Council for Responsible Nutrition
1828 L Street, NW, Suite 510 • Washington, DC 20036-5114
(202) 204-7700 • fax (202) 204-7701 • www.crnusa.org

December 29, 2015

Via Electronic Mail

Mr. Ted Elkin
Deputy Director for Regulatory Affairs
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
Room 4B-006, HFS-2
College Park, MD 20740

Re: The Welch Declaration re Picamilon

Dear Mr. Elkin:

We write in response to your letter of November 19, 2015, responding to our letter of October 27, 2015 (enclosed), in which the Council for Responsible Nutrition ("CRN") expressed its serious concerns about the process by which FDA, through Dr. Cara Welch, announced a decision regarding the legal status of picamilon. We explained that providing a declaration (the "Welch Declaration") about the legal status of an ingredient to a state attorney general as the first public announcement of an official determination by FDA, particularly in a legal matter in which FDA is not even a party, is bad policy.

We agree with FDA that picamilon should have been the subject of a new dietary ingredient ("NDI") notification to the agency, and that, as you noted in your response, the individual notifiers would then have had full notice of FDA's view of the status of picamilon. Our concern, however, is with the broader implications for the dietary supplement industry of FDA's apparent conclusion about what may be a lawful combination dietary ingredient under DSHEA, and about the apparent expression of that conclusion first in a declaration to a state attorney general. As detailed below, the approach expressed in that declaration appears to take a very narrow view of what constitutes a "combination" dietary ingredient under Section

201(ff)(1)(F) of the FDCA (to the extent this provision was even considered), in a manner that seems inconsistent with prior FDA guidance to industry.

Section 201(ff) defines a "dietary supplement," in relevant part, as a product "that bears or contains one or more" dietary ingredients.[1] Section 201(ff)(1)(F) further states that a dietary ingredient includes a "combination of any [dietary] ingredient."[2] In discussing section 201(ff)(1)(F), the Welch Declaration did not expressly address the "combination" provision in that section. Dr. Welch did, however, state that "[p]icamilon is formed by synthetically combining niacin with GABA"[3] and that "[w]hile picamilon is a synthetically modified version of niacin and GABA, both dietary ingredients on their own, it is a different chemical entity."[4] These statements suggest that Dr. Welch either did not consider the "combination" provision of Section 201(ff)(1)(F) in evaluating the dietary ingredient status of picamilon, or she concluded that picamilon – which she acknowledged was a combination of niacin with GABA – was not a "combination" under Section 201(ff)(1)(F). To the extent that either case reflects FDA's position on what constitutes a "combination" dietary ingredient under that provision, such position appears to have been previously uncommunicated to the dietary supplement industry, and should not have been first expressed in a declaration to a state attorney general.

The term "combination" in Section 201(ff)(1)(F) must mean something more than two ingredients merely present together (such as simply mixing multiple vitamins into a single product). Section 201(ff) already addresses such a situation when it states that a dietary supplement "bears or contains one or more . . . dietary ingredients."[5] It is a well-settled rule of statutory interpretation that every word in a statute should be given effect and redundancies

---

[1] 21 U.S.C. §321(ff).

[2] *Id.* § 321(ff)(1)(F). The Senate report describing what would become this subsection state: "In addition, concentrates, metabolite, constituents, extracts, or combinations of the items previously described may be included in a dietary supplement." Sen. Rpt. 103-410 (Sept. 8, 1994).

[3] Welch Declaration, para 2.

[4] Welch Declaration, para 9.

[5] *Id.* § 321(ff)(1).

avoided.[6] Thus, "combination" here must mean that dietary ingredients are, in fact, combined. The standard dictionary definition of "combination" includes "the act or process of combining; *especially*: that of uniting to form a chemical compound."[7] The best reading of "combination" is its plain meaning: "combination" in Section 201(ff)(1)(F) includes chemical combinations of dietary ingredients, including chemical compounds formed by covalent bonds that produce a "different chemical entity."

FDA appears to have embraced this plain meaning of "combination" in its 2011 draft guidance on NDI notifications. There the agency wrote about covalent combinations:

> **What additional chemistry information should I submit if my ingredient is a covalently modified derivative of a dietary ingredient?** Examples include covalent bonding of one dietary ingredient to another or exchanging a functional group (e.g. an alcohol) for another (e.g. an acid or an ester). The chemical structure of the new ingredient should be described explicitly and clearly.[8]

In this passage, FDA acknowledges that a covalent combination of two dietary ingredients is, itself, a dietary ingredient, and that such combination would be a different chemical entity. The agency's explanation of the information that should be provided in an NDI notification clearly anticipates that such combinations could constitute dietary ingredients themselves. Why would

---

[6] This rule is so old it comes from the Roman Empire: "Verba cum effectu accipienda sunt," which translates as "words are to be interpreted so as to give them effect." Ulpian, *Digesta* 2.7.5.2 (third century A.D.). *See also* A. Scalia & Bryan Garner, *Reading Laws: The Interpretation of Legal Texts* 174 (2012) ("If possible, every word and every provision is to be given effect. . . . None should be ignored. None should needlessly be given an interpretation that causes it to duplicate another provision or to have no consequence."); *Reiter v. Sonotone Corp.*, 442 U.S. 330, 339 (1979) ("In construing a statute, we are obliged to give effect, if possible, to every word Congress used.").

[7] "Combination" *in* Merriam-Webster Dictionary, http://www.merriam-webster.com/dictionary/combination.

[8] FDA Draft Guidance, Dietary Supplements: New Dietary Ingredient Notifications and Related Issues (July 2011).

the agency expressly discuss the requirements for an NDI notification in this context if the new ingredient could not be a dietary ingredient in the first place?[9]

In sum, CRN remains concerned that the Welch Declaration potentially represents a significant statement of FDA policy about what constitutes a "combination" dietary ingredient. CRN believes such statements should not be made in the context of a declaration provided to a state attorney general without any prior announcement or guidance to industry. To the extent that FDA intends to express what the agency believes does or does not qualify as a "combination" dietary ingredient under section 201(ff)(1)(F), FDA should do so through an updated NDI guidance that would allow for stakeholder comment.

We appreciate your thoughtful consideration on this issue and look forward to hearing back from FDA on this matter.

Sincerely yours,

Steven M. Mister
President & CEO

cc: Michael Taylor, Office of Foods and Veterinary Medicine
Robert Durkin, Division of Dietary Supplement Programs
Elizabeth Dickinson, Office of the Chief Counsel
Douglas Stearn, Office of Enforcement and Import Operations

Enclosure: CRN Letter of October 27, 2015

[9] To be sure, not every covalently modified derivative of a dietary ingredient qualifies as a dietary ingredient. For example, when one functional group is exchanged for another (a type of covalent modification discussed in the NDI draft guidance), the newly formed molecule is not a combination of dietary ingredients. This new molecule may still be a dietary ingredient under Section 201(ff)(1)(F), *e.g.*, if it is a "metabolite" of the original ingredient, and FDA's NDI draft guidance goes on to state that this must be considered.

Council for Responsible Nutrition
1828 L Street, NW, Suite 510 • Washington, DC 20036-5114
(202) 204-7700 • fax (202) 204-7701 • www.crnusa.org

October 27, 2015

Mr. Ted Elkin
Deputy Director for Regulatory Affairs
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
Room 4B-006, HFS-2
College Park, MD 20740

Via email: Ted.Elkin@fda.hhs.gov

Dear Mr. Elkin:

The Council for Responsible Nutrition (CRN), the leading trade association for the dietary supplement and functional food industry, writes to express our grave concern regarding the enclosed Declaration, which was signed by Dr. Cara Welch and executed on September 28, 2015. We understand that Dr. Welch, on behalf of FDA, provided this Declaration to certain state attorneys general who sought clarification as to whether picamilon (also referred to as pikatropin) is legal dietary ingredient under Section 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act (FD&CA).

The Declaration was then used by the state AGs as primary evidence in a cease and desist letter delivered on retailers demanding they immediately remove this product from sale or face penalties under state law. This letter is not intended to raise questions with regard to the substance of FDA's determination—we will raise our concerns about the classification of picamilon and the proper interpretation of Section 201(ff)(1) in a separate correspondence to the agency. Our difficulty here is with the provision of a Declaration privately to a state law enforcement agency on an issue of law that has never been raised by FDA. CRN believes this sets a dangerous precedent regarding the cooperation between FDA and state law enforcement on matters of federal law not previously noticed to the industry.

In the Declaration, Dr. Welch concludes that picamilon, which is formed by combining niacin with GABA, "does not fit any of the dietary ingredient categories in section 201(ff)(1)(A)-(F)" of the FD&CA. This process did not occur in a public forum, and therefore precluded any input from the industry in response to FDA's characterization of the ingredient or the chance to present its own evidence as to why this ingredient can qualify as a legal dietary ingredient. It also prevented industry from gaining valuable insight into the agency's views on synthetically created dietary ingredients and dietary ingredients that are combined to create another dietary ingredient, as permitted by Section 201(ff)(1)(F). As you are aware, this issue is of tremendous interest to the supplement industry, especially given the lack of clarity found in the statute and the lack of regulatory guidance on this issue.

As you know, 21 CFR §20.1 requires that for testimony to be provided to a state agency, the Commissioner or his designee must determine that the "testimony will be in the public interest and will promote the objectives of the act and the agency." FDA's own staff guide, *Requests for Testimony of FDA Personnel in Non-FDA Proceedings,* provides, "FDA will usually decline to authorize any employee to testify unless compelling circumstances exist…," and also states, "It ordinarily is considered not to be in the public interest to interrupt the duties of FDA personnel in the implementation and enforcement of the laws subject to the agency's jurisdiction in order to participate in proceedings to which FDA is not a party."[1] It does acknowledge, however, that "Testimony requested by Federal, state, and local governments is often, but not always, deemed to be in the public interest." We believe that is not the case here.

FDA has never made any public statements with regard to picamilon: it has not released any warning letters to the companies marketing picamilon, issued any recall on this ingredient, or announced any consumer advisories on it. In fact, we are not aware that FDA has ever communicated publicly about picamilon in any regard. Moreover, we are not aware that picamilon has been the source of any significant number of adverse event reports or any other signals that it may present a public health or safety concern. Rather, the matter of picamilon's status as a new dietary ingredient, or even as a dietary ingredient at all, is purely a matter of legal interpretation deserving of due notice to industry. Given FDA's position on so many other issues—that the public interest and FD&CA are best served by providing adequate notice to industry prior to beginning an enforcement action—it is difficult to understand how that interest is served here. Certainly FDA's long history of slow, deliberate action on such actual safety issues as DMAA, pure powdered caffeine, and numerous products tainted with illegal prescription drugs would counsel for thoughtful action from the FDA with an opportunity for industry input prior to issuing a Declaration to be used in a state action.

Moreover, we are deeply troubled by what appears to be an abdication of federal authority under the FD&CA by FDA to state law enforcement. In the wake of the investigation by the New York Attorney General earlier this year using faulty DNA testing of herbal supplements, the industry has witnessed a significant increase in the interest of state attorneys general in our products. While the interest of state law enforcement to assist the FDA in enforcing the requirements of the FD&CA and to assure safe and quality products to their constituents may be beneficial, that interest demands cautious and prudent evaluation of those efforts by FDA. As the recent New York AG allegations regarding devil's claw illustrate, not all technical violations of the statute are matters of public safety, or even consumer protection. Such may be the case with picamilon as well. The FDA has an obligation to evaluate the interests of the agency in preserving its supremacy over the regulation of products under its jurisdiction. Providing testimony to a state agency on a matter in which the agency has not spoken undermines the interests of the FDA rather than promoting it.

---

[1] http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm183021.htm.

We believe that FDA, after being made aware of the presence of this ingredient in the marketplace, should have issued a warning letter stating the reasons why picamilon is not a legal dietary ingredient. Alternatively, and perhaps the more appropriate option, the agency also could have declared the products containing this ingredient adulterated under Section 402(f)(1)(B) as a new dietary ingredient (NDI) which requires notification. Although we understand that FDA has limited resources and must prioritize its enforcement action based on public health risk, this situation presents an important opportunity for the agency to clarify its view on this category of ingredients and encourage submission of NDI notifications. The agency missed a significant opportunity to educate the industry regarding its view of synthetically combined dietary ingredients.

In summary, CRN believes there are substantial policy implications stemming from this Declaration, not only for dietary supplements, but for other FDA-regulated products as well. The lack of public notice deprived industry of the ability to participate in the regulatory process and does a disservice to an industry that is seeking to comply fully with the law and regulations. It undermines the supremacy of the FD&CA and the ability of FDA to implement and enforce that law. While we appreciate FDA's use of enforcement discretion and the need to prioritize resources, we respectfully urge the agency to reconsider the use of Declarations or other testimony in state actions to which it is not a party and where the industry could benefit from FDA's direct engagement.

We appreciate your thoughtful consideration on this issue and look forward to hearing back from FDA on this matter.

Sincerely yours,

Steven M. Mister
President & CEO

cc: Michael Taylor, Office of Foods and Veterinary Medicine
Robert Durkin, Division of Dietary Supplement Programs
Elizabeth Dickinson, Office of the Chief Counsel
Robert Califf, Office of Medical Products and Tobacco
Stephen Ostroff, Acting Commissioner of Food and Drugs
Douglas Stearn, Office of Enforcement and Import Operations

Enclosure, *Declaration of Dr. Cara Welch*