July 15, 2019

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

Re: Docket No. FDA-2019-N-1388: “Responsible Innovation in Dietary Supplements; Public Meeting; Request for Comments.”

To Whom It May Concern:

Amarin Corporation plc is a pharmaceutical company focused on improving cardiovascular health. Amarin Pharma, Inc., on behalf of the Amarin group of companies (“Amarin”), respectfully submits these comments to the docket for the May 16, 2019 public meeting, titled “Responsible Innovation in Dietary Supplements.” Amarin applauds the efforts of the Food and Drug Administration (“FDA” or the “Agency”) to facilitate responsible innovation in the dietary supplement industry while at the same time fulfilling its oversight obligations under the federal Food, Drug, and Cosmetic Act (“FDCA” or the “Act”). Amarin has long advocated for increased oversight of dietary supplements. It is particularly concerned about dietary supplements that are deceptively marketed in a manner that distracts patients from seeking medical attention, and if appropriate, obtaining treatment with proven drug therapies that reduce the risk of cardiovascular disease, the number one killer in the United States.

Although the Dietary Supplement Health and Education Act of 1994 (“DSHEA”), which revised the FDCA, contains important *marketing* and *structural* distinctions between “drugs” and “dietary supplements,” FDA’s ability to police those distinctions has been out-paced by the ballooning dietary supplement industry. As FDA recently observed, when DSHEA was first enacted in 1994, the dietary supplement industry was a $4 billion industry, and there were only approximately 4,000 unique dietary supplements on the market.¹ Today, the dietary supplement industry is a $40 billion industry with “more than 50,000 – and possibly as many as 80,000 or even more – different products available to consumers.”²

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² *Id.*

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FDA does not have sufficient resources to oversee that volume of products. Currently, FDA has approximately 25 employees in the Office of Dietary Supplement Programs (“ODS”) to police the promotion of 50,000-80,000 products. By way of comparison, the Office of Prescription Drug Promotion (“OPDP”) in the Drug Center has approximately 70 employees who oversee the promotion of what is likely fewer than 1,500 branded prescription drugs. (See Figure 1).

Figure 1

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<table>
<thead>
<tr>
<th>Products on Market per Regulating Office¹</th>
<th>Workforce per Office²</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODS</td>
<td>OPDP</td>
</tr>
<tr>
<td>0, 20,000, 40,000, 60,000, 80,000, 100,000</td>
<td>0, 20, 40, 60, 80</td>
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ODS employees’ ability to police the market is also limited by the fact that they, unlike OPDP employees, may not know which manufacturers are selling which products because dietary supplement companies are not subject to listing requirements similar to those for drug companies (indeed, FDA does not even have sufficient information to accurately estimate the size of the supplement industry).

Because FDA lacks adequate tools and resources to police dietary supplements, volumes of unapproved “new drugs” have flooded the shelves of retail pharmacies and the internet, masquerading as “dietary supplements.” Too many of these products pose risks to the public health because they are unsafe or ineffective, and because they divert patients from getting the medical attention and proven therapies they need. These risks can be magnified by healthcare professionals who, like consumers, may also be confused about the role of drugs (i.e., prescription drugs and over-the-counter drugs) compared to dietary supplements.

The unlawful evasion of the “new drug” approval process also undermines incentives for legitimate drug manufacturers to invest in drug development. Purported dietary supplement companies that unlawfully bypass the “new drug” approval process are not only able to avoid the

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4 See FDA, OPDP Organizational Listing, https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm154886.htm
5 See Sean Williams, The FDA Has Never Approved a Drug like This in Its 111-Year History, The Motley Fool (June 25, 2017), https://www.fool.com/investing/2017/06/25/the-fda-has-never-approved-a-drug-like-this-in-its.aspx Although there are, of course, many more generic drugs, comparing the number of employees overseeing the promotion of branded prescription drugs to those overseeing the promotion of dietary supplements is apt because typically, generic drugs are not advertised or promoted.
costs and risks associated with drug development, they are also able to (1) undercut exclusivity that has been granted to innovator drugs and 505(b)(2) drugs, (2) avoid submitting 505(b)(2) applications and abbreviated new drug applications (“ANDAs”), and (3) evade the patent notification procedures established by the Hatch-Waxman provisions. Taking these unlawful shortcuts allows purported supplement companies to unfairly compete with legitimate drug manufacturers. Investing in drug development is risky enough, without the added risk that a drug company may not be able to recoup its investment in a successful product, due to unlawful competition. The lack of incentives for legitimate drug manufacturers to invest in drug development also takes a toll on the public health. If legitimate drug manufacturers do not invest in drug development, the actual therapeutic potential of a substance may never be realized and the safety profile of the product may never be known.

In order to fulfill its oversight obligations, FDA should take steps to interpret and enforce the definition of “dietary supplement” in the FDCA in a manner that is consistent with Congress’s intent and does not undermine the drug-approval provisions and the Hatch-Waxman provisions in the statute. Those provisions are fundamental to the operation of the Act, and Congress established them to protect the public health and to incentivize investment in drug development and innovation. FDA’s steps should include fairly enforcing the structural and marketing limitations imposed on dietary supplements by DSHEA. These limitations are discussed in detail below, but they include the limitation imposed by subsection 201(ff)(1)(E) of the Act. Significantly, in its Federal Register notice announcing the public meeting, FDA was particularly interested in comments regarding the appropriate scope of that provision.

Enforcing the structural and marketing limitations on dietary supplements will preserve the statutory distinctions between “drugs” and “dietary supplements.” Failing to preserve these distinctions would be inconsistent with the statute’s structure and design, expose the public to unsafe and/or ineffective products, and create disincentives for drug development and innovation, such that the therapeutic benefit of certain substances may never be realized. Significantly, given that up to 50% of FDA-approved drugs over the last 30 years have either directly or indirectly been derived from natural products,⁷ the public health impact of such a failure could be substantial.

The Agency is at a critical crossroad regarding the issues raised in this docket. If it fails to take action now to enforce the statute and protect consumers, in 30 years the drug and dietary supplement marketplaces could be almost indistinguishable in important respects. That would be a step backwards, not forward, in fostering innovation and protecting the public health. In addition to taking immediate steps to enforce the statute, FDA should seek additional resources from Congress that would enable it to effectively enforce the limitations that DSHEA imposed on dietary supplements, as well as listing authority, which would enable the Agency to quickly identify the manufacturers of unlawfully marketed products.

Amarin plans to engage in the Citizen Petition process within weeks, explaining that a product with synthetic eicosapentaenoic acid (“EPA”) – that is, chemically concentrated forms of EPA that are not found in natural substances – cannot be lawfully marketed as a dietary supplement. Such marketing would be inconsistent with the law (and FDA’s past actions enforcing the law). Synthetic omega-3 does not comply with the structural limitations on dietary supplements in DSHEA (i.e., synthetic omega-3 does not meet the definition of “dietary supplement” in the Act because (1) it does not qualify as a “dietary ingredient,” and (2) it is excluded from the definition of “dietary supplement” by the exclusionary clause). Notably, many of Amarin’s comments below are germane to these issues.

I. FDA Should Interpret And Enforce DSHEA In A Manner That Preserves The Statutory Distinctions Between “Drugs” And “Dietary Supplements”

Under DSHEA, Congress carved out products that meet the definition of “dietary supplement” from the definition of “drug” in the FDCA. Products that comply with the limitations that DSHEA imposes on “dietary supplements” are not subject to the “new drug” approval process and other drug authorities. These limitations include both marketing limitations (i.e., limitations on promotional claims) and structural limitations (i.e., limitations on what substances the products can contain).

With regard to marketing limitations, “dietary supplements” may not be marketed to affect disease without losing “dietary supplement” status and invoking “new drug” status – which subjects them to the “new drug” approval requirements and the Hatch-Waxman requirements in the Act, among other drug authorities. However, “dietary supplements” may be marketed to affect the structure/function of the body without losing their effective safe harbor from the “drug” definition.

With regard to structural limitations, a product will not qualify as a “dietary supplement” in the first place, unless (1) the product bears or contains a “dietary ingredient,” and (2) the “article” at issue is not excluded from the definition of “dietary supplement” by the “exclusionary clause” – a clause that excludes from the definition of “dietary supplement” articles that were first studied or approved as drugs. Significantly, products that do not meet the definition of “dietary supplement” for structural reasons – like all other articles – invoke “drug” status when they are marketed either to affect the structure or function of the body or to affect disease.

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8 Amarin’s engagement will be reactive, in response to a Citizen Petition asking FDA to make an exception to the statutory requirements for synthetic omega-3.
9 See infra, discussion at Section I(A)(1)(a).
10 See 21 U.S.C. § 321 (g), (ff).
11 See, e.g., 21 U.S.C. §§ 321(g), (ff), 355.
12 Id. §§ 321(g)(1)(B), 343(r)(6); 21 C.F.R. § 101.93(f), (g); 65 Fed. Reg. 1000 (Jan. 6, 2000).
13 21 U.S.C. §§ 321(g)(1)(B), (C), (ff)(1), 343(r)(6); 21 C.F.R. § 101.93(f).
As discussed below, FDA should take steps to fairly enforce the structural limitations and the marketing limitations on dietary supplements in DSHEA. Failure to do so would be inconsistent with the statute’s structure and design, pose significant risks to the public, and disincentivize drug development and innovation.

A. FDA Should Fairly Enforce The Structural Limitations On “Dietary Supplements” Imposed By DSHEA

To qualify as a “dietary supplement,” DSHEA dictates that a product must, among other things, (1) bear or contain a “dietary ingredient,” and (2) not be excluded from the definition of “dietary supplement” by the “exclusionary clause.” FDA should continue to interpret the definition of “dietary ingredient” in a manner that is fully consistent with the drug authorities in the statute, and it should interpret the “exclusionary clause” in the same manner. The Agency should also fairly and consistently enforce the law against companies that market purported dietary supplements that fail to meet the statutory definition.

1. FDA should enforce the provision in DSHEA requiring dietary supplements to bear or contain a “dietary ingredient”

Under subsection 201(ff)(1) of the FDCA, “dietary ingredients” include the following:

(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 total dietary intake; or

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

It is well-established and understood that “synthetic” substances derived from natural substances that qualify as “dietary ingredients” under subsections 201(ff)(1)(C), (E), and (F) of the FDCA, or synthetic copies of such natural substances – are not themselves “dietary ingredients” unless they are commonly, or customarily, used in the conventional food supply (in which case they would qualify as “dietary ingredients” under subsection (E)). Importantly, and as explained in more detail below, the term “synthetic” refers to ingredients that are synthesized in a laboratory from natural starting materials as well as unnatural starting materials – i.e., substances that
themselves do not occur in natural products. In other words, substances are “synthetic” if they are either wholly or partially synthesized in a laboratory.

The well-established requirement for synthetic substances, under subsections (C), (E), and (F), makes sense because it appropriately ensures that most synthetic versions of, and derivatives of, botanicals and other natural substances go through the drug approval process, which was established by Congress to protect the public health and to incentivize investment in drug development and innovation. It also prevents these types of products from evading other important drug provisions in the statute, such as the Hatch-Waxman provisions. Subjecting these synthetic substances to drug approval, and to regulation as drugs more generally, is important because companies often partially or wholly synthesize versions of, or derivatives of, natural products to increase potency or stability, or to otherwise affect the safety and/or efficacy profile of the substance. Indeed, up to 50% of FDA-approved drugs over the last 30 years have either directly or indirectly been derived from natural products.

The importance of the requirement for synthetic substances under these subsections is underscored by the recent safety concerns regarding vinpocetine. In 2016, FDA observed in a Federal Register notice that vinpocetine cannot be a “dietary ingredient” because it is “a synthetic compound, derived from vincamine, an alkaloid found in the Vinca Minor plant” (i.e., it undergoes transesterification and/or dehydration of vincamine in ethanol). Although FDA has not yet finalized its decision regarding vinpocetine, in June of this year, the Agency promised to do so soon – in conjunction with a statement warning women of childbearing age that vinpocetine may cause miscarriages or harm fetal development. It is critical that FDA remind stakeholders of the requirements in subsections (C), (E), and (F), through warning letters or other actions, so that dietary supplement companies are reminded – before marketing harmful synthetic substances as dietary supplements – that the products are subject to the “new drug” approval process. Doing so may prevent harmful substances like vinpocetine from being marketed in the first place.

Subsections I(A)(1)(a) and (b) below, summarize the statutory requirements regarding synthetic substances, and their ability to qualify as “dietary ingredients.” Subsection (c) explains that these requirements are imperative from a statutory and public health perspective and should be reinforced; subsection (d) urges FDA to clarify that, under the statute, the “back door” to “dietary ingredient” status – i.e., showing that a synthetic substance is commonly/customarily

15 See, e.g. Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry (Draft), August 2016 (NDI Guidance), at 37-41; see also 81 Fed. Reg. 61700, 61702 (Sept. 7, 2016); FDA Letter to Quincy Bioscience Manufacturing Inc., dated Oct. 16, 2012 (concluding that synthetic apoaequorin manufactured from “rapidly dividing host cells,” which are natural materials, is not a “dietary ingredient); FDA Letter to Syntech (SSPF) International, dated December 6, 2004 (finding that betaphrine, an ingredient chemically synthesized from substances that are themselves “dietary ingredients,” is not a “dietary ingredient”).


17 81 Fed. Reg. at 61702.

used in conventional food – cannot be used to evade the drug authorities in the statute; and subsection (e) calls on FDA to remind stakeholders that a “new dietary ingredient” (“NDI”) notification cannot turn a substance into a “dietary ingredient” if the substance does not meet the definition of “dietary ingredient” in the first place.

a. FDA has long excluded certain “synthetic” substances from the definition of “dietary ingredient” in accordance with the statute

Synthetic vitamins, minerals, and amino acids are not excluded from the definition of “dietary ingredient.” But, synthetic substances derived from substances that qualify as “dietary ingredients” under subsections 201(ff)(1)(C), (E), and (F) of the FDCA, or synthetic copies of such natural substances – are typically excluded.

The latter requirement is based on the plain language of subsections (C), (E), and (F) of DSHEA’s definition of “dietary ingredient.” As FDA has recognized, subsection (C) of the definition incorporates only “herb[s]” and “botanical[s]” – not synthetic copies of herbs or botanicals that have been wholly or partially made in a laboratory, because those synthetic substances themselves have never been part of an herb or botanical. As mentioned, as recently as September 2016, FDA applied that requirement to vinpocetine. Indeed, this requirement is well recognized by the trade press in the supplement industry.

FDA also has determined that a synthetic constituent or extract, etc. of an herb or botanical is not a “dietary ingredient” under subsection (F) because it was never part of, or an extract of, the actual herb or botanical. In 2001, FDA observed that even though “some forms of synthetic ephedrine alkaloids may be chemically indistinguishable from, botanical ephedrine alkaloids; . . . a substance that has never been physically part of a whole cannot be a constituent or extract of that whole.” In other words, substances that are synthesized in a laboratory are synthetic – even if they are chemically identical to the natural substance. Notably, in 2014, FDA also applied that principle to synthetic fish oil fatty acids – i.e., synthetic omega-7 – recognizing that it does not qualify as a “dietary ingredient” under the statute.

19 See NDI Guidance, at 37-40.
20 See id. See also 81 Fed. Reg. at 61702 (noting that vinpocetine, an alkaloid found in the Vinca minor plant, is not a “dietary ingredient” because it undergoes transesterification and/or dehydration of vincamine in ethanol); FDA Letter to AIBMR Life Sciences, Inc., dated March 19, 2014 (finding that synthetic fish oil fatty acid esters were “not constituents of a dietary substance for use by man under Section 201(ff)(1)(F)”).
21 Nagel Letter.
22 81 Fed. Reg. at 61702.
23 See, e.g., Hank Schultz, “Do synthetic ingredients have a place in the ‘natural’ products industry,” NUTRAnutrients-usa.com, March 22, 2019 (“At the moment, FDA is of the opinion that a synthetic copy of a botanical ingredient is not a legal dietary ingredient, because it does not meet the definition laid down in DSHEA”).
24 See NDI Guidance at 36; see also Nagel Letter.
25 Nagel Letter.
26 FDA Letter to AIBMR Life Sciences, Inc., dated March 19, 2014. In that letter, FDA specifically found that synthetic omega-7 fatty acid ethyl esters derived from fish oil “do not fit within the statutory definition of ‘dietary ingredient’ because they are not
FDA has appropriately recognized that a synthetic substance may qualify as a “dietary ingredient” under subsection (E) – only in limited circumstances, namely if it is commonly, or customarily, used in conventional food. In interpreting subsection (E), FDA has referred to commonly accepted dictionary definitions, noting that the term “dietary” means “of or relating to the diet” and that the term “diet” means “an organism’s usual food and drink.” Then, reading that definition in conjunction with the statutory phrase – “for use by man” – FDA has recognized that Congress intended the term “dietary substance” to mean “a substance commonly used as human food or drink.” As FDA has explained, the last phrase in subsection (E), “to supplement the diet by increasing the total dietary intake,” is further evidence that Congress intended the term “dietary substance” to refer to “foods and food components that humans eat as part of their usual diet” because “one cannot increase the total dietary intake of something that is not customarily part of the diet in the first place.”

Examples of synthetic ingredients that are common, or customarily, in the conventional food supply are vanillin and cinnamic acid. In contrast, synthetic substances that are not commonly, or customarily, used in the conventional food supply are not “dietary substances” that fall within the scope of subsection (E) of the FDCA. Indeed, FDA has issued warning letters and rejected “new dietary ingredient” notifications, in part, on this ground – i.e., when the use of a synthetic substance in the conventional food supply has not been common/customary.

Significantly, FDA’s understanding of how Congress intended synthetic substances to be treated under subsections (C), (E), and (F) has been consistent over the last 18 years and has never been changed by Congress. When purported “dietary supplements” have contained a synthetic substance that is not commonly, or customarily, used in conventional foods, FDA has: (1) brought enforcement actions, (2) denied citizen petitions, (3) advised other federal constituents for use by man under section 201(ff)(1)(F).” Id. In other words, it is unlawful to market synthetic omega-7 as a “dietary supplement” because synthetic omega-7 is not a “dietary ingredient.” Given FDA’s conclusion regarding synthetic omega-7 fatty acid ethyl esters, it is surprising that synthetic omega-3 fatty acid ethyl esters derived from fish oil have proliferated in dietary supplements, and that synthetic omega-3 fatty acids in the re-esterified form have proliferated as well. There is no principled reason to distinguish between synthetic omega-3 fatty acids and synthetic omega-7 fatty acids. Both should be presumed not to be “dietary ingredients.” As discussed herein, that presumption can only be overcome if the sponsors of the supplements can show common/customary use of synthetic omega-3 fatty acids in the conventional food supply.

27 See NDI Guidance, at 38-39; see also Nagel Letter (“one cannot increase the total dietary intake of something that is not customarily part of the diet in the first place”) (emphasis added).

28 See NDI Guidance, at 38-39; see also Nagel Letter.

29 See NDI Guidance, at 38-39; see also Nagel Letter.

30 Nagel Letter (“one cannot increase the total dietary intake of something that is not customarily part of the diet in the first place”) (emphasis added); see also NDI Guidance at 38-39.

31 See NDI Guidance at 38-39.

32 See, e.g., FDA Letter to Threshold Enterprises Ltd., dated Feb. 14, 2003 (finding that a synthetic analog of coenzyme Q10 does not fall within subsection 201(ff)(1)(E) because it “is not food, nor is it used for food”); FDA Letter to Christopher & Weisberg, P.A., dated Aug. 29, 2002 (“Humans do not commonly use chemically manufactured or synthetic CLA as food or drink”); see also FDA Warning Letter to ATS Labs, LLC, dated February 3, 2016 (“To the best of FDA’s knowledge, synthetically produced DMBA is not commonly used as food or drink”).

33 See, e.g., 69 Fed. Reg. 6787, 6793 (Feb. 11, 2004) (citing United States v. 1009 Cases * * * No. 2:01CV-820C (D. Utah filed October 22, 2001)).

34 See, e.g., Letter from FDA to Ullman, Shapiro, & Ullman LLP, Docket No. FDA-2009-P-0298, dated Feb. 23, 2011 (citizen petition response stating that synthetic homotaurine may not be marketed as a “dietary supplement” because it is not a “dietary ingredient”).

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agencies on this basis,\textsuperscript{35} (4) announced in the Federal Register that certain substances cannot be sold as “dietary supplements,”\textsuperscript{36} (5) issued warning letters,\textsuperscript{37} and (6) rejected NDI notifications.\textsuperscript{38}

\textbf{b. The term “synthetic” refers to substances that themselves do not occur in natural products}

As mentioned, the term “synthetic” refers to ingredients that are synthesized in a laboratory from natural starting materials as well as unnatural starting materials – i.e., substances that themselves do not occur in natural products.\textsuperscript{39} In other words, substances are “synthetic” if they are either wholly or partially synthesized in a laboratory. This makes sense because neither wholly, nor partially, synthesized substances were ever physically part of a natural substance.

That commonsense definition of “synthetic” is also consistent with the dictionary definition of that term – “of, relating to, or produced by chemical or biochemical synthesis, especially: produced artificially.”\textsuperscript{40} And, the term “synthesis” is defined as (a) “the composition or combination of parts or elements so as to form a whole,” and (b) “the production of a substance by the union of chemical elements, groups, or simpler compounds or by the degradation of a complex compound.”\textsuperscript{41}

A synthetic substance may be created, for example, by altering the chemical structure of a substance that is a “dietary ingredient” under subsection (C), (E), or (F). Notably, that synthetic substance may or may not also be a “dietary ingredient.” As FDA has explained:

Altering the chemical structure of a dietary ingredient (e.g., creation of new stereoisomers, addition of new chemical groups as in esterification) creates a new substance that is different from the original dietary ingredient. The new dietary ingredient is not

\textsuperscript{35} See, e.g., Nagel Letter.
\textsuperscript{36} 69 Fed. Reg. at 6793 (acknowledging that synthetic ephedrine hydrochloride “and other synthetic sources of ephedrine cannot be dietary ingredients because they are not constituents or extracts of a botanical, nor do they qualify as any other type of dietary ingredient”).
\textsuperscript{37} See, e.g., FDA Warning Letter to ATS Labs, LLC, dated February 3, 2016 (finding that 1,3-dimethylbutylamine (“DMBA”) is not a “dietary ingredient” because it is synthetic and to the best of FDA’s knowledge it is not used in conventional foods); FDA Warning Letter to DBM Nutrition, dated Nov. 30, 2015 (finding that picamilon, “a unique chemical entity synthesized from the dietary ingredients niacin and aminobutyric acid” does not fall within any of the “dietary ingredients” categories in the statute, and therefore, is not a “dietary ingredient”); FDA Warning Letter to Quincy Bioscience Manufacturing Inc., dated Oct. 16, 2012 (finding that synthetic apoaerugin is not a “dietary ingredient”); FDA Warning Letter to Supplementstogo.com LLC, dated March 8, 2006 (finding that methasterone, a synthetic steroid, is not a “dietary ingredient”);
\textsuperscript{38} See, e.g., FDA Letter to Syntech (SSPF) International, dated December 6, 2004 (finding that betaphrine, a chemically synthesized substance is not a “dietary ingredient”).
\textsuperscript{39} See, e.g., NDI Guidance, at 37-41; see also 81 Fed. Reg. at 61702; FDA Letter to Quincy Bioscience Manufacturing Inc., dated Oct. 16, 2012 (concluding that synthetic apoaerugin manufactured from “rapidly dividing host cells,” which are natural materials, is not a “dietary ingredient”); FDA Letter to Syntech (SSPF) International, dated December 6, 2004 (finding that betaphrine, an ingredient chemically synthesized from substances that are themselves “dietary ingredients,” is not a “dietary ingredient.”).
\textsuperscript{40} Merriam-Webster (“synthetic”), https://www.merriam-webster.com/dictionary/synthetic
\textsuperscript{41} Merriam-Webster (“synthesis”), https://www.merriam-webster.com/dictionary/synthesis
considered to be a dietary ingredient merely because it has been altered from a substance that is a dietary ingredient, and therefore, is in some way related to the dietary ingredient. In some cases, however, the new substance may independently qualify for one of the dietary ingredient categories listed in section 201(ff)(1) of the [FDCA].

\[42\]

\[c.\] The synthetic/natural distinction in subsections 201(ff)(1)(C), (E), and (F) of the FDCA is consistent with other sections of the statute

The synthetic/natural distinction in subsections 201(ff)(1)(C), (E), and (F) of the Act drives more synthetic versions of, and derivatives of, botanicals and other natural substances toward the drug approval process, which was established by Congress to protect the public health and to incentivize investment in drug development and innovation. The synthetic/natural distinction also ensures that these types of products cannot evade other important drug provisions in the statute, such as the Hatch-Waxman provisions.

Without the synthetic/natural structural distinction, manufacturers could market the following types of products, among others, to affect the structure/function of the body without the safety and effectiveness data required for FDA drug approval (indeed, even with the structural distinction in place, this is already happening):

- **Failed/discontinued synthetic investigational drugs derived from natural products.** If the synthetic/natural distinction were not in place, sponsors of failed or discontinued synthetic investigational drugs that are derived from natural products could try to market their products as “dietary supplements.” In 2009, one company tried to do just that. That company manufactured synthetic homotaurine derived from seaweed, and it petitioned FDA to issue a regulation overriding the operation of the “exclusionary clause,” so that it could market synthetic homotaurine as a dietary supplement. The company had been conducting a phase III study under an investigational new drug application (“IND”) but decided to discontinue developing the product as a drug to pursue marketing the product as a dietary supplement. FDA rejected the Citizen Petition because it determined that synthetic homotaurine was not a “dietary ingredient” under subsection 201(ff)(1) – including subsections (E) and (F) – and therefore, could not be marketed as a “dietary supplement” regardless of whether FDA issued a regulation overriding the operation of the “exclusionary clause.”\[43\] If the synthetic/natural distinction were not in place, FDA would likely receive a flood of similar requests to override the exclusionary clause, so that failed products – products that have not been, or cannot be, shown to be safe and effective – can be marketed as “dietary supplements.”

- **Synthetic copies and synthetic analogs of FDA-approved drugs.** Even with the existing synthetic/natural distinction, there are already a number of products unlawfully marketed as dietary supplements, that are actually copies of synthetic FDA-approved drugs that are.

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\[42\] NDI Guidance, at 41.

derived from natural substances. This is not surprising given the size of the dietary supplement market, the limited resources that FDA has to police it, and FDA’s ability to exercise enforcement discretion. For example:

- **Dietary Supplement Copies of Razadyne and Razadyne ER** – Amarin believes that synthetic copies of Razadyne and Razadyne ER, and their generics, are being unlawfully marketed as dietary supplements. Razadyne, which contains galantamine hydrobromide, is a drug that was first FDA-approved in 2001 for mild to moderate dementia of the Alzheimer’s type, in dosages of 4 mg, 8 mg, and 12 mg. FDA later approved an extended release version of the product, Razadyne ER, in dosages of 8 mg, 16 mg, and 24 – in 2005.

Internet research suggests that galantamine hydrobromide does *not* occur in natural products. Rather, it is either wholly or partially synthesized in laboratories. When it is partially synthesized in a laboratory, the galantamine free base is extracted from Narcissus or several other genera of the Amaryllidaceae family and then combined with the hydrobromide salt.\(^ \text{"44} \) Assuming that is correct, galantamine hydrobromide is a synthetic. It is therefore not a “dietary ingredient” and should not be marketed as a “dietary supplement” (unless it is commonly/customarily used in the conventional food supply, which does not appear to be the case). Yet, galantamine hydrobromide is sold in multiple dietary supplements in similar dosage strengths to FDA-approved drugs – to preserve and support memory function and increase and induce lucid dreaming.\(^ \text{"45} \) Many of the products are marketed without warnings and precautions equivalent to the FDA-approved drugs (e.g., warnings/precautions regarding serious skin reactions, gastrointestinal bleeding, and potential fetal harm).

These supplements appear to be unlawful synthetic copies of branded and generic drugs that have evaded the “new drug” approval process. In other words, supplement companies are putting synthetic drugs into dietary supplements. Given the number of these supplements on the market, it is likely that thousands, of patients have been exposed to these products. And, some patients may be using these products instead of seeking appropriate medical attention and drugs that are proven to work. Moreover, these products *may* have been marketed before the patents and exclusivity for the branded galantamine hydrobromide products expired, such that they *may* have beaten generic versions of the drug to market. There is also potential, of course, for supplement manufacturers to unlawfully market different synthetic chemical forms of galantamine (e.g., galanthamine methiodide or galanthaminium, 7-methyl-, hydroxide) – drug products that would ordinarily require ANDAs or even 505(b)(2) applications – as dietary supplements, without being detected.

Without the synthetic/natural distinction, the number of copies and synthetic analogs – of synthetic FDA-approved drugs derived from natural products – that are unlawfully


\(^ \text{45} \) Specific citations are not included so as not to single out specific companies or products.

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Amarin Pharma, Inc.
marketed as “dietary supplements” would inevitably increase, and likely substantially so. And if FDA fails to robustly and fairly police the synthetic/natural distinction, that failure may inadvertently send a message to the drug industry as a whole that the Agency is unwilling to comply with Congress’s decision to value investment in drug development and innovation.

- **Dietary Supplement Copies of, and Analogs to, Omega-3 Drugs** – Amarin believes that synthetic copies and slightly altered versions of FDA-approved prescription omega-3 drugs are being unlawfully marketed as dietary supplements. Amarin’s FDA-approved prescription drug, Vascepa, is synthetically derived from common fish oil, and its active ingredient – icosapent ethyl – is highly purified and highly concentrated EPA in the ethyl ester chemical form. Although it is only a small company, Amarin invested more than $500 million in the development of Vascepa and undertook significant risk to successfully complete a landmark cardiovascular outcomes trial (known as “REDUCE-IT”) that has been hailed as the most significant development in the treatment of cardiovascular disease since statin therapy.

Notably, Amarin completed the REDUCE-IT trial with strong encouragement and support from FDA. In a 2014 letter to Amarin, John Jenkins, M.D., then FDA’s Director, Office of New Drugs, Center for Drug Evaluation and Research, stated that the completed REDUCE-IT study “data would be of significant public health value.” He went on to state, “I strongly urge Amarin to complete the trial and I know [FDA’s clinical data review division for cardiovascular-focused drugs], is ready and willing to work with Amarin to address any issues that may arise as you work to that end.”

Vascepa is the only FDA-approved prescription drug that contains – as its active ingredient – purified, stable, and highly concentrated EPA in the ethyl ester form. There are branded and generic FDA-approved drugs that contain highly concentrated omega-3 mixtures (e.g., EPA and docosahexaenoic acid (“DHA”)) in the ethyl ester chemical form, as well. Since the launch of these FDA-approved omega-3 drugs, dietary supplement manufacturers have increasingly mislabeled and promoted concentrated synthetic EPA – in either the ethyl ester form or in the re-esterified form – as a dietary supplement.

FDA-approved labeling for all omega-3 drugs has warnings/disclosures related to increases in liver enzymes in people with poor liver function and prolonged bleeding times, particularly when used in conjunction with drugs affecting coagulation. In addition, the FDA-approved labeling for the prescription omega-3 drugs containing DHA

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46 FDA Letter to Amarin Pharma, dated September 11, 2014.
47. Id.
48 See Jennifer Grebow, Ultra-High Concentrates and the Next Omega-3, Supply Side West Report, Nutritional Outlook, Oct. 14, 2015, (“Omega-3 suppliers . . . are now taking omega-3 concentrates for dietary supplements into near-pharmaceutical territory . . . .”); see also Hank Schultz, EPA-only nutraceuticals ride pharma’s coattails into marketplace, NUTRA Ingredients-usa.com, Oct. 21, 2013.
49 See, e.g., Vascepa Full Prescribing Information, https://www.vascepa.com/assets/pdf/Vascepa_PI.pdf

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has warnings/disclosures related to increased bad cholesterol (LDL-C) and more frequent recurrences of symptomatic atrial fibrillation.\(^{50}\)

It is not possible to produce natural fish oil with a collective concentration of EPA and DHA that is greater than approximately 30% by weight of the oil. Oils with a concentration of EPA and DHA that is greater than approximately 30% must be chemically synthesized in a laboratory. Synthetic oils with higher concentrations of EPA and/or DHA that are available today (and are unlawfully marketed as dietary supplements) are commonly in either the ethyl ester form or the re-esterified triglyceride form.

The first step in the process of synthesizing common fish oil to yield higher concentrations of omega-3 (EPA and DHA) involves a chemical reaction wherein the glycerol backbone of each triglyceride molecule in the fish oil is removed, resulting in “free fatty acids” and a “free glycerol” molecule. The free fatty acid forms of EPA and DHA are then chemically reacted with ethanol through a process known as esterification. Esterification changes the free fatty acids into ethyl ester form.

The resulting ethyl ester form allows manufacturers to substantially heighten the level of EPA or DHA or to alter the naturally occurring ratio of EPA to DHA (which is typically 18:12, respectively), using molecular distillation or supercritical fluid technology. These synthetically produced ethyl ester fatty acids can also be further chemically converted to the re-esterified triglyceride form using enzymes in a chemical process called glycerolysis. Food-grade enzymes separate the ethanol molecule from the fatty acid, creating a free fatty acid and a free ethanol molecule. When glycerol is reintroduced to the solution, the enzymes then re-esterify the fatty acids back onto a glycerol backbone, creating re-esterified triglyceride oil.

Omega-3 mixtures in ethyl ester or re-esterified triglyceride form (as well as purified EPA or DHA in ethyl ester or re-esterified triglyceride form) are different from common fish oil in a number of ways: (1) the levels of EPA and DHA are often much higher, (2) the ratios between EPA and DHA may be dramatically different than 18:12, and (3) the molecules are distinct from their natural triglyceride forms. These differences can affect the safety and/or the efficacy of the product (e.g., heightened levels of EPA and/or DHA can lead to greater efficacy, but heightened levels of DHA also have been associated with certain unwanted effects, such as significant increases in bad cholesterol, particularly in diseased patients with severely high levels of triglycerides in the blood).

Yet, a quick search of the internet reveals that concentrated synthetic omega-3 products – in both the ethyl ester and re-esterified form – are sold in multiple dietary supplements. Not surprisingly, many of the products are marketed without warnings and precautions equivalent to the FDA-approved drugs.

\(^{50}\) See, e.g., Lovaza Prescribing Information, https://www.gsksource.com/pharma/content/gsk/source/us/en/brands/lovaza.html

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The supplements containing concentrated synthetic EPA and/or omega-3 in the ethyl ester form are unlawful synthetic copies or slightly altered versions of branded and generic drugs, and they have evaded the “new drug” approval process. In other words, here again, supplement companies are putting synthetic drugs in dietary supplements. Given the number of these supplements on the market, it is likely that thousands of patients have been exposed to these products. And some patients may be using these products instead of seeking appropriate medical attention and/or using drugs that are proven to work. In some cases, these products were marketed before the patents and exclusivity on the branded drugs expired, such that the dietary supplement versions of the branded drugs were marketed before it was legal to market generics.

The same concerns apply to supplements containing concentrated synthetic EPA and/or omega-3 in the re-esterified form. These purported supplements are synthetic analogs of the FDA-approved omega-3 drugs that have unlawfully evaded the “new drug” approval process. These products, like the ethyl ester versions, in many cases were marketed before the patents and exclusivity on the branded omega-3 drugs expired, such that the dietary supplements versions of the branded drugs were marketed before it was legal to market generics.

If companies wish to market these types of products, they can do so lawfully, by studying the drugs in adequate and well-controlled clinical trials and submitting the data to FDA through the “new drug” approval process. If FDA fails to enforce the statutory requirements by not robustly and fairly policing the synthetic/natural distinction, it is effectively enabling unlawful unapproved “new drugs” to masquerade as dietary supplements. That failure to enforce would disincentivize drug innovation and expose the public to untested products, putting them at risk.

- The exclusionary clause in the definition of “dietary supplement,” alone, cannot protect incentives to develop innovative drugs – The relative impotence of the exclusionary clause to protect drug development incentives in this context (i.e., in the absence of the synthetic/natural distinction) is illustrated by the following example. Currently, there are numerous chemical forms of lithium marketed as dietary supplements – including lithium sulfate monohydrate, lithium orotate, and lithium aspartate – despite the fact that lithium carbonate and lithium citrate have been approved as drugs. Under the law, as reflected in the NDI Guidance, synthetic minerals, like synthetic lithium, are “dietary ingredients”51 – so there is no synthetic/natural “dietary ingredient” distinction for lithium products (as discussed, synthetic vitamins, minerals, and amino acids are treated differently than other synthetic substances). Thus, any lithium salt may be marketed as a dietary supplement, so long as it is not excluded from the definition of “dietary supplement” by the exclusionary clause (unless the product otherwise violates the FDCA).

To evaluate whether each lithium salt – lithium sulfate monohydrate, lithium orotate, and lithium aspartate – is excluded from the definition of “dietary supplement” by the exclusionary clause, FDA would have to evaluate whether each salt was studied or

51 NDI Guidance, at 38.
approved as a drug before it was marketed in a food or a dietary supplement. It is likely that those types of historical records, for each salt, may be hard to come by. In the alternative, FDA could evaluate whether the lithium moiety was not legally marketed as a food or a dietary supplement before its various salts were studied or approved as a drug. If the latter approach were taken, FDA might well find that all lithium salts are excluded from the definition of “dietary supplement” by the exclusionary clause, but that approach may be even more resource-intensive than the former approach.

Regardless, exclusionary clause analysis is very fact specific, and it may be so resource-intensive that using it for enforcement purposes would be cost-prohibitive. The synthetic/natural distinction for these types of substances establishes an imperfect, but brighter line, making it more useful and cost-effective than the exclusionary clause to deter unlawful supplement marketing and for enforcement purposes.

Moreover, the exclusionary clause – unlike the synthetic/natural distinction – in some circumstances, cannot operate to prevent synthetic analogs of FDA-approved drugs from being marketed as dietary supplements. Without the synthetic/natural distinction in subsections 201(ff)(1)(C), (E), and (F) – unless FDA engaged in the latter type of analysis under the exclusionary clause and determined that all chemical forms of a naturally derived moiety (e.g., galantamine) were excluded from the definition of “dietary supplement” – companies could argue that it is lawful to market synthetic analogs of an FDA-approved drug containing that moiety (e.g., galantamine hydrobromide), like galanthamine methiodide, as dietary supplements.

- **Synthetic substances derived from natural products (more generally).** Scientists have hypothesized that flavonoids in the common banana may have antimicrobial or other therapeutic properties, and that certain components of mushrooms may potentially be active in fighting cancer. If the synthetic/natural distinction for certain “dietary ingredients” is not reinforced and well-policed, a company could synthetically isolate potentially active components in a banana or mushroom, significantly increase the dosage strength, and market the isolate as a dietary supplement to support “immune health” – without an understanding of whether the product is safe or efficacious. Although such products are required to be safe, and although “immune health” claims have to be substantiated by “competent and reliable scientific evidence,” – without premarket approval requirements there would be nothing to stop the sponsor of the product from “fool[ing] the public” until FDA (or the Federal Trade Commission) “finally catches up.” Synthetic vinpocetine is a case in point.

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52 See generally, FDA Response to Biostratum, Inc. Citizen Petition, Docket No. FDA-2005-P-0259, Jan. 12, 2009 (“Biostratum Petition Response”) (finding that an “article” can be both an active ingredient and an active moiety).
53 See id.
Moreover, even when FDA does catch up, post-market tools can be ineffective, as exemplified by FDA’s actions regarding 1,3-dimethylamylamine (“DMAA”), a synthetic amphetamine, that is often marketed in purported supplements. Despite the fact that FDA has caught up to a number of manufacturers marketing the dangerous product and sent warning letters, marketing of the purported supplements persists.57

Further, and importantly, marketing these types of products – synthetic isolates of natural substances – as dietary supplements could deter drug development of the isolates. As a result, their actual therapeutic potential may never be realized.

d. FDA should take steps to clarify that the “back door” to “dietary ingredient” status cannot be gamed by supplement companies seeking to evade drug regulation

The synthetic/natural distinction in subsections 201(ff)(1)(C), (E), and (F) of the FDCA is fundamental to the operation of the statute. Therefore, FDA should also take steps to enforce the statutory requirements and clarify that the so-called “back door” to “dietary ingredient” status in subsection 201(ff)(1)(E) – which requires a showing that the synthetic substance at issue is common/customary in the conventional food supply – cannot be gamed by supplement companies seeking to evade drug regulation. For example, FDA should take action clarifying that GRAS status, alone, cannot be enough to confer “back door” “dietary ingredient” status. GRAS status allows companies to legally market a substance in conventional food, but it does not show that a substance is commonly/customarily used in conventional food. Moreover, companies can technically market new substances in food on the basis of self-GRAS determinations – which do not require FDA notification or any Agency review of the underlying safety data. FDA should also take action to clarify that, at a minimum, the terms “commonly” and “customarily” require evidence that the substance has a substantial history of, and a substantial frequency of, consumption of a substance. Any other definition would undermine Congress’s intent and undermine the drug approval and Hatch-Waxman provisions.

e. FDA should clarify that an NDI notification cannot be used to turn a substance into a “dietary ingredient” if it does not meet the definition of “dietary ingredient” in the first place

Based on the statutory language in the FDCA, determining whether a substance that is intended to be used in a dietary supplement requires an NDI notification requires a three-part analysis: (1) is the substance at issue a “dietary ingredient,” and if so, (2) is it a “new dietary ingredient,” and if so, (3) does it meet the statutory exception to the NDI notification requirement.58 Unfortunately, many skip over the first step in the analysis – they assume that all substances are “dietary ingredients,” such that they focus exclusively on whether manufacturers of the substance must submit an NDI notification. But that focus is flawed. If a substance is not a “dietary ingredient” in the first place, it cannot be marketed as a dietary supplement, 21 U.S.C.

§ 321(ff)(1), and the questions of whether it is a “new dietary ingredient” or whether it requires an NDI notification are obviated.59

Yet, some have argued that the mere submission of an NDI notification (and FDA’s failure to reject that notification) shows that a substance is a “dietary ingredient.” But that is not true. A substance cannot be a “new dietary ingredient” unless it is a “dietary ingredient” in the first place, and an NDI notification to which FDA does not respond with a specific objection does not change that fact. FDA has recognized this in the guidance: “Because ‘new dietary ingredient’ is defined to mean a dietary ingredient that was not marketed in the U.S. before October 15, 1994, a substance cannot be a new dietary ingredient unless it is also a dietary ingredient.”60

FDA has also recognized this in practice. As mentioned, on September 7, 2016, FDA observed in a Federal Register notice that vinpocetine (1) does not meet the definition of a dietary ingredient, and (2) is excluded from the definition of a “dietary supplement” by the exclusionary clause in the definition of “dietary supplement.”61 In the Federal Register notice, FDA acknowledged that it had received five NDI notifications for vinpocetine, the first of which was received in 1997, and that FDA did not object to any of them.62 In a later interview, the Agency explained that when it issued the Federal Register notice, it had subsequent information that led it to believe “this is not an ingredient [that FDA] should acknowledge regardless of what happened in the 1990s.”63 Accordingly, it is clear that the submission of an NDI notification, and FDA’s lack of objection, does not turn a substance into a “dietary ingredient” if it does not meet that definition in the first place.

The broader purpose of this clarification is to remind stakeholders that, under the statute, not all substances qualify as “dietary ingredients.” It is incumbent upon FDA to reinforce its position on this point to avoid future situations like vinpocetine.

2. FDA should enforce the “exclusionary clause” in a manner that incentivizes investment in drug development and innovation, consistent with the FDCA

Section 201(ff)(3)(B) of the FDCA provides that the term “dietary supplement” does not include:

(i) an article that is approved as a new drug under section 505 . . .

or (ii) an article authorized for investigation as a new drug . . . for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public,

59 NDI Guidance, at 14.
60 Id. (emphasis added).
62 See id.
63 Paul Fassa, Why Does the FDA Want To Ban This Supplement that has Been Around for Decades?, Health Impact News, http://healthimpactnews.com/2017/why-does-the-fda-want-to-ban-this-supplement-that-has-been-around-for-decades/
which was not before such approval . . . or authorization marketed as a dietary supplement or as a food.64

FDA has referred generally to the whole of subsection 201(ff)(3)(B) as the “prior market clause,”65 but the Tenth Circuit has more accurately recognized that the text has two clauses.66 The Tenth Circuit refers to the provision in subsection 201(ff)(3)(B) that excludes from the definition of “dietary supplement” any “article” that is (1) approved as a new drug or (2) clinically studied as a new drug (where substantial clinical investigations have been instituted) – as the “exclusionary clause.” It refers to the savings clause – which saves a prior marketed “article” from exclusion – as the “prior market clause.”67

Subsection 201(ff)(3)(B) establishes:

a system for determining whether articles will be deemed dietary supplements or drugs, and regulated accordingly, depending on how such articles were marketed and categorized when they first entered the marketplace. Stated simply, the statute prohibits the marketing as dietary supplements of articles that have gained recognition in the marketplace as new drugs by either being approved or studied as new drugs. [This provision] reflects Congress’s determination that to allow such an article to be marketed as a dietary supplement would not be fair to the pharmaceutical company that brought, or intends to bring, the drug to market, and would serve as a disincentive to the often significant investment needed to gain FDA approval of new drugs. The statute does, however, permit continued marketing of an article that was marketed as a food or a dietary supplement even if that article is subsequently shown to have a therapeutic benefit and is studied or approved as a new drug. In such a case, the dietary supplement was on the market first and should not be penalized simply because some drug manufacturer chooses to seek approval for the product as a new drug.68

Subsection 201(ff)(3)(B) is an important part of the statute. As the Tenth Circuit and FDA have observed, permitting “manufacturers to market dietary supplements with components identical to the active ingredients in prescription drugs” would undermine the FDCA’s incentive structures for drug development,69 and it would “serve as a disincentive to the often significant investment needed to gain FDA approval of new drugs.”70 Indeed, protecting drug innovation is such a

65 See BioStratum Petition Response, at 3.
66 See generally, Pharmanex v. Shalala, 221 F.3d 1151 (10th Cir. 2000) (“Pharmanex II”).
67 Id. at 1159.
69 See Pharmanex II, 211 F.3d at 1159.
70 See FDA Administrative Determination on Cholestin, dated May 20, 1998, at 4-5.

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critical underpinning of the FDCA that Congress later enacted a separate clause – in section 301(ll) of the FDCA\textsuperscript{71} – to prohibit substances that have gained recognition in the marketplace by being studied as, or approved as drugs, from being incorporated into “food,” unless those substances were first marketed in a “food.” Because that clause applies to dietary supplements as well as conventional food, substances first studied or approved as drugs cannot be marketed as “dietary supplements” or indeed as any product other than a drug.\textsuperscript{72}

Given the clear congressional intent to protect innovation by including an exclusionary clause in DSHEA, the provision should be applied in a manner consistent with Congress’ intent to protect the drug approval process. Toward that end, FDA should (1) emphasize that an article is not saved from the exclusionary clause by the \textit{prior illegal marketing} of a food or a dietary supplement, (2) clarify that an “article” is not saved from the exclusionary clause by the prior marketing of a different “article” as a food or a dietary supplement, and (3) clarify that the exclusionary clause is triggered when an article is \textit{first legally studied in a substantial clinical investigation that has been made public}, even if the investigation was not the subject of an IND (at least in the context of clinical investigations that commenced before 1987, when the modern IND regulations were promulgated).\textsuperscript{73}

\begin{itemize}
  \item \textit{FDA should reinforce that, under the statute, an “article” is not saved from the exclusionary clause by the prior illegal marketing of a food or a dietary supplement}
\end{itemize}

FDA should reinforce that, under the statute, an “article” is not saved from the exclusionary clause by the prior illegal marketing of that “article” as a food or dietary supplement. In other words, the savings clause – the prior market clause – should not be triggered by the marketing of an “article” illegally. This is an obvious point. Illegal articles that were “marketed as” food or dietary supplements before they were studied or approved as a drug – such as unapproved food additives, components of illegal street drugs (e.g., marijuana), unapproved “new drugs,” or substances that were deceptively labeled – should not be permitted to be marketed as “dietary supplements” after they are studied or approved as drugs. Such a policy would circumvent the statute, reward illegal behavior, and undercut other policy objectives.

FDA has already recognized as much. For example, in 2013, FDA sent a warning letter to a company for marketing anatabine as a “dietary supplement.” In that letter, FDA stated:

\begin{quote}
According to your product labeling, your Anatabloc product contains anatabine. Anatabine became authorized for investigation as a new drug under an investigational new drug application (IND) that went into effect on June 8, 2012. According to press releases [on your website] . . . you began marketing CigRx, containing
\end{quote}

\textsuperscript{71} 21 U.S.C. § 331(ll).

\textsuperscript{72} See FDA Letter to Formulife, Inc. June 17, 2013 (finding that the introduction into interstate commerce of dietary supplements containing dimethylamine (“DMAA”) was prohibited by Section 301(ll) because DMAA was approved as a drug in 1948 and there was no evidence that it was prior marketed as a food or dietary supplement); see also FDA Letter to Pure Energy Products, dated Sept. 6, 2013.

\textsuperscript{73} 52 Fed. Reg. 8831 (March 19, 1987).
anatabine, on August 5, 2010, followed by Anatabloc, also containing anatabine, on August 11, 2011. Although these products were labeled and promoted as dietary supplements, they were not legally marketed as dietary supplements before the authorization of the IND because the products were adulterated due to the presence of anatabine, a new dietary ingredient that fails to meet the requirements of the Act . . . [i.e., no NDI notification was submitted].

b. **FDA should clarify that an “article” is not saved from the exclusionary clause by the prior marketing of a different “article” as a food or a dietary supplement**

FDA should clarify that an “article” is not saved from the exclusionary clause by the prior marketing of a different “article” as a food or a dietary supplement, even if the articles are somehow related. This is another obvious point, but one that is subject to confusion. To explain why, it is worth reviewing the language in section 201(ff)(3)(B), which excludes an “article” from the definition of “dietary supplement” as follows:

(i) an article that is approved as a new drug under section 505 . . . or (ii) an article authorized for investigation as a new drug . . . for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public,

which was not before such approval . . . or authorization marketed as a dietary supplement or as a food.

The prior market clause – “which was not before such approval . . . or authorization marketed as a dietary supplement or as a food” – clearly refers to the “article” at issue in the exclusionary clause. Thus, as a matter of statutory construction, the “article” used for the purposes of the exclusionary clause has to be the same article used for the purposes of the prior market clause. In other words, the prior market clause cannot be triggered by the marketing of a substance that is different from the substance at issue in the exclusionary clause.

This is so straightforward, it is reminiscent of children’s’ Mad Libs books – if the law (or the Mad Libs) requires the use of the same “article” (or noun) in two clauses or sentences, then the same “article” (or noun) must be used in both clauses or sentences. A few illustrative hypotheticals and a real world example follow:

- **Hypothetical 1** – The “article” for the purposes of the exclusionary clause is peanut butter, and it was approved as a drug in 2016 to treat cancer. Peanut butter was “marketed as” a conventional food prior to 2016. The prior marketing of peanut butter as a conventional food saves peanut butter from being excluded from the definition of

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"dietary supplement" by the exclusionary clause. Thus, moving forward, peanut butter can be marketed both as a drug and a dietary supplement. Notably, the article used for the purposes of the exclusionary clause is the same as the article used for the purposes of the prior market clause, in this hypothetical. The prior marketing of an article can only save the same article from exclusion from the definition of “dietary supplement.”

- **Hypothetical 2** – The “article” for the purposes of the exclusionary clause is peanut butter, and it was approved as a drug in 2016 to treat cancer. Peanut butter was not “marketed as” a conventional food or dietary supplement prior to 2016, but jelly was. The prior marketing of jelly does not save peanut butter from exclusion from the definition of “dietary supplement” – despite the conceptual relationship between peanut butter and jelly. The prior market clause is not triggered by the marketing of a different article. Under this hypothetical, peanut butter cannot be marketed as a “dietary supplement,” but jelly certainly can.

- **Hypothetical 3** – The “article” for the purposes of the exclusionary clause is a synthetic peanut protein (“SPP”). SPP was synthesized by first extracting a naturally occurring peanut protein (“PP”) from a peanut, and then chemically altering that PP to stabilize the molecule, to increase its potency, and to make it safer for people with peanut allergies. The synthetic SPP and the naturally occurring PP are different molecules (although they have some chemical similarities), and SPP was never part of an actual peanut. SPP was approved as a drug in 2016 to treat cancer. SPP was not “marketed as” a food or dietary supplement prior to 2016, but PP was “marketed as” a food. Because they are different articles, the prior marketing of PP would not save SPP from being excluded from the definition of “dietary supplement” by the exclusionary clause – even though SPP and PP have some chemical similarities. The prior market clause is not triggered by the marketing of a different substance (or article). Under this hypothetical, SPP cannot be marketed as a “dietary supplement,” but PP certainly can.

- **Real World Example** – The “article” for the purposes of the exclusionary clause is aspirin (acetylsalicylic acid), which was approved as a drug by FDA in 1965. Aspirin was initially synthesized from botanicals, such as willow bark, containing salicin. Aspirin was not “marketed as” a food or dietary supplement, prior to 1965 – at least FDA is not aware of any such evidence and has issued Warning Letters stating that aspirin cannot be used in dietary supplements due to the operation of section 201(ff)(3)(B).

But salicin may have been prior “marketed as” a food or dietary supplement (e.g., in willow bark tea marketed as a conventional food). Assuming that salicin was “marketed as” a conventional food prior to aspirin being approved as a drug, aspirin would not be saved from exclusion from the definition of “dietary supplement” by the exclusionary clause because aspirin and salicin are different substances (or articles), despite chemical

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76 See FDA Letter to Bayer HealthCare L.L.C., dated Oct. 27, 2008 (“the presence of aspirin in Bayer Heart Advantage excludes this product from the definition of “dietary supplement” [under the “exclusionary clause”] because a new drug application for aspirin was approved . . . before any marketing of aspirin as a dietary supplement for a food”).

77 See id.
similarities. The prior market clause is not triggered by the marketing of a different substance (or article). Under this example, aspirin cannot be marketed as a “dietary supplement,” but willow bark extract certainly can.

To be clear, though, every drug approved or studied can yield a number of potential articles for the purposes of section 201(ff)(3)(B), because an “article” can be a finished drug product, an active ingredient, and/or another active drug component. For example, in 2009, in response to a citizen petition filed by the Biostratum, Inc., FDA concluded that both the active ingredient (pyridoxamine dihydrochloride) and the active moiety (pyridoxamine) in a drug were “articles” studied as a drug for the purpose of section 201(ff)(3)(B). FDA’s determination that both were appropriate articles was grounded in the fact that the active ingredient (pyridoxamine dihydrochloride) was the subject of the IND, and the fact that “the substance that [was] actually being studied for its physiological or pharmacological action [was] pyridoxamine.”

Importantly, this does not unduly complicate the analysis under section 201(ff)(3)(B). It just means that there may be occasions for multiple, yet separate, section 201(ff)(3)(B) analyses. In other words, each article may be analyzed under section 201(ff)(3)(B) separately. Hypothetically, one could analyze pyridoxamine dihydrochloride under section 201(ff)(3)(B) – using pyridoxamine dihydrochloride as the “article” for the purposes of both the exclusionary clause and the prior market clause – and find that pyridoxamine dihydrochloride is excluded by the exclusionary clause because it was not prior “marketed as” a food or a dietary supplement. But then one could analyze pyridoxamine under section 201(ff)(3)(B) – using pyridoxamine for the purposes of both the exclusionary clause and the prior market clause – and find that it is saved from exclusion by the prior market clause because pyridoxamine was prior “marketed as” a food or a dietary supplement. In that instance, moving forward, pyridoxamine dihydrochloride could not be marketed as a “dietary supplement” but other chemical forms of pyridoxamine could (assuming they also otherwise meet the definition of “dietary ingredient”).

Of course, because the “article” has to be the same for the purposes of both the exclusionary clause and the prior market clause, one cannot argue that the prior marketing of pyridoxamine as a food or dietary supplement prevents pyridoxamine hydrochloride from being excluded from the definition of “dietary supplement” by the exclusionary clause. Remember, the prior market clause is not triggered by the marketing of an “article” that is different from the “article” at issue in the exclusionary clause. If pyridoxamine dihydrochloride is the “article” for the purposes of the exclusionary clause because it was studied as a drug, it cannot be saved from exclusion from the definition of “dietary supplement” by the prior marketing of a different “article” – pyridoxamine – even though the articles have chemical similarities.

Hypotheticals aside, in the actual case of pyridoxamine, FDA found no evidence that pyridoxamine was “marketed as a dietary supplement or as a food” before it was studied as a drug, and thus, FDA concluded that “a product containing pyridoxamine is not a dietary

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78 See Pharmanex II, 211 F.3d at 1151 (finding that an article can be either a finished drug product or an active component of a drug product); FDA Administrative Determination on Cholestin, dated May 20, 1998 (same); see also Biostratum Petition Response”) (finding that an “article” can be both an active ingredient and an active moiety).
79 See Biostratum Petition Response, at 5.
80 Id. at 5-6.
supplement as defined in 21 U.S.C. 321(ff) and may not be marketed as such.”\(^{81}\) In other words, no chemical form of pyridoxamine can be marketed as a “dietary supplement.”

In any event, FDA should clarify that, under the statute, an “article” (e.g., an active ingredient in a drug) is not saved from the exclusionary clause by the prior marketing of a different “article” as a food or dietary supplement (e.g., a substance with the same moiety as an active ingredient of a drug, in a different chemical form). Any conclusion to the contrary would belie the plain language in subsection 201(ff)(3)(B), which requires the “article” used in the exclusionary clause to be the same as the article in the “prior market clause.” Moreover, any such conclusion would undermine drug company incentives to derive drugs (e.g., aspirin) from natural products (e.g., willow bark) – to standardize formulations and to develop formulations that optimize safety and efficacy. Indeed, such a conclusion could have an enormous impact, given that up to 50% of drugs approved overall in the last 30 years were derived from natural products,\(^{82}\) and given that we expect the same to be true over the next 30 years, if appropriate incentives exist.

c. **FDA should clarify that the exclusionary clause is triggered when an article is first legally studied in a substantial clinical investigation that has been instituted in accordance with the law and made public – even if the investigation is not subject to an IND**

The exclusionary clause is triggered when the “article” at issue has been “authorized for investigation as a new drug . . . for which substantial clinical investigations have been instituted . . . [and made public].”\(^{83}\) Although an IND certainly triggers the exclusionary clause when the related study has been made public – the exclusionary clause may be triggered in the absence of an IND as well. For the reasons explained below, the phrase “article authorized for investigation as a new drug” does not require affirmative permission from FDA to conduct a clinical investigation; nor does it require an IND.

First, it would not make sense, under the law, to interpret the phrase “Authorized for investigation as a new drug” to require affirmative permission from FDA. If affirmative permission were required, then some INDs would trigger the exclusionary clause and others would not because section 505(i) of the FDCA allows an IND to go into effect without affirmative approval.\(^{84}\) Thus, it makes more sense to interpret “Authorized for investigation as a new drug” to simply mean *instituted in compliance with the law*. That interpretation, at a minimum, would capture all INDs.

Second, it would not make sense, under the law, to interpret the phrase “Authorized for investigation as a new drug” to require an IND, given the history of the IND process and the purpose of the exclusionary clause. “Although FDA had authority under the 1938 [version of the FDCA] to establish rules governing the use of investigational drugs, FDA did not employ this

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\(^{81}\) Id.


\(^{84}\) Id. § 355(i)(2) (providing that typically a “clinical investigation of a new drug may begin 30 days after [FDA] has received” a submission regarding the drug and the clinical investigation); 21 C.F.R. § 312.40(b)(1).
authority until 1961.”85 Moreover, the IND process was not established in its modern form until FDA issued final regulations on March 19, 1987.86

It cannot be that Congress, in enacting DSHEA in 1994, intended the “authorized for investigation as a new drug” portion of the exclusionary clause to be triggered only by clinical investigations that started after March 19, 1987, or even after 1961. As mentioned above, the exclusionary clause “seeks to establish a system for determining whether articles will be deemed dietary supplements or drugs, and regulated accordingly, depending on how such articles were marketed and categorized when they first entered the marketplace.”87 This system would not work, if the term “authorized for investigation as a new drug” only enabled look-backs to 1987 or even 1961.

Finally, interpreting the full phrase “authorized for investigation as a new drug . . . for which substantial clinical investigations have been instituted . . . [and made public]” – to be triggered regardless of whether the clinical investigations at issue are subject to INDs – would ensure that the standard for triggering the exclusionary clause is the same as the standard for triggering a similar clause in section 301(ll) of the FDCA.88 The clause in section 301(ll) prohibits the marketing of any dietary supplement that contains an “article” studied in a substantial clinical investigation that has been made public, unless the “article” was prior marketed in a food or dietary supplement. If the standards in the DSHEA exclusionary clause and the similar clause in section 301(ll) were different, it would lead to absurd results. Notably, the absurdity canon of statutory construction dictates that, if a statute is ambiguous, courts and other arbiters must not adopt an interpretation that leads to absurd results.89

For example, assume that “Article X” was the subject of a substantial clinical investigation that was made public in the late 1950s, but that the investigation was not subject to an IND (because FDA was not requiring INDs at the time). If the exclusionary clause is not triggered unless “Article X” was the subject of an IND, but the clause in section 301(ll) is triggered without an IND – then the exclusionary clause in DSHEA would permit the marketing of “Article X” as a dietary supplement, at the same time the clause in section 301(ll) prohibits it.

85 Suzanne White Junod, Ph. D, FDA and Clinical Drug Trials: A Short History, FDA, (“The reference to investigational drugs under section 355(i) of the 1938 Act was brief. ‘The Secretary shall promulgate regulations for exempting from the operation of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety of drugs.’ Food, Drug, and Cosmetic Act, 52 Stat. 1040 (75th Cong. 3d Sess (1938))”), https://www.fda.gov/downloads/AboutFDA/History/ProductRegulation/UCM593494.pdf
87 FDA Administrative Determination on Cholestin, dated May 20, 1998, at 4-5.
89 See, e.g., Sorrells v. United States, 287 U.S. 435, 450 (1932) (“To construe statements so as to avoid absurd or glaringly unjust results, foreign to the legislative purpose, is . . . a traditional and appropriate function of the courts.”); United States v. Kirby, 74 U.S. 482, 486 - 87 (1868) (“It will always therefore be presumed that the legislature intended exceptions to its language, which would avoid [injustice, oppression, or absurd consequences]”).
B. FDA Should Better Police the Marketing Limitations Imposed on Dietary Supplements by DSHEA and Seek Additional Resources from Congress to Do So

As previously discussed, there are certain statutory marketing limitations imposed on dietary supplements. Supplements may \textit{not} be marketed to affect disease without losing “dietary supplement” status and invoking “new drug” status – which subjects them to the “new drug” approval process.\footnote{21 U.S.C. §§ 321(g)(1)(B), 343(r)(6); 21 C.F.R. § 101.93(f), (g); 65 Fed. Reg. at 1000.} However, supplements may be marketed to affect the structure/function of the body without losing their effective safe harbor from the “drug” definition.\footnote{21 U.S.C. §§ 321(g)(1)(B), (C), (ff)(1), 343(r)(6); 21 C.F.R. § 101.93(f).}

FDA can only police marketing violations, post-market. It is the manufacturer – not FDA – that elects prior to market, whether the product is a “drug” and therefore, a “new drug” subject to the approval process, or a dietary supplement.\footnote{See 21 C.F.R. § 101.93; 65 Fed. Reg. at 1000.} That election turns on whether a product meets the definition of “dietary supplement” (i.e., whether the product conforms to the structural limitations in the Act), and on whether the manufacturer intends to market the product with disease claims or structure/function claims.\footnote{See 21 C.F.R. § 101.93.} If the manufacturer makes the wrong decision, FDA can only police that decision after the fact.

Unfortunately, there are a number of purported supplements being marketed with blatant disease claims\footnote{Disease claims include claims to treat damage to an organ, or a structure in the body that does not function well. See \textit{id.} § 101.93(g)(1).} that FDA apparently has not had the tools or resources to police. For example, the internet advertisement below, which contains a number of disease claims, appears in association with an omega-3 product being marketed as a dietary supplement.

\begin{itemize}
  \item Omega-3s keep brain cells alive (\textit{neuro-protection})\footnote{21 U.S.C. §§ 321(g)(1)(B), (C), (ff)(1), 343(r)(6); 21 C.F.R. § 101.93(f).}
  \item Omega-3s reduce \textit{swelling in the brain}\footnote{21 U.S.C. §§ 321(g)(1)(B), (C), (ff)(1), 343(r)(6).}
\end{itemize}

\begin{quote}
When the rescuers found him in the rubble, he had brain, heart, liver and kidney failure. He was barely clinging to life. After he was transported to West Virginia School of Medicine, \textit{the hospital neurosurgeons tube-feed him very large doses of fish oil. Randy has since made a remarkable recovery.}
\end{quote}
In addition, another omega-3 dietary supplement is marketed with a testimonial suggesting that the product treats autism, gastrointestinal issues, eczema, and depression, among other diseases:

“My sons and I have been taking [the omega-3 dietary supplement] for just over three months now . . . . My youngest is diagnosed with PDDNOS (Autistic Spectrum Disorder) as well as gastrointestinal issues. His reflux has lessened and he is recovering quickly from bouts of anger. My eldest son’s eczema is clearing. I am diagnosed with Hashimoto’s Thyroid Disease, Type II Diabetes, and a ‘bout or two’ with depression. I need to say that I feel the best I have in a LONG time.”

Further, a number of dietary supplement companies use the term “pharmaceutical grade” or “pharmaceutical quality” – in a clear attempt to confuse and mislead consumers into believing that dietary supplement is a drug or can be used instead of drugs. Examples follow:

As these examples demonstrate, FDA simply does not have adequate tools and resources to police the 50,000-80,000 different types of dietary supplements on the market. As a result, there are likely thousands of unapproved “new drugs” on the market that are masquerading as “dietary supplements.” FDA should seek additional authorities from Congress to help it better police the industry. For example, product listing requirements – which would at a minimum allow FDA to quickly identify the brand manufacturer of particular products, as well as the location of the facilities where the specific products are actually manufactured – would help. In addition, the Agency should seek the additional resources necessary to adequately police the industry.
II. Conclusion

As explained above, Amarin has long advocated for increased oversight of dietary supplements. Although the FDCA contains marketing and structural distinctions between “drugs” and “dietary supplements,” FDA’s ability to enforce those distinctions has long been out-paced by the ballooning dietary supplement industry – which is now estimated to encompass 50,000-80,000 different products.95 FDA does not have sufficient resources to oversee that volume of products.

As a result, there are an enormous number of unapproved “new drugs” on the market that are masquerading as “dietary supplements.” These products have unlawfully bypassed FDA’s drug approval process and other drug provisions in the FDCA, including the Hatch-Waxman provisions. As such, they pose significant risks to the public health and threaten to undermine incentives for legitimate pharmaceutical manufacturers to invest in drug development.

FDA needs additional resources to prevent supplement companies from skirting the law. Until that time, the Agency should use the tools and resources it has to strengthen the oversight of dietary supplements. Toward that end, it is essential that FDA interpret and enforce DSHEA in a manner that preserves the distinctions between “drugs” and “dietary supplements” and that does not undermine the drug authorities in the FDCA. If FDA fails to do so, DSHEA, which was intended to provide a narrow exception to drug regulation, may effectively swallow the rule. As mentioned, up to 50% of FDA-approved drugs over the last 30 years have either directly or indirectly been derived from natural products.96 Moving forward, if such products continue to evade the drug provisions in the FDCA, the ability of those provisions to protect the public health and incentivize drug innovation will be eviscerated.

Specifically, FDA should:

- Reinforce the requirement that subsections 201(ff)(1)(C), (E) and (F) exclude synthetic substances related to natural products from the definition of “dietary ingredient,” unless those substances have been commonly/customarily, and lawfully used in conventional food, and fairly police products marketed as “dietary supplements” accordingly. If FDA fails to do so, or fails to otherwise remind stakeholders of this statutory requirement, supplement companies will market the following types of products as “dietary supplements” rather than drugs – in even greater magnitude than they do today: (1) failed/discontinued synthetic investigational drugs derived from natural products, (2) synthetic copies and synthetic analogs of FDA-approved drugs derived from natural products, and (3) synthetic substances derived from natural products (more generally). All of these products may be ineffective and prevent consumers from getting the therapies they need, or they, like vinpocetine, may pose safety risks to consumers. Moreover, these products are likely to unfairly compete with FDA-approved drugs, and stymie drug development and innovation.

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• Confirm that, under the statute, the “back door” to “dietary ingredient” status in subsection 201(ff)(1)(E) – which requires a showing that the synthetic substance at issue is common/ customary in the conventional food supply – cannot be gamed by supplement companies seeking to evade drug regulation. For example, FDA should take action clarifying that GRAS status, alone, cannot be enough to confer “back door” “dietary ingredient” status. GRAS status allows companies to legally market a substance in conventional food, but it does not show that a substance is “commonly,” or “customarily,” used in conventional food. Moreover, companies can technically market new substances in food on the basis of self-GRAS determinations – which do not require FDA notification or any Agency review of the underlying safety data. FDA should also take action to clarify that, at a minimum, the terms “commonly” and “customarily” require evidence that the substance has a substantial history of, and a substantial frequency of, consumption of a substance. Any other definition would undermine the drug approval and Hatch-Waxman provisions.

• Reinforce that, under the statute, an NDI notification cannot be used to turn a substance into a “dietary ingredient” if it does not meet the definition of “dietary ingredient” in the first place. The broader purpose of this reinforcement is to remind stakeholders that not all substances are “dietary ingredients.” If this were top of mind, vinpocetine, for example, may never have been marketed as a “dietary supplement,” and the public would have been better protected. Moreover, supplement companies would not be tempted to use NDI notification as a defense to, or a justification for, illegally marketing a substance that is not a “dietary ingredient” as a “dietary supplement.”

• Reinforce that, under the statute, an “article” is not saved from being excluded from the definition of “dietary supplement” by the exclusionary clause – by the prior illegal marketing of the “article” as a food or a dietary supplement. For example, marketing an “article” as a purported supplement – with disease claims, which actually render the product an illegal unapproved “new drug” – before the “article” is studied or approved as a drug should not save the “article” from being excluded from the definition of “dietary supplement” by the exclusionary clause. This makes sense as a matter of law and public policy. Any other interpretation would effectively reward past illegal behavior and be inconsistent with the statute.

• Confirm that, under the statute, an “article” is not saved from being excluded from the definition of “dietary supplement” by the exclusionary clause – by the prior marketing of a different “article” as a food or dietary supplement. As explained above, this makes sense as a matter of statutory construction and public policy. Any other interpretation – i.e., an interpretation that would allow aspirin to be saved from the exclusionary clause by the prior marketing of willow bark tea (which has some chemical similarities to aspirin) – would be inconsistent with the law and would disincentivize the development of naturally occurring substances into drugs.
• Confirm that the exclusionary clause in DSHEA is triggered when an article is first legally studied in a substantial clinical investigation that has been made public – even if the clinical investigation was not the subject of an IND (at least in the context of clinical investigations that commenced before 1987, when the modern IND regulations were promulgated). This is consistent with the statute, and it makes sense given the operation and history of the IND provisions and the purpose and history of the exclusionary clause in DSHEA. If the provision in the exclusionary clause, regarding clinical investigations, was triggered only by clinical investigations subject to an IND, then clinical investigations conducted prior to the promulgation of the modern IND regulations in 1987, or prior to FDA’s exercise of its IND authority in 1961, may not count. This would undermine the objective of the exclusionary clause, which rewards the first industry – either the drug or the dietary supplement industry – to discover the therapeutic benefits of an “article.” This also ensures that the standard for triggering the exclusionary clause is consistent with the standard for triggering the clause in section 301(ll) of the FDCA, which prohibits the marketing of any dietary supplement that contains an “article” studied in a substantial clinical investigation that has been made public, unless the “article” was prior marketed in a food or dietary supplement. If the standards were different, it would lead to absurd results.

For example, assume that “Article X” was the subject of a substantial clinical investigation that was made public in the late 1950s, but that the investigation was not subject to an IND (because FDA was not requiring INDs at the time). If the exclusionary clause in DSHEA is not triggered unless “Article X” was the subject of an IND, but the clause in section 301(ll) is triggered without an IND – then the exclusionary clause in DSHEA will permit the marketing of “Article X” as a dietary supplement, at the same time the clause in section 301(ll) prohibits it.

• Take robust and expeditious action against dietary supplement companies that market their products to affect disease. Those types of promotional claims render the purported supplements unlawful unapproved “new drugs;” they put patients at risk; and they divert patients from getting appropriate medical attention and/or obtaining necessary therapies. FDA should remind stakeholders that this type of egregious evasion of the drug approval process will not be tolerated.

Sincerely,

/S/ Joseph T. Kennedy
EVP, General Counsel and Strategic Initiatives
Amarin Pharma, Inc.