reasons for its decisions."[12] Even if FDA has statutory authority to reclassify vinpocetine, it nevertheless must "provide a reasoned explanation for" its decision.[13] In the words of the district court in *Prevor v. FDA*, "One of the core tenets of reasoned decision-making is that an agency [when] changing its course . . . is obligated to supply a reasoned analysis for the change."[14] Before issuing the notice on vinpocetine, FDA determined repeatedly that it was a dietary ingredient by accepting NDI notifications without objection.[15] Although FDA briefly refers to this history in a footnote,[16] it does not directly acknowledge the regulatory consequences of its prior actions. Further, while the notice lays out some arguments for its new

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[10] The Dietary Supplement Label Database (DSLD) is a joint project of two NIH units, the Office of Dietary Supplements and National Library of Medicine. *See* http://www.dsld.nlm.nih.gov/dsld/index.jsp. The NIH database is only a sampling of the dietary supplements marketed in the United States, suggesting that there may be many hundreds of products that may be affected by the FDA's decision on vinpocetine.

[11] *See FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009); *Ramaprakash v. FAA*, 346 F.3d 1121, 1124–25 (D.C. Cir. 2003).

[12] *Encino Motorcars, LLC v. Navarro*, 136 S. Ct. 2117, 2125 (2016).

[13] *Id.*

[14] *Prevor v. FDA*, 895 F. Supp. 2d 90, 97 (Dist. D.C. 2012) ("One of the core tenets of reasoned decision-making is that an agency [when] changing its course . . . is obligated to supply a reasoned analysis for the change.") (internal citations omitted).

[15] Revised NDI Draft Guidance, at 54 ("[Y]ou may expect a letter acknowledging receipt of the notification and stating the date on which the notification was filed. Examples of the types of response letters FDA commonly sends include: •Letter of acknowledgment without objection; . . . and • Letter raising other regulatory issues with the NDI or dietary supplement (e.g., the NDI is not a dietary ingredient under 21 U.S.C. 321(ff)(1) . . . .").

[16] *See* 81 Fed. Reg. at 61,702 n.4.

conclusions about vinpocetine, the agency has not given a sufficient explanation for why it is changing course now.

FDA also has not adequately considered the industry's reliance interests. Hundreds of products contain vinpocetine, and such products have been marketed for nearly 20 years. The notice does not address either of these points, and thus the agency's action is arbitrary and capricious because it "entirely failed to consider an important aspect of the problem."[17] To the extent FDA proposes to take enforcement action against dietary supplement companies for manufacturing and marketing practices occurring before FDA issues its final decision, its approach is inconsistent with a long line of cases, including *Christopher v. SmithKline Beecham*.[18] Along these lines, we urge FDA to give companies a reasonable time to comply with the agency's new conclusion about vinpocetine, if and when it finalizes its reversal on the status on vinpocetine in accordance with the requirements for reasoned agency decision-making.

CRN again thanks FDA for providing the opportunity to voice our comments and we look forward to answering any questions FDA may have. Please do not hesitate to contact us.

Sincerely yours,

Douglas MacKay, N.D.
Senior Vice President, Scientific & Regulatory Affairs

[17] *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

[18] *Christopher v. SmithKline Beecham Corp.*, 132 S. Ct. 2156, 2167 (2012).