



Council for Responsible Nutrition

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October 22, 2012

VIA ELECTRONIC MAIL

The Honorable Margaret Hamburg, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Bldg. 1
Room 2217
Silver Spring, MD 20993

Re: Lawful Status of Synthetic Botanical Constituents as
Dietary Ingredients

Dear Commissioner Hamburg:

The Council for Responsible Nutrition (CRN)¹ submits this letter to urge FDA to reverse its position that synthetic constituents of botanicals cannot be dietary ingredients. The agency's position is contrary to the language of and congressional intent behind the Dietary Supplement Health and Education Act of 1994 (DSHEA); it stands in conflict with decades of FDA precedent; and it is neither scientifically justified, logical, nor in the interest of the public health. As

¹ CRN, founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN companies produce a large portion of the dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands, as well as the store brands marketed by major supermarket, drug store, and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. In addition to complying with a host of federal and state regulations governing dietary supplements in the areas of manufacturing, marketing, quality control, and safety, our 75 plus manufacturer and supplier members also agree to adhere to additional voluntary guidelines, as well as CRN's Code of Ethics. Learn more about us at www.crnusa.org.

long as a synthetic botanical constituent has the same biological activity as its naturally-derived counterpart, it is also a botanical or botanical constituent as a matter of law and science.

In establishing the framework for the regulation of dietary supplements, Congress intended to strike a suitable balance between securing consumer access to a wide variety of dietary ingredients and dietary supplements while providing FDA with appropriate oversight over these articles. Congress concluded that “a rational Federal framework must be established to supersede the current ad hoc, patchwork regulatory policy on dietary supplements.”² The Senate Report accompanying DSHEA noted that in the years prior to its enactment, FDA had “a long history of bias against dietary supplements”³ and “pursued a heavy-handed enforcement agenda” against these products by attempting to restrict their marketing in a variety of ways.⁴ Congress enacted DSHEA to “correct this abuse by rationalizing the treatment of dietary supplements according to the pattern of the existing statute, and in conformity with the original congressional intent.”⁵

FDA’s current policy of excluding synthetic botanical constituents from the definition of “dietary ingredients,” while acknowledging that all other articles listed in that definition may be used in synthetic form, is not rational, for the reasons detailed in this letter, and particularly because synthetic botanicals such as synthetic vanilla and other flavor ingredients have been in the food supply far longer than synthetic versions of other types of dietary ingredients. Rather, it appears reflective of FDA’s historical bias against dietary supplements, which Congress had sought to

² Pub. L. No. 103-417, § 2(15).

³ S. REP. NO. 103-410 (1994), at 14.

⁴ *Id.*

⁵ *Id.* at 22.

correct in enacting DSHEA. FDA expressed this view most emphatically in its Draft Guidance on New Dietary Ingredient Notifications (“NDI Draft Guidance”) issued in July 2011.⁶ However, this misinterpretation of the statute predates the NDI Guidance, going back at least as far as 2004 when the agency made similar statements in its regulation to ban ephedra,⁷

Each time, CRN has expressed its concern about the agency’s mistaken position on synthetic botanical constituents, including in CRN’s December 2011 comments on the NDI Draft Guidance. And each time, the agency has disregarded the legal arguments put forth and maintains its position without addressing the overwhelming arguments against this view. CRN is writing to you now because FDA has been increasing its enforcement activities against such constituents, through import holds,⁸ warning letters,⁹ and recalls that were directed by the agency.¹⁰ Because

⁶ FDA/CFSAN, “Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues” (July 2011), Section IV(D)(2), in which the question-and-answer guidance states:

“Is a synthetic copy of a constituent or extract of an herb or other botanical a dietary ingredient?”

No. A synthetic copy of a constituent of a botanical was never part of the botanical and thus cannot be a ‘constituent’ of the botanical that qualifies as a dietary ingredient under section 201(ff)(1)(F) of the FD&C Act (21 U.S.C. 321(ff)(1)(F)). Similarly, a synthetic version of a botanical extract is not an ‘extract’ of a botanical under section 201(ff)(1)(F) because it was not actually extracted from the botanical.”

⁷ 69 Fed. Reg. 6788 (February 11, 2004); see also Letter from Michael M. Landa, Acting Director, Center for Food Safety and Applied Nutrition, Food and Drug Administration to Marc Ullman, Esq. (Feb. 23, 2011) (denying a manufacturer’s petition to have a synthetically manufactured algae extract called homotaurine classified as an NDI); Letter from Felicia B. Satchell, Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, Food and Drug Administration to Jason Crush (Aug. 29, 2002) (responding negatively to an NDI notification for synthetic conjugated linoleic acid, arguing that the substance did not fit the definition of a dietary supplement under the FDCA).

⁸ CRN is aware of at least two shipments of vinpocetine that have been the subject of FDA holds at the port of entry because agency personnel took the position that it is not a dietary ingredient because of its synthesis. Vinpocetine is an ingredient derived from vincamine, which is a substance that is extracted from *Vinca minor* (periwinkle) or African vocanga seeds as well as synthesized chemically. The Merck Index 1570, 1572 (11th ed. 1989) (entries 9888, 9894).

⁹ E.g., the ten warning letters regarding DMAA available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302133.htm>.

such enforcement actions are not grounded in the law, they exceed FDA's statutory authority and must be ceased. CRN is also deeply concerned about the recent remarks that senior FDA personnel have made to the trade and consumer press that synthetic botanical constituents cannot qualify as lawful dietary ingredients.¹¹ Again, because these assertions are incorrect under DSHEA and in conflict with agency precedent, CRN urges FDA to take steps to ensure that such erroneous statements are not made in the future and that all District Offices are immediately and expressly instructed this misinterpretation of DSHEA should not be enforced in any manner.

Nor should this remain unresolved until the other aspects of the NDI Draft Guidance are resolved. Indeed, FDA's position on this matter is not relevant to the discussion of NDIs nor is it one about the safety of a particular ingredient. Rather it is definitional: if FDA's current position prevails, these ingredients would be prohibited from use in dietary supplements—period. By persisting in this view, FDA is effectively denying consumers access to a range of ingredients without sufficient justification or a determination of safety. FDA's actions and comments are having an immediate chilling effect on the industry and are irrevocably damaging commerce, innovation and investment.

I. FDCA Section 201(ff)(1)(A)-(D) Makes No Distinctions Between Synthetic and Natural Dietary Ingredients

¹⁰ FDA Enforcement Report – Week of July 18, 2012, Recall Number F-1729-2012, available at http://www.accessdata.fda.gov/scripts/enforcement/enforce_rpt-Product-Tabs.cfm?action=select&recall_number=F-1729-2012&w=07182012&. (stating that the products contained ingredients “which are constituents or extracts of an herb or other botanical, and the that a synthetic copy of a constituent or extract of an herb or other botanical is not a dietary ingredient, and such ingredients must be approved for use in supplements”).

¹¹ *E.g.*, comments of Daniel Fabricant, director of FDA's Division of Dietary Supplement Programs, cited in *Vitamins & Supplements: 10 Dangers That May Surprise You*, Consumer Reports, September 2012, at 18, 22. (hereinafter, “Consumer Reports”).

DSHEA added the definitions of “dietary supplement” and “dietary ingredient” to the Federal Food, Drug, and Cosmetic Act (FDCA) in Section 201(ff)(1). That provision states:

The term “dietary supplement”—

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin;

(B) a mineral;

(C) an herb or other botanical;

(D) an amino acid;

(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

Vitamins, minerals, and amino acids are all constituents of food. Because Congress could not name individually all of the constituents of botanicals that could be used as dietary ingredients, it used the broader terms “herb or other botanical” at Section 201(ff)(1)(C) and then added Section 201(ff)(1)(F) to capture such constituents.

Congress made no reference to the source of the dietary ingredients as natural or synthetic, nor did Congress specify that only some of these categories of dietary ingredients may be produced synthetically while others must only come from natural sources. This stands in contrast to the statutory language in FDCA Section 411, added by the Proxmire Amendments in 1976 to bar FDA from imposing maximum limits on the potency of “any synthetic or natural vitamin or mineral” and from classifying “any natural or synthetic vitamin or mineral” as a drug solely because it exceeds the

level of potency which FDA determines is nutritionally rational or useful.¹² This language makes clear that Congress did not view the terms “vitamin” and “mineral,” standing alone, as inherently meaning the natural form of these dietary ingredients; otherwise, there would have been no need in the Proxmire Amendments to specify natural as well as synthetic vitamins and minerals.

These amendments document that by 1976, Congress was well aware that vitamins and minerals were marketed in both natural and synthetic forms. Once Congress had established in the Proxmire Amendments that vitamins and minerals should be treated the same way by FDA regardless of whether they are naturally or synthetically derived, it did not need to specify this fact again in DSHEA, after those amendments had been effective for nearly twenty years. And just as Congress was aware, by the time of the Proxmire Amendments, that vitamins and minerals were marketed in both natural and synthetic forms, it is also presumed to have been aware that synthetic botanical constituents had been in the food supply for many decades by the time DSHEA was enacted, as detailed in the following section. If Congress had intended to limit other dietary ingredient categories to only natural forms, it plainly could have done so, but did not. Accordingly, where Section 201(ff)(1)(A)-(D) identifies vitamins, minerals, botanicals, and amino acids as dietary ingredients, Congress intended to include both the naturally and synthetically derived forms.

II. Botanical Constituents Used in the Food Supply Have Been Synthesized Longer than Vitamins, Minerals, or Amino Acids

Botanical constituents have been synthesized long before vitamins, mineral nutrients, and amino acids were synthesized. Thus, there are no grounds to conclude that Congress intended to carve out the long-established category of synthetic botanical constituents from the definition of dietary ingredients.

¹² FDCA § 411(a)(1)(A) & (B).

For example, cinnamic acid and related cinnamates, which can be obtained from oil of cinnamon or from balsams, have been synthesized for over a century.¹³ Dozens of synthetic flavors derived from botanicals were in wide use in the food supply before the Food Additives Amendment of 1958 and thus were generally recognized as safe (GRAS), as reflected in FDA's GRAS regulation for synthetic flavoring substances and adjuvants.¹⁴ In particular, that listing includes synthetic botanical constituents such as cinnamaldehyde and vanillin. Vanillin is a constituent that occurs naturally in vanilla but was synthesized in the 1950s¹⁵ and is generally used in food in its synthetic form. Similarly, FDA's food additive regulation for synthetic flavoring substances and adjuvants, currently codified at 21 C.F.R. § 172.515, listed numerous synthetic botanical constituents such as cinnamates or related substances even when first promulgated in 1964.¹⁶

This long and robust history of FDA's authorization of synthetic constituents of botanicals for food use and the marketing of such substances belies the agency's current contention that synthetic botanical constituents cannot be dietary ingredients. The regulatory history described above makes clear that synthetic botanical constituents have long been in the diet and are therefore

¹³ 2 Thomas E. Thorpe, *A Dictionary of Applied Chemistry* 17 (1912), available at <http://www.ebooksread.com/authors-eng/t-e-thomas-edward-thorpe/a-dictionary-of-applied-chemistry-volume-2-hci/page-17-a-dictionary-of-applied-chemistry-volume-2-hci.shtml> (citing Farb. vorm. Meister, Lucius and Briinii-r, D. B. P. 53671 ; Eng. Pat. 4946; J. Soc. Chem. Ind. 1891, 358 ; Rainer Ludwig Claisen, Zur Darstellung der Zimmtsäure und ihrer Homologen, 23 Ber. 976 (1890), available at <http://gallica.bnf.fr/ark:/12148/bpt6k90720c/f978.image.r=berichte%20der%20deutschen%20chemischen.langEN>, in support of the statement that “[e]thyl cinnamate may be obtained direct from benzaldehyde by means of ethyl acetate and sodium.”).

¹⁴ 21 C.F.R. § 182.60, originally codified at 21 C.F.R § 121.101. 26 Fed. Reg. 3991 (May 9, 1961).

¹⁵ The Merck Index 1419 (10th ed. 1983).

¹⁶ 29 Fed. Reg. 14625 (October 27, 1964).

“dietary ingredients.” Further, this regulatory and scientific history makes clear that there is nothing unusual or unique about synthetic botanical constituents, though statements by FDA officials have made these seem strange and novel.

In contrast to the century-old synthesis of botanical constituents, vitamins and amino acids were synthesized more recently. Although niacin was synthesized in 1867, it was not until 1933 that another vitamin – Vitamin C – was synthesized.¹⁷ The rest of the vitamins were synthesized between 1935 and 1972.¹⁸ While some amino acids had been synthesized by 1950,¹⁹ synthetic amino acids were developed in earnest in the early 1960s as part of research for the space program, when the aerospace industry worked to create complete chemical food products, using crystalline amino acids and the essential vitamins and minerals that could provide adequate nutrition without bulk.²⁰

The foregoing documents that synthetic botanical constituents were ingredients in the food supply, and were therefore “dietary ingredients,” long before synthetic versions of the other dietary ingredients listed in FDCA Section 201(ff)(1)(A)-(D) entered the food supply. Thus, there is no basis upon which FDA might reasonably conclude that synthetic botanical constituents may not

¹⁷ 3 Encyclopedia of Food Science and Technology 2689, Table 2, “History of Vitamins (in years),” (Y.H. Hui, ed., 1992).

¹⁸ *Id.*

¹⁹ 2 Encyclopedia of Chemical Technology 508 (Jacqueline I. Kroschwitz, ex. ed. & Mary Howe-Grant ed., 4th ed. 1992).

²⁰ Peter Barton Hutt, *Government Regulation of Health Claims in Food Labeling and Advertising*, 41 Food Drug Cosm. L. J. 11, 69 (1986); R. Shapiro, Historical Development and Limitations of “Elemental” Diets, *in* Defined Formula Diets for Medical Purposes 1-5 (M.E. Shils, ed, 1977).

be dietary ingredients while synthetic vitamins, minerals, and amino acids may. This position is wholly irrational, in direct contravention of Congress's directive to FDA in enacting DSHEA.

Additionally, the industry-compiled lists of dietary ingredients that were marketed prior to DSHEA include a number of botanical constituents that had been marketed in synthetic form for many years. These include, for example, caffeine, citric acid, carboxymethyl cellulose and croscarmellose sodium. Congress was also well aware of these, and certainly did not mean to carve out of the definition of "dietary ingredient" those synthetic botanical constituents that were already being marketed widely in dietary supplement products. Congress plainly did not intend to exclude synthetic botanical constituents from being dietary ingredients under DSHEA.

III. Dietary Ingredients Are Defined By Their Biological Activity, Not By Their Source or Chemical Structure

FDA personnel have expressed the view that vitamins, by definition, may be synthetic while botanicals may not. Most notably, an article in the September 2012 issue of Consumer Reports cites Daniel Fabricant, director of FDA's Division of Dietary Supplement Programs, as follows:

"Vitamins can be synthetic because, by definition, a vitamin doesn't have to come from nature," says Fabricant at the FDA. They just have to perform the biological activity of vitamins, he added, whereas a "botanical" means that it was alive at some point. In other words, botanicals and their extracts must come from actual living plants, not a test tube.²¹

²¹ Consumer Reports, *supra* note 5, at 22.

CRN completely agrees with Dr. Fabricant that it is biological activity that defines a dietary ingredient, but his assertion that vitamins by definition do not have to come from nature while botanicals do is simply false.

A. Dictionary Definitions Refer to All Four Dietary Ingredient Categories as Natural

The plain English dictionary definitions of “vitamin,” “mineral,” “amino acid,” and “botanical,” which are the common definitions Congress was likely to have presumed when drafting DSHEA, refer to all four dietary ingredient categories as natural. The U.S. Supreme Court typically uses dictionary definitions that are contemporaneous with the statutory provisions being analyzed.²² Accordingly, an analysis of the relevant definitions of these four categories in the 1993 Merriam-Webster’s Collegiate Dictionary is instructive.

“Vitamin” is defined as “any of various organic substances that are essential in minute quantities to the nutrition of most animals and some plants, act esp. as coenzymes and precursors of coenzymes in the regulation of metabolic processes but do not provide energy or serve as building units, and are present in natural foodstuffs or sometimes produced within the body.”²³

“Mineral” is defined, in relevant part, as “a solid homogenous crystalline chemical element or compound that results from the inorganic processes of nature.”²⁴ “Botanical” is defined as “a plant part or extract used esp. in skin and hair care products.”²⁵ “Amino acid” is defined as “an

²² *E.g.*, *District of Columbia v. Heller*, 554 U.S. 570, 581 (2008) (analyzing dictionaries contemporaneous with the drafting of the Bill of Rights); *F.A.A. v. Cooper*, 132 S. Ct. 1441, 1449 (2012) (relying on the “latest edition of Black’s Law Dictionary available” when Congress enacted a law).

²³ Merriam-Webster’s Collegiate Dictionary 1321 ([10th ed. 1993]).

²⁴ *Id.* at 740.

²⁵ *Id.* at 134.

amphoteric organic acid containing the amino group NH₂; esp: any of the alpha-amino acids that are the chief components of proteins and are synthesized by living cells or are obtained as essential components of the diet.”²⁶

Thus, by dictionary definition, vitamins, minerals, amino acids, and botanicals all come from nature, but FDA clearly 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)(A),(B), and (D), or as concentrates, metabolites, constituents, or extracts of these dietary ingredients under FDCA Section 201(ff)(1)(F). Because there are no definitional grounds upon which to require botanicals and botanical constituents to be natural while the other types of dietary ingredients may be natural or synthetic, FDA must likewise accept synthetic botanical constituents as botanicals or botanical constituents under FDCA Section 201(ff)(1)(C) and (F).

B. Dietary Ingredient Categories are Characterized by Their Biological Activity, and Thus Synthetic Dietary Ingredients Need Only Be Biologically Equivalent to Their Natural Counterparts

The type of chemical identity required for an abbreviated new drug application for an active pharmaceutical ingredient has never been required by FDA for food ingredients. Synthetic vitamins, minerals, and amino acids are not chemically identical in all respects to their natural counterparts, and yet FDA has long accepted them as dietary ingredients. The relevant measure is biological equivalence, not chemical identity.

CRN wholly agrees with Dr. Fabricant’s statement in Consumer Reports that vitamins by definition “just have to perform the biological activity of vitamins” and that they need not be

²⁶ *Id.* at 37-38.

naturally derived to do so.²⁷ Indeed, this approach is supported by numerous definitions of “vitamin” in food science encyclopedias, which, like the dictionary definitions cited above, refer to vitamins as organic, in food, or otherwise coming from nature, but focus on the function of vitamins rather than their source.

For example, the 1993 Encyclopaedia of Food Science, Food Technology, and Nutrition states, “Vitamins are defined as a group of complex organic compounds present in small amounts in food that the body requires for its normal metabolism yet cannot be synthesized by the body. . . . Each vitamin consists of a mixed group of chemical compounds which may not be related to each other chemically and are therefore classified by function.”²⁸ The Encyclopedia of Food Science and Technology likewise defines vitamins as “specific organic compounds that participate as cofactors or coenzymes in the hundreds of thousands of mammalian biochemical reactions and which the human body cannot synthesize at all or in sufficient quantity for its metabolic needs.”²⁹ Thus, a wide variety of substances are defined as vitamins because they function in the body as vitamins. Similarly, as noted in the dictionary definition of “amino acid” cited above, these dietary ingredients are defined both by their chemical structure as well as by their biological activity as the building blocks from which proteins are constructed. Synthesized amino acids have long been accepted by FDA as dietary ingredients because they likewise function in the body as the building blocks for proteins.

²⁷ Consumer Reports, *supra* note 5.

²⁸ 7 Encyclopaedia of Food Science, Food Technology, and Nutrition 4816 (R. Macrae, et al. eds., 1993).

²⁹ 4 Encyclopedia of Food Science and Technology 2687 (Y.H. Hui, ed., 1992).

It therefore follows that synthesized versions of botanical constituents likewise fall within the statutory definitions of “botanical” and “botanical constituent” where they function in the body in the same way as the desired constituents in their naturally-derived counterparts. There are no grounds for treating synthetic botanical constituents differently in this regard if they function in a biologically equivalent manner to their natural counterparts, regardless of their molecular structure or the chirality of the compound. While entire botanicals are generally complex, the same is certainly true for vitamins, as recognized by the food science encyclopedia definitions quoted above, and is also true for minerals. It would be extremely difficult to synthesize entire vitamins and minerals in all their complexities and with all of their naturally-inherent impurities, and it would not be desirable from a nutritional perspective to do so. Rather, just the active principle of these substances is synthesized, and it is that synthetic material that FDA has long accepted as falling within the statutory categories of dietary ingredients.

With botanicals, the synthetic dietary ingredients of greatest interest to the dietary supplement industry are synthesized versions of the well-characterized and purified components of botanicals. The synthetic versions of components that have the same biological activity as the equivalent naturally-occurring components readily fall within FDCA Section 201(ff)(1)(F) as botanical constituents. And just as a synthesized version of the active principle of a naturally-occurring vitamin is regarded as a vitamin under FDCA Section 201(ff)(1)(A), the synthesized active principle of a botanical is likewise a botanical under FDCA Section 201(ff)(1)(C), or at least a constituent of a botanical under FDCA Section 201(ff)(1)(F). There are no scientifically justifiable grounds for treating synthetic botanical constituents differently where they are biologically equivalent to their naturally occurring counterparts.

Of course, if a constituent is not actually present in a botanical, or the synthesized version does not have the same biological activity as the naturally-occurring constituent, then FDA should not allow it to be marketed as a synthetic botanical constituent, and the agency has ample authority to preclude the marketing or take enforcement action against such products.

C. Chemically Equivalent Materials Must Be Treated Equally, Regardless of Their Source

Many botanical constituents are, in fact, chemically equivalent to their naturally-occurring counterparts. Certainly for these materials, there is no legal or scientific basis upon which to treat them differently from their natural equivalents. Indeed, FDA has viewed synthesized and naturally-derived chemically equivalent materials as the same when it sought to ban a substance. In the preamble to its final rule banning ephedrine alkaloids, FDA disagreed with comments that asserted that naturally-sourced ephedrine alkaloids were safer than synthetic versions of the same isomer. The agency stated:

We are not persuaded by any of the available evidence that ephedrine from botanical sources is materially different from ephedrine from pharmaceuticals with respect to chemistry, potency, or physiological and pharmacological effects. Chemically, any isomer with the same conformation from one source, including botanical sources, is identical to the same isomer from another source. For example, (-)-ephedrine from *Ephedra* (*Ephedra sinica* Stapf) is chemically indistinguishable from synthetic (-)-ephedrine manufactured by a pharmaceutical company.

...

We do not agree, therefore, that current evidence establishes that ephedrine alkaloids from botanical sources, including from botanical

extracts, are different from, or are any safer than, pharmaceutical ephedrine alkaloids.³⁰

Thus, FDA treated chemically indistinguishable synthetic and natural botanical constituents as equivalent when the agency sought to ban a dietary ingredient, but when it comes to allowing even demonstrably safe synthetic botanical constituents, such as vinpocetine, FDA treats such substances as irreconcilably different from their natural counterparts. This difference between the agency's approaches in these two scenarios appears to reflect FDA's longstanding bias against dietary supplements, as there are no legal or scientific grounds upon which the agency could legitimately make such a distinction.

IV. Synthetic Botanical Constituents Lawfully May Be Dietary Ingredients Under FDCA Section 201(ff)(1)(E)

In addition to being dietary ingredients under FDCA Sections 201(ff)(1)(C) and (F), synthetic botanical constituents intended for use to supplement the diet may be dietary ingredients under Section 201(ff)(1)(E). Contrary to FDA's assertions, this provision does not require that a substance have a history of common use in food or drink to be a dietary ingredient under that section.

A. DSHEA Legislative History and FDA Precedent Confirm That Historic Use in Food or Drink is Not Required

Congress expressly intended to allow a broad range of dietary ingredients to be available in dietary supplements, limited only by the requirements that such ingredients not be previously-authorized drugs, antibiotics, or biologics, or ingredients previously authorized for investigation as a new drug, antibiotic, or biologic for which substantial clinical investigations have

³⁰ 69 Fed. Reg. 6788, 6807 (February 11, 2004).

been instituted and made public.³¹ To facilitate this broad goal, Congress included among the list of dietary ingredients FDCA Section 201(ff)(1)(E), effectively sweeping into this category a virtually limitless variety of dietary ingredients, provided that they are intended to supplement the diet and meet other provisions of the statute.

FDA has taken the position, including in warning letters and in initially rejecting a new dietary ingredient (NDI) notification for conjugated linoleic acid (CLA), that synthetic botanical constituents may be dietary ingredients under Section 201(ff)(1)(E) only if they are “commonly used as a food or drink.”³² FDA argued in the letters surrounding the CLA NDI notification that the statutory language – “for use by man to supplement the diet by increasing the total dietary intake” – supported its “common use” requirement, asserting that “one cannot increase the total dietary intake of something that is not customarily part of the diet in the first place.”³³

FDA’s approach is flatly contradicted by the legislative history of FDCA Section 201(ff)(1)(E), which makes clear that Congress intended to include a range of dietary ingredients that had not been customarily part of the diet. The Senate Report accompanying DSHEA, for example, identified Coenzyme Q 10 (commonly synthesized), glucosamine, and primrose oil – none of which is commonly used in food or drink – as examples of substances expected to be included in

³¹ FDCA § 201(ff).

³² *E.g.*, Warning letter from Michael W. Roosevelt, Acting Director, Center for Food Safety and Applied Nutrition to USP Labs, LLC (April 24, 2012); Letter from Felicia B. Satchell, Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, Food and Drug Administration to Jason Crush (Aug. 29, 2002) (responding negatively to an NDI notification for synthetic CLA, arguing that the substance did not fit the definition of a dietary supplement under the FDCA) (hereinafter, “Satchell letter”).

³³ Satchell letter, *supra*.

the provision.³⁴ Notably, the language in this provision had shifted from “nutritional substance” in earlier draft bills to “dietary substance” in the enacted DSHEA so that a wider range of products would be covered.

FDA itself acknowledged that subparagraph (E) includes substances that were not commonly used as food or drink in the preamble to its regulation on requirements for nutrient content claims, health claims, and statements of nutritional support for dietary supplements.³⁵ In explaining why it had authority to extend its rules governing nutrient content claims under the Nutrition Labeling and Education Act of 1990 (NLEA) to a broad range of dietary ingredients in dietary supplements, the agency stated:

. . . the legislative history of “other nutritional substances” reveals that its coverage is broad and could, in appropriate circumstances, include dietary ingredients without RDI’s or DRV’s (136 Congressional Record S 16609 (October 24, 1990)). In a discussion between Senators Metzenbaum and Symms before the passage of the 1990 amendments, Senator Symms stated: * * * ‘What follows is a list of a few of the items and foods that I believe would fall under the “other similar nutritional substances” category established by this bill: Primrose oil, black currant seed oil, coldpressed flax seed oil, “Barleygreen” and similar nutritional powdered drink mixes, Coenzyme Q 10, enzymes such as bromelain and quercetin, amino acids, pollens, propolis, royal jelly, garlic, orotates, calcium-EAP (colamine phosphate), glandulars, hydrogen peroxide (H2O2), nutritional antioxidants such a superoxide dismutase (SOD), and herbal tinctures.’ Based on this colloquy, the agency interprets the list of dietary ingredients that fall under the definition of “dietary supplement” in section 201(ff) of the act as an explication of “other similar nutritional substances.”³⁶

³⁴ S. REP. NO. 103-410 (1994), at 8-9.

³⁵ 62 Fed. Reg. 49859 (Sept. 23, 1997).

³⁶ *Id.* at 49859-60.

This list includes numerous dietary ingredients that were not customarily part of the diet, such as hydrogen peroxide, in addition to those noted above. FDA's acceptance of this broad range of dietary ingredients is consistent with the fact that neither the language of DSHEA nor the legislative history reveals any Congressional intent to exclude from the definition of "dietary ingredient" those particular synthetic botanical constituents that had not previously been used to supplement the diet.

Rather, as is the case with most FDCA definitions of articles regulated by FDA, the intended use of a substance determines its regulatory category. "Dietary substance" means one that is intended to serve a dietary function in supplementing the diet, not one for which there is a history of dietary use. A substance that is intended for use to supplement the diet by increasing the total dietary intake (even if that increase is from zero intake) is therefore a "dietary substance" that may be a dietary ingredient under Section 201(ff)(1)(E) as long as it meets the other requirements of DSHEA.

B. Other Provisions of DSHEA Confirm No Common Use in Food or Drink Requirement under Section 201(ff)(1)(E)

The statutory provisions relating to new dietary ingredients make clear that synthetic botanical constituents need not have been commonly used in food and drink in order to be dietary ingredients within the meaning of section 201(ff)(1)(E).

Section 413 defines "new dietary ingredient" as a dietary ingredient not marketed in the United States before October 15, 1994, which does not include any dietary ingredient marketed in the United States before that date.³⁷ That section also requires that an NDI be the subject of a notification to FDA unless the dietary ingredients "have been present in the food supply as an article

³⁷ FDCA § 413(c).

used for food in a form in which the food has not been chemically altered.”³⁸ It is readily apparent from these provisions that when Congress treated chemically altered or synthesized materials differently from substances found in nature or wanted to impose a historical use requirement on dietary ingredients, it did so plainly.

These provisions stand in marked contrast to section 201(ff)(1)(E), which includes no such limitations on chemically altered or synthesized ingredients nor any requirement for historical use of a substance to supplement the diet. FDA’s attempt to impose such requirements run afoul of the fundamental canon of statutory interpretation, “*expressio unius est exclusio alterius*” (the inclusion of one is the exclusion of others). That is, in light of the special and specific provisions for non-natural dietary ingredients and for historical uses in section 413 of the FDCA, the absence of such provisions in Section 201(ff)(1)(E) makes clear that Congress intended to apply no such limitations on the dietary ingredients encompassed by subparagraph (E).

In sum, FDA’s current position of accepting botanical constituents from natural sources as dietary ingredients regardless of prior use but demanding a history of common use in food and drink for the equivalent substance produced synthetically finds no basis in the statutory language or the legislative history of DSHEA, nor does it make any sense from a safety or public health standpoint. Synthetic botanical constituents are to be regulated in the same way as their naturally occurring counterparts as long as they have the same biological activity.

V. Decades of FDA Precedent Make Clear that Synthetic Botanical Constituents Can Be Dietary Ingredients

³⁸ FDCA § 413(a)(1).

FDA has a long history of recognizing that synthetic ingredients can be equivalent to natural ingredients and should be treated no differently. Most significantly, FDA's nutrition labeling regulation states that a food would be deemed misbranded if its labeling states or implies "That a natural vitamin in a food is superior to an added or synthetic vitamin."³⁹ This prohibition dates back to the late 1960s, when the agency vigorously defended its position on this issue during two years of public hearings on special dietary food regulations.⁴⁰ These hearings took place between 1968 and 1970, after which FDA reiterated its conclusion that "There is no nutritional difference between a vitamin provided by a synthetic source and the same vitamin provided by a natural source...."

As recently as the late 1990s, FDA reaffirmed the validity of the prohibition against claims of superiority for natural forms of a vitamin, stating 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."⁴¹ Denying the validity of synthetic botanical constituents would suggest that FDA now views a material distinction between synthetic and natural versions of identical ingredients. This radical shift makes no sense in light of the agency's historical policy.

As CRN has previously emphasized in comments and other submissions to FDA, several concrete examples illustrate that the agency recognizes the equivalence of naturally extracted sources and synthetic sources of ingredients. Most significantly, FDA has acknowledged NDI

³⁹ 21 C.F.R. § 101.9(k)(4).

⁴⁰ 38 Fed. Reg. 2143, 2147, 2150 (January 19, 1973) (summarizing FDA's conclusions based on the hearings).

⁴¹ 62 Fed. Reg. 49826, 49841 (Sept. 23, 1997).

notifications for synthetic botanical ingredients without objection in the past.⁴² Notably, although FDA has placed at least two shipments of synthetic vinpocetine on hold at the port of entry, the agency had previously accepted at least five NDI notifications for vinpocetine.⁴³

FDA has taken a comparable approach to nutrients for use as food ingredients, finding the natural and synthetic forms to be equivalent. The agency has affirmed as generally recognized as safe (GRAS) both natural and synthetic riboflavin,⁴⁴ vitamin A,⁴⁵ and vitamin D.⁴⁶ FDA approved the food additive Vitamin D3 in both natural and synthetic forms.⁴⁷

FDA's approval or acceptance of synthetic forms of dietary ingredients is consistent with the agency's longstanding position that the method of a product's manufacture is not a material fact unless it renders a substantive change in the finished product itself. FDA articulated this position most clearly and vigorously in the domain of genetically engineered foods. Despite receiving many comments from stakeholders requesting that the agency impose mandatory disclosure requirements for foods or food ingredients that came from bioengineered sources, the agency stated that it was "not aware of any information showing that foods derived by these new

⁴² *E.g.*, Roche Vitamins, Inc./zeaxanthin (March 22, 2001) (stating that "Roche synthetic zeaxanthin is identical to natural zeaxanthin.") (FDA Report No. 96).

⁴³ FDA has classified the following five NDI notifications for vinpocetine as "filed without comment": Amrion, Inc. (July 8, 1997); Leiner Health Products (Oct. 20, 1998); Leiner Health Products (Mar. 24, 1999); General Nutrition Corporation (Apr. 16, 1999); and Pharmavite Corporation (May 12, 1999). CRN believes, but cannot confirm from the publicly-available portions of these notifications, that all relate to wholly synthesized vinpocetine.

⁴⁴ 21 C.F.R. § 184.1695(a).

⁴⁵ 21 C.F.R. § 184.1930(a).

⁴⁶ 21 C.F.R. § 184.1950.

⁴⁷ 21 C.F.R. § 172.380(a).

methods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding.”⁴⁸ Even in this controversial domain, FDA clearly found the manner of manufacture not to be “material” within the meaning of the FDCA, and therefore concluded that the agency lacked statutory authority to require any special labeling for genetically engineered foods.⁴⁹

The foregoing reveals that for decades, FDA has maintained that there is no basis for treating synthetically-derived ingredients differently from naturally-sourced versions of the same ingredient. FDA’s assertion that synthetic botanical constituents cannot be dietary ingredients simply because they are synthesized stands in conflict with this longstanding and well-grounded precedent. Similarly, FDA’s attempt to impose additional requirements on synthetic botanical constituents – namely, the agency’s assertion that these must have been “commonly used for food and drink” in order to qualify as dietary ingredients – is wholly at odds with its historic, firm position that the method of manufacture of an ingredient is no grounds for imposing additional regulatory hurdles for its use. The question is simply whether a synthetic botanical constituent has the same biological activity as its naturally-sourced counterpart. If so, then the synthetic version is not materially different from the natural constituent and must be regulated in the same manner,

⁴⁸ 57 Fed. Reg. 22984, 22991 (May 29, 1992). The agency reaffirmed this belief in developing its 2001 guidance on this same topic. See Draft Guidance for Industry: Voluntary Labeling Indicating Whether Foods Have or Have Not Been Developed Using Bioengineering (January 2001) (stating that “[t]he agency is still not aware of any data or other information that would form a basis for concluding that the fact that a food or its ingredients was produced using bioengineering is a material fact that must be disclosed under sections 403(a) and 201(n) of the act.”).

⁴⁹ FDA’s position has been upheld in court. See, e.g., *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166 (D.D.C. 2000) (rejecting a direct challenge to FDA’s 1992 Statement of Policy regarding the labeling of bioengineered foods); *Stauber v. Shalala*, 895 F. Supp. 1178 (W.D. Wis. 1995) (finding that FDA did not act arbitrarily and capriciously in not requiring the labeling of dairy products derived from cows treated with Bovine Somatotropin (BST)).

consistent with longstanding agency precedent. If a synthetic botanical constituent does not have the same biological activity as the natural version, then the substance likely would need to be the subject of an NDI notification, and thus, a demonstration of a reasonable expectation of safety. If governing safety criteria are satisfied, then FDA should accept such a notification and permit the substance as a dietary ingredient under FDCA Section 201(ff)(1)(E). In contrast, the apparent position of the agency that a synthetic botanical constituent cannot be a dietary ingredient – period – precludes any opportunity to demonstrate either equivalent biological activity or the safety of the ingredient; the ingredient is denied from being recognized as a “dietary ingredient” entirely.

VI. Public Health, Safety, and Environmental Considerations Counsel in Favor of Synthetic Botanical Constituents

There are no public health or safety grounds on which to bar synthetic botanical constituents from being dietary ingredients. On the contrary, manufacturers typically have more control over synthetic processes than over natural extraction processes, and this can yield tangible safety and quality benefits for consumers. Synthetic processing can eliminate potentially harmful variables such as pesticide contamination, the presence of foreign materials, and the uptake of minerals and toxins from the soil. Chemical synthesis also ensures greater consistency in output quality, as variations in climate or geographic region no longer pose concerns.

Discouraging the industry’s use of synthetic processing also may negatively affect the environment. For example, if a chemical component of a plant has beneficial health effects, but turns out to be virtually impossible to extract from its natural source on a commercial scale or such an extraction is environmentally detrimental, FDA’s position would prohibit the use of a synthetic version with the same biological activity. The result would be to deny consumers access to a safe

and beneficial ingredient or to force a manufacturer to produce it in an unsustainable or environmentally irresponsible manner. This simply is not what Congress intended.

VII. FDA's Definitional Bar Against Synthetic Botanical Constituents is Illogical Because it Has No Practical Effect on Such Substances that are GRAS

Finally, FDA's position that synthetic botanical constituents cannot be dietary ingredients by definition is illogical because such substances could come on the market lawfully through other means. Presuming such substances are GRAS, which they will be if their naturally-sourced counterparts are GRAS and they have the same biological activity, the synthetic botanical constituents could simply be used in products that would be labeled as conventional foods rather than as dietary supplements. Because dietary supplements are food under the FDCA for all relevant purposes,⁵⁰ such products may be marketed as food as long as all of the ingredients are either FDA-approved food additives or GRAS substances and the product satisfies all FDA requirements for food labeling. Thus, if FDA will not accept products containing synthetic botanical constituents as dietary supplements because the agency does not consider the synthetic botanical constituents to be dietary ingredients, those products could just be labeled as conventional food and be marketed immediately. Alternatively, synthetic botanical constituents could first be marketed in traditional conventional foods and subsequently in dietary supplements even in accordance with FDA's erroneous approach to synthetic botanical constituents described above. If such constituents are included in marketed conventional foods, then they would be "dietary substances" in accordance with FDA's narrow approach to FDCA Section 201(ff)(1)(E) and thus could subsequently be dietary ingredients in a dietary supplement.

⁵⁰ FDCA Section 201(ff) ("Except for purposes of section 201(g) and 417, a dietary supplement shall be deemed to be a food within the meaning of this Act.").

Thus, FDA's unfounded policy against synthetic botanical constituents does nothing to preclude such substances from ultimately coming to market in dietary supplements or other products, but merely creates undue hurdles and delay for such substances, and deters firms from using the 75-day premarket safety notification process that was specifically established for dietary ingredients. This is precisely the type of irrational regulatory approach that Congress intended to stop when enacting DSHEA. It has no practical effect, is not grounded in science, has no benefit to the public health. Rather, FDA's approach serves only to burden the industry with respect to products it apparently disfavors.

* * *

The foregoing discussion establishes that FDA's position that synthetic botanical constituents cannot be dietary ingredients is contrary to the language of and congressional intent behind DSHEA, violates decades of FDA precedent with respect to synthetic ingredients, is not grounded in science, and is not in the interest of the public health. Indeed, as Senators Hatch and Harkin – the principal authors of DSHEA – wrote to you in December of last year, the agency's assertion that synthetic botanical constituents can never be dietary ingredients is “wholly without statutory basis, and in fact contradicts longstanding FDA policy.”⁵¹ For these reasons, CRN asks FDA to reverse its position, to cease taking or threatening enforcement action against synthetic

⁵¹ Letter from Senators Tom Harkin and Orrin Hatch to Margaret Hamburg, M.D., December 22, 2011.

The Honorable Margaret Hamburg, MD

October 22, 2012

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botanical constituents, and to stop asserting in the trade and consumer press that such substances are not lawful dietary ingredients.

Sincerely yours,



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