REGULATORY SURVEY DEEP DIVE

Natural Products Insider®

How we feel today about FDA, legislative priorities and mandatory product listings

Natural Products Insider conducted an in-depth industry member survey of 191 professionals. The results should serve to enlighten and provide insights that may guide you in facilitating fruitful conversations with colleagues, FDA, trade association partners, members of Congress and other stakeholders.

Natural Products Insider®

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SURVEY SAYS:

How we feel today about FDA, legislative priorities and mandatory product listings

by Josh Long

Dietary supplement firms should be required to list their products with the Food and Drug Administration because FDA cannot effectively regulate what it cannot see.

That's a seemingly straightforward and logical position held by industry stakeholders in favor of so-called mandatory product listing (MPL). But in my decade-plus years of reporting on this industry, I have rarely encountered a proposition as divisive, and which elicits such powerful emotions, as FDA's legislative proposal for MPL.

Those who support and oppose the idea are equally zealous—so fervent and dug in on their positions that occasionally personal character attacks have overshadowed the substantive debate over the pros and cons of a listing requirement.

The 117th Congress in 2022 moved closer than U.S. lawmakers ever have to passing a bill that would require dietary supplement products to be listed with FDA. This escalated the rhetoric, including on Capitol Hill, where Sen. Dick Durbin (D-Ill.)—MPL's most prominent advocate in Congress—made an impassioned speech that some in industry condemned as misleading.

At the 2022 SupplySide West/Food ingredients North America trade show in Las Vegas, during an education session co-moderated by myself and veteran attorney Marc Ullman, some of you may recall just one brave soul raising his hand in support of MPL.

I commend regulatory and product development consultant Blake Ebersole for having the guts to confront the mob that day.

I later wondered: Was the hostility expressed toward MPL at SupplySide West representative of "industry's" views on the issue? Or was Blake speaking for the silent majority? Or do the fiery MPL debates among trade associations and others simply demonstrate no clear consensus exists on whether FDA's proposal is a good or bad idea?

To answer those questions and obtain greater clarity on the reasons that stakeholders support or oppose MPL, Natural Products Insider and SupplySide (both part of Informa Markets) surveyed 191 industry professionals, in collaboration with New Hope Network's NEXT custom research team.

Respondents included contract manufacturers, consultants, finished goods manufacturers/brands, ingredient suppliers/producers, lawyers, a select number of retailers and wholesalers/third-party distributors, as well as other businesses.

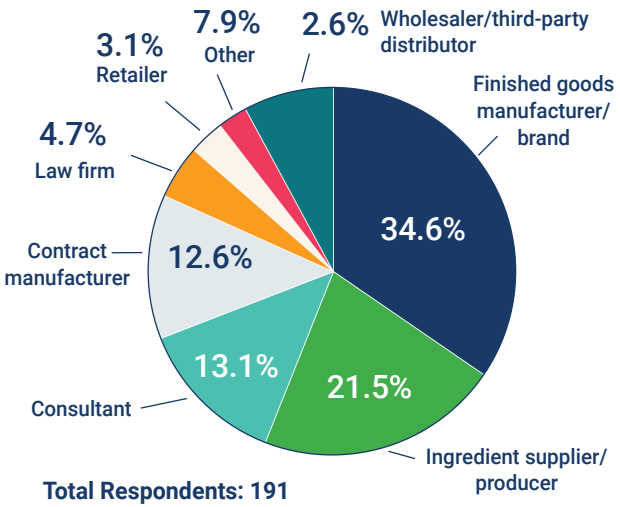
JOSHLONG • • •

Josh Long is associate editorial director for Natural Products Insider. He has reported on the dietary supplement market for over a decade, with a substantial focus on the regulatory framework and law applicable to the $61 billion-a-year category.

Josh has been a journalist since 1997, holds a J.D. from the University of Wyoming College of Law, and was admitted to practice law in Colorado in 2008. In 2023, he was granted UNPA's award for excellence in journalism..

Outside work, he enjoys his family, ice hockey, cheese curds and a good bottle of Scotch.

Which Best Reflects Your Company's Primary Business?



Total Respondents: 191

HIGH-LEVEL FINDINGS

As summarized in this report, the responses to our survey reflect a wide range of views regarding MPL. This report further highlights stakeholders' perspectives on two related regulatory issues: legislative priorities and the effectiveness of FDA enforcement of the regulations and law applicable to dietary supplements. A final section of this report features recent, exclusive, in-depth reporting that focuses on the issue of FDA enforcement.

Before we dive deep, let's start with three high-level findings, based on our survey results.

- A higher percentage of respondents expressed their support for MPL compared to those who opposed it, with a minority remaining undecided.
- Businesses tend to prefer other legislative reforms over MPL as their top priority, such as broader reform of the Dietary Supplement Health and Education Act of 1994 (DSHEA), when given five options in our survey to choose from.
- A greater percentage of industry respondents believe FDA is not very or not at all effective in enforcing the law applicable to dietary supplements, compared to those who rated the agency extremely or somewhat effective.

MANDATORY PRODUCT LISTING

Matt Kennedy, director of market research for New Hope Network, who was instrumental in preparing the survey and analyzing the findings, said most businesses interviewed (81%) are at least somewhat familiar with FDA's legislative proposal. "However, there is likely room and opportunity to further educate manufacturers, suppliers and retailers/distributors on what it means for their business," he said.

Only 11% of manufacturers and suppliers reported being "extremely familiar" with FDA's proposal, Kennedy disclosed, compared to 59% of legal and consultant businesses. He cautioned the number of respondents in the legal and consultant groups was small (51). Long story short, opinions on MPL remain divided.

Kennedy stated, "41% of businesses selling to the U.S. are at least somewhat supportive, 37% are somewhat or strongly opposed and 22% are undecided." But this point is worth emphasizing: He noted businesses selling to the U.S. generally believe other legislative priorities are more important than MPL.

Of the 169 total industry professionals who described their reaction to FDA's proposed legislation, 44% strongly (20.7%) or somewhat (23.1%) support MPL, while 36% somewhat (14.8%) or strongly (20.7%) oppose the idea. A total of 21% of respondents are undecided.

Larger companies (with at least $25 million in sales) were more likely to oppose MPL (48% of the 40 respondents) than smaller companies (35% of the 78 respondents). (Although 169 total respondents expressed their opinion on MPL, fewer people who took the survey answered a later question on the size of their company).

Kennedy shared that 19% of smaller companies strongly opposed MPL, and 15% were somewhat

> **Some respondents to the regulatory survey worried that required disclosures would compromise the confidentiality of their information, such as all the ingredients in a proprietary blend and locations where the product is manufactured.**

opposed. By comparison, 25% of larger companies strongly opposed MPL, and 23% were somewhat opposed.

"In reality, awareness and opinions of MPL, and related legislative priorities, may differ more by company type than other factors," the market researcher divulged.

> **We welcome higher standards and greater transparency with FDA, as we are more than equipped to thrive in such an environment. We believe MPL is an important step toward better transparency and leveling the playing field."** (Finished goods manufacturer/brand)

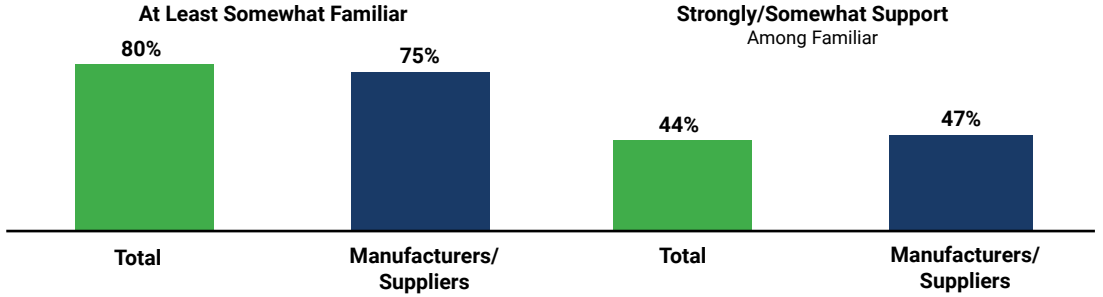
For instance, he noted 47% of manufacturers and suppliers support MPL, 28% are opposed and 25% are neutral. By comparison, just 35% of consultants and lawyers support a listing requirement, with 51% in opposition and 14% neutral.

Survey respondents expressed strong opinions when asked to comment on the reasons for their selections, including those who characterized their position on MPL as neutral.

Supporters of a product listing requirement tended to cite the benefits of giving FDA and

Opinions Are Mixed on Proposed Mandatory Product Listing Legislation

- FDA has room to educate manufacturers/suppliers more to what MPL means for their business; 34% are extremely or very familiar compared to 59% of legal/consultants.
- Directional evidence shows legal/consultant firms are **more familiar** but are **less likely to support.**



others—including consumers—transparency into the market. Pro-MPL respondents also:

- Said other countries have imposed similar requirements.
- Argued the burden of compliance would be minimal.
- Expressed hope that a listing requirement would help FDA identify and better prioritize enforcement, potentially weeding out bad actors.
- One executive (under the title of VP/SVP/EVP) of a finished goods manufacturer/brand brushed aside "conspiracy theories that FDA will abuse this new policy."

"We welcome higher standards and greater transparency with FDA, as we are more than equipped to thrive in such an environment," the executive commented. "We believe MPL is an important step toward better transparency and leveling the playing field."

MPL opponents argued a listing requirement would burden firms, is unnecessary and would not dissuade or hold accountable bad actors, including those who sell products spiked with pharmaceutical drugs. Several of the anti-MPL respondents expressed fears that FDA is seeking to limit access to dietary supplement products through a listing requirement.

Some respondents expressed concerns about specific MPL language passed in 2022 by the Senate Committee on Health, Education, Labor and Pensions. For instance, they worried that some of the required disclosures would compromise the confidentiality of their information, such as all the ingredients in a proprietary blend and locations where the product is manufactured.

TOP 10 RESPONSES

We highlighted 10 responses below to capture a sense of the range of opinions on the issue. (Some responses have been copy edited and/or condensed for clarity.)

UNDECIDED: Contract manufacturer

"If this would further [legitimize] the industry, I would be in favor. However, understanding the influence and control that the pharma industry has on the FDA, I have to believe there is a hidden agenda behind further regulation. Also, I see no need for further legislation or regulation because of the DSHEA rules that already govern this."

STRONGLY OPPOSED: Law firm

"It sets up FDA as a gatekeeper for all supplement products and opens the door to pre-approval. If the agency cared to do its job, using 'The Google' would provide it with all of the information it needs to engage in real enforcement for a decade. Anyone who [thinks] an MPL will change the behavior of the scofflaws … is engaged in very dangerous magic thinking."

UNDECIDED: Ingredient supplier/producer

"Because the road to hell is paved by good intentions, and the FDA is indentured to the pharma industry, so what is born out of good intentions in the hands of the FDA bureaucrats and politicians can quickly become a nightmare for business operators."

STRONGLY IN SUPPORT: Finished goods manufacturer/brand (operates internationally but not in U.S.)

"Companies acting properly have nothing to fear from mandatory registration. In Germany, e.g., food supplements need to be registered. As long as no additional documents need to be submitted like clinical trials, etc., I don't see any major issue. The main question is how the registration list will be worked with. Will there be somebody within the FDA controlling the registrations and taking action if needed, or will it just be a list?"

SOMEWHAT IN SUPPORT: Finished goods manufacturer/brand

"Honestly, for companies who are already doing [the] right thing, this is going to be minimal work after an initial organizational effort. Many companies are already doing similar listings for voluntary databases. If you are doing anything international (Australia, Canada, etc.), you are already doing more. On the other side, shady companies who are already not in compliance with even the basics of DSHEA probably won't comply with MPL either. So I [don't] see that this does harm, but I am also not convinced it does a whole lot of good."

STRONGLY IN OPPOSITION: Consultant

"For FDA or the supporting government and trade association entities to think mandating label transparency is going to solve the chronic core problem of blatant, unethical behavior by certain industry players, is an effort in futility and one dream shy of disillusionment. The solution to the problem is not add another mandatory rule. It begins with FDA agency introspection so to speak. Consider a cop sitting at an intersection. Cars repeatedly run the red light. How many cars can he/she pull over? How long does it take the cop to respond? Are there enough cops at the intersection, well trained and able to respond? How are they prioritizing which driver to pull over? … Does adding another red light to the multiple red lights and stop signs at the intersection solve the problem? Not rhetorical. The answer is 'no.' It comes down to behavior (of all the humans involved), accountability, taking timely action [and] resources.

"Dr. Robert Califf spent lots of money having the Reagan-Udall Foundation perform a 'gap analysis' on the Human Foods Program in 2022; but it did not include dietary supplements, yet, this is a 'food' subcategory. There are more appropriate and effective approaches to solving the noncompliant issues facing the supplement industry (and by the way, the drug industry as well); but adding another 'burdensome' (FDA approved word usage) and costly layer to this saturated mix is just imprudent, unwise and a waste of hardworking taxpayers' dollars."

SOMEWHAT OPPOSED: Company

"It is not necessary. FDA has shown an unwillingness to fully implement DSHEA for 28+ years since its passage. The agency lacks credibility on this topic because of its intentional and blatant failure to enforce the law. It has a long history of bias against the dietary supplement sector and has repeatedly acted to harm the sector. The agency lacks transparency. The only way I would support something like this is as a trade-off for larger FDA reform and accountability related to dietary supplements."

SOMEWHAT IN SUPPORT: Finished goods manufacturer/brand
"Our company is moderately in favor of the transparency involved in providing FDA with a simple label notification of our products. Principally we are OK with this if it helps FDA further regulate the booming marketplace, and more swiftly identify and take action against noncompliances in the market. However, as the bill was proposed, the requirements were not acceptable. The resource burden to the company to both provide and actively manage the notification information was enormous; it was not a simple upload of a label and digital extraction of such information. Further to the manual burden, the request to disclose proprietary information such as the full content of proprietary blends (which is permitted and written into regulation) and the request to disclose manufacturing site information creates a confidentiality concern and is information FDA always had the authority to request during any company audit.

"Notification of food supplement launches is a common practice in international markets, and reputable companies would not be afraid to provide this information in a simple and digital way. However, as drafted, it is onerous and cumbersome to industry with minimal, if any, benefit to these same companies. I don't believe companies should be afraid of this request by FDA in principle, though I would encourage caution whether this is only the first step in a long series of steps for FDA to begin to over-manage dietary supplements in a pseudo-drug/registration format in the coming years."

STRONGLY IN FAVOR: Law firm
"Supplement world remains rife with noncomplying companies and products. Listing is a modest but necessary step in cleaning up the market."

SOMEWHAT IN SUPPORT: Consultant
"This would help the FDA crack down on illegitimate companies selling supplements with illegal/unapproved ingredients. It may also cause regulatory headaches for supplement companies that are doing business 'the right way.'"

LEGISLATIVE PRIORITIES

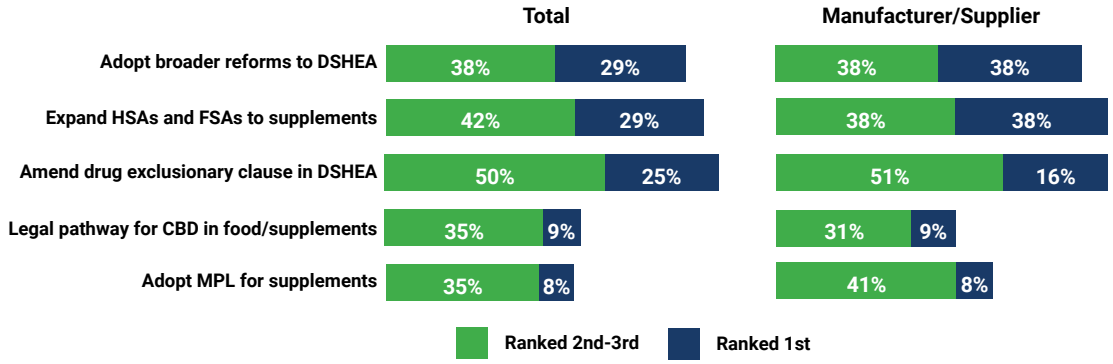
Another one of our survey objectives was to determine where mandatory product listing ranked among other legislative priorities for industry stakeholders. We asked respondents to rank the following five legislative reforms from 1 to 5:

- Adopt broader reforms to DSHEA.
- Expand health savings and flexible spending accounts to supplements.
- Amend the so-called drug exclusionary clause in DSHEA.
- Create a legal pathway for CBD in food and supplements.
- Adopt MPL.

> **Smaller businesses are somewhat more likely to favor working with existing regulations over a new MPL policy."**
>
> **– MATT KENNEDY, DIRECTOR OF MARKET RESEARCH, NEW HOPE NETWORK**

Businesses Tend to Prefer Other Reforms Besides Adopting MPL

Directional evidence shows legal/consultant firms strongly favor amending the drug exclusionary clause.



MPL

The responses (113 answering) revealed few businesses considered MPL their top legislative priority.

"Just 8% of interviewees ranked MPL adoption No. 1 among the five options provided, with another 35% ranking it 2 or 3," Kennedy, the market researcher, shared. It's also worth noting that 58% of respondents ranked MPL as their fourth or fifth priority.

"Smaller businesses are somewhat more likely to favor working with existing regulations over a new MPL policy," Kennedy concluded.

He shared the following:

1. **Companies with less than $25 million in revenue (54 responses to question about legislative priorities) were roughly twice as likely as large companies (33 responses) to select amending the drug exclusionary clause as their top priority (35% for smaller companies, compared to 18% for larger firms).**

2. **Companies with $25 million or higher were more likely to favor, and less likely to oppose, broader reforms to DSHEA.**
   - Of the larger firms, 36% ranked broader DSHEA reform as their No. 1 priority, and just 18% ranked it 4 or 5. By comparison, 22% of smaller companies ranked DSHEA reform as their first priority and 39% selected it as their fourth or fifth legislative pick.

Any reform to DSHEA can't happen unless mandatory product listing is first implemented, according to one of the respondents.

"MPL has become the baseline of any changes to DSHEA," the respondent wrote. "FDA and other influential stakeholders (including potential congressional sponsors) want MPL. So it's a fool's game to think about any change without MPL. The key is getting the right MPL that is not overly burdensome and provides FDA with the correct info, at the same time adding things that industry wants to see improved in DSHEA, like ensuring more facilities are inspected by FDA, possibly by authorizing third parties to conduct cGMP [current good manufacturing practice] audits."

An executive of a finished goods manufacturer/brand placed MPL fourth among the five choices of legislative priorities, although described it as "pretty innocuous in the end."

"Which is why I'm not sure why it has caused such uproar in the industry, other than the burden it may put on industry due to the manual nature of the proposal," the executive wrote.

Despite ranking MPL far down the list of priorities, this person perceived benefits in a listing requirement, rejected the idea that MPL would limit future industry growth, and concluded FDA's proposal doesn't require premarket approval. "But I do think it could positively support the well-being of the industry. If we assume it moves forward in a less cumbersome and exhaustive way than initially drafted, the small step of uploading a label to FDA as a 'listing' would help ensure companies are transparent with our regulator," the industry professional stated. "Majority of companies would not have

a problem with this step, and it goes a small way toward building the reputation and trust of the category. It also, theoretically, does actually allow FDA to know what's on the market, better prioritize their enforcement strategies, and have a clear pathway to engaging with the companies who choose not to use the listing—to either bring them into compliance or remove them from the market."

CBD

Like MPL, creating a legal pathway for CBD (cannabidiol) wasn't among the top legislative priorities identified by survey respondents. Just 9% of respondents selected CBD reform as their No. 1 legislative priority, 1% higher than MPL. The number of positive-CBD respondents may have been higher in the last few years, but several factors have contributed to the hemp CBD market losing its sheen (to say the least). With the market a shadow of its former self way back in, oh, 2019, a lot of companies have simply walked away from the "opportunity."

HEALTH AND FLEXIBLE SAVINGS ACCOUNTS

Among all respondents who ranked legislative priorities, health savings accounts (HSA) and flexible savings accounts (FSA) expansion to supplements and adopting broader reform to DSHEA ranked as the top picks, with about 29% of respondents selecting HSA/FSA reform and the same percentage preferring DSHEA modernization. A C-level executive of a finished goods manufacturer/brand selected expanding HSAs as their top pick.

"It is 100% ridiculous that this and coverage of essential nutrition by SNAP [Supplemental Nutrition Assistance Program] doesn't already exist," wrote the executive, who also indicated interest in creating a pathway to CBD and amending the drug exclusion clause.

"I think MPL is important, but not the top priority in this list," a representative of an ingredient supplier/producer stated in the questionnaire. "Expanding health savings/FSA seems like a no-brainer and has real health benefits for consumers."

DRUG EXCLUSIONARY CLAUSE

About 25% of respondents preferred to amend the drug exclusionary clause. Among consultants and law firms, 42% picked this reform as their No. 1 priority, compared to 16% for manufacturers/suppliers, Kennedy shared. The exclusionary clause in the law, which essentially creates a race to market between the pharmaceutical and supplement industries, has been the subject of significant coverage in the trade press. That's due to FDA determinations that certain ingredients are excluded from dietary supplements because they were either approved as a drug or authorized for investigation as a new drug before being lawfully marketed in supplements. CBD, NAC (N-acetyl-L-cysteine) and NMN (beta-nicotinamide mononucleotide) are among the ingredients subject to the latter FDA determinations.

A C-level executive of a finished goods manufacturer/brand who answered the survey characterized MPL as the least important priority.

"The drug exclusionary clause is currently being enforced in a way that prohibits innovation through supplements and forces Americans to improve their health and well-being through drugs alone," wrote the executive, who also expressed his or her support for reimbursements for purchases of dietary supplements via HSAs/FSAs.

"Amending the drug exclusionary clause is most important because it is a ticking time bomb, impacts/undermines research, and, as an isolated, easily definable 'problem,' should be easier to resolve than other 'big issues,'" the CEO of a consultancy declared.

The consultant noted the survey excluded as a priority "vigorous enforcement of existing [dietary supplement] regulations."

"Without enforcement," the consultant added, "the bad guys will continue to [do] bad things. To me, that is job No. 1."

A director/senior director of a finished goods manufacturer/brand also underscored the importance of reforming the drug exclusionary clause.

"The industry is shackled by the exclusionary rule, and it needs to be eliminated as it stifles access to legitimate supplement ingredients for the health of consumers," the director stated. "For MPL, it is an unnecessary requirement and undue burden on legitimate companies. It does nothing to protect the consumer, and if FDA cannot enforce or is not given resources to do its job, then MPL is useless."

EFFECTIVENESS OF FDA ENFORCEMENT

Responses to our survey highlighted that many industry professionals believe FDA is failing to adequately enforce its regulations and the law.

"This is some enforcement," a manager/senior manager of a finished goods manufacturer/brand succinctly declared, "but not nearly enough."

Three-fifths (114) of professionals who completed the survey weighed in on FDA enforcement.

> **"Dysfunctional," "reactionary" and a "toothless tiger" were among respondents' descriptions of FDA.**

A total of 41% of respondents opined FDA was not very, or not at all, effective in enforcing DSHEA and the broader Federal Food, Drug & Cosmetic Act (FDCA). (DSHEA amended the FDCA). Roughly 34% of respondents viewed FDA enforcement as extremely or somewhat effective, with 25% having a "neutral" opinion on the matter.

Among consultants and lawyers (41 respondents), 37% have a favorable opinion of FDA, 49% have an unfavorable view of the agency, and 15% are neutral, Kennedy said. By comparison, among manufacturers/suppliers (69 respondents), 30% have a favorable view of FDA, 38% have an unfavorable opinion and 32% are neutral, he added.

Respondents who believe FDA is ineffective in its enforcement cited myriad reasons for their views, including a lack of follow-up action to warning letters, limited resources and cowardice. They also criticized the agency for not conducting enough inspections of smaller manufacturers and said FDA has trouble retaining qualified staff.

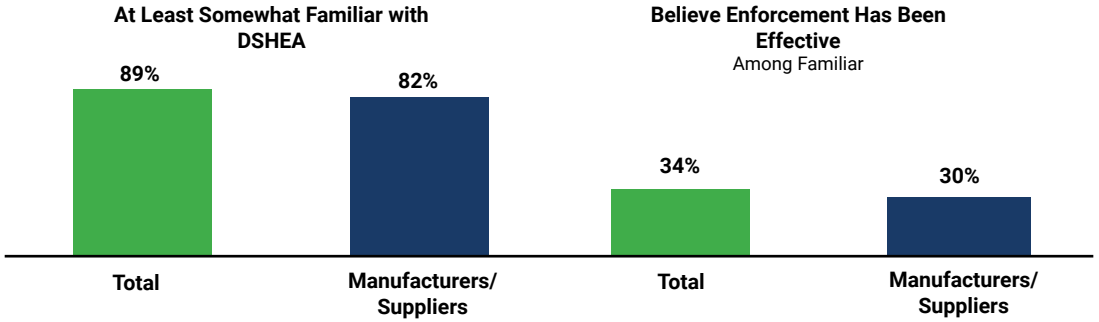
"Dysfunctional," "reactionary" and "a toothless tiger" were among respondents' descriptions of FDA.

One person who answered the questionnaire and identified themselves under the category of VP/SVP/EVP stated FDA has failed to fully implement DSHEA nearly three decades after it was passed into law.

"For 10+ years following passage of DSHEA, the commissioner of the FDA (Dr. David Kessler) ordered the agency to not implement or enforce DSHEA, believing this would encourage rogue companies to run wild and lead to the overturning of DSHEA," this person wrote. "The agency lacks any credibility on the topic of dietary supplements and continues to attempt to restrict access to these products and information about them. Even as science continues to show that supplements have a positive impact on public health and are extremely cost-effective, the agency resists this truth. The agency and its leadership should be held accountable for decades of failure and malice."

Businesses Also Have Divided Views on FDA Enforcement of DSHEA

- Businesses overall are slightly more likely to feel enforcement has been ineffective.
- Directional evidence shows legal/consultant businesses have a less favorable view of FDA enforcement.



Another respondent also suggested FDA remains biased against supplements, although science has shown them to be effective.

FDA officials "seem incapable of dealing with actual enforcement efforts [against] the bad actors and instead focus on securing additional financial resources that will not improve compliance," a CEO declared in a survey response. "In addition, they are [averse] to scientific developments showing health improvements through supplementation and actively oppose scientific research outcomes [that] validate effectiveness."

While most of the written comments tended to be critical of FDA, an executive of a finished goods manufacturer/brand who rated the agency's enforcement as "extremely effective" cited its practice of sending warning letters. "FDA at any given time is issuing warning letters, which include fundamental aspects of DSHEA," the executive observed. "Supplements are a subset of foods and do not require a heavy administrative or regulatory framework. I would even argue that supplements are better regulated than foods, and the FDA should focus on food regulation first."

10 RESPONSES

Below are 10 (copy edited and/or condensed) additional responses to the question of whether FDA has been effective in its enforcement.

SOMEWHAT EFFECTIVE: President of wholesaler/third party distributor
"FDA is mostly reactive. Enforcement [is] inconsistent across the FDA districts. Inspector priorities vary and shift."

SOMEWHAT EFFECTIVE: VP/SVP/EVP
"FDA, and most in the industry today, is struggling with resources. The FDA overall has a dysfunctional and out-of-date management system. Compared to an industry position, the FDA staff is underpaid and overworked and therefore, the agency has a difficult time retaining good staff. They depend on recent college graduates who come in low on the General Schedule (GS) payscale but have no experience, background or training in the commodities they regulate."

The executive also suggested staff turnover will make it challenging for FDA to operate consistently or enact change.

NOT VERY EFFECTIVE: VP/SVP/EVP of ingredient supplier/producer
"I see quality and composition issues raised by industry that are well grounded in facts and science, and the FDA refuses to act or intervene for the good of the consumer. They are [beholden] to big pharma and are afraid to move on matters that may be perceived to rock the status quo. They have the power and the mandate. They need to lose the cowardice to act!"

NOT VERY EFFECTIVE: C-level executive of finished goods manufacturer/brand
"In the 22 years I have been in industry, we have seen repeat examples of FDA not fulfilling their side of the bargain. The biggest failures have been in enforcement. I could give a lot of examples from not responding on notifications, to NDIN (new dietary ingredient notification) backlogs, to allowing companies that are blatantly violating the law to operate unmitigated for years or decades. This ongoing challenge creates a public perception of lack of responsibility and oversight, which really should not have to be shouldered by the industry this many years after the passage of DSHEA."

NOT AT ALL EFFECTIVE: CEO of consultancy
"Limited enforcement resources = a part-time job = part-time results. Training and inspection priorities need review. When violators put the public health in danger, and sell dangerous drugs labeled as dietary supplements, why are they still in business?"

NEUTRAL: VP/SVP/EVP of finished goods manufacturer/brand
"There are still bad actors marketing products of questionable quality, safety and efficacy, which reflects poorly on the overall industry."

NOT VERY EFFECTIVE: C-level executive of finished goods manufacturer/brand
"They ignore product testing and going after the long-time offenders manufacturing subpotent and dangerous supplements. The few actions they do are pushed by media or congressional pressure and are uneven. Prop 65 and class action trials are more powerful than the FDA for enforcing product quality."

NOT VERY EFFECTIVE: Director/senior director of finished goods manufacturer
"Too many examples to highlight in the time I have. CBD is an obvious example of mismanagement and poor decision-making, without actively protecting or educating consumers about the ubiquitous ingredient. Their management of the IND (investigational new drug) preclusion in the CBD case as well as several other key ingredients seems wholly arbitrary. Even companies that have GRAS (generally recognized as safe) dossiers and NDIN acknowledgments aren't safe.

"While FDA does prioritize safety in their day-to-day work, they do nothing to manage known noncompliances that mislead the consumers. I've even gone as far as emailing both CDER (Center for Drug Evaluation and Research) and CFSAN (Center for Food Safety and Applied Nutrition) about a noncompliant product on the market that contained both an OTC drug and a dietary supplement, co-packed in a way that was misleading to the consumer and would be considered a new combination drug. Both offices [responded] with a benign response and no action. Eighteen months later, that product was the target of a class action lawsuit.

"I regularly tell my corporate business partners that when I assess a new ingredient, new claim, new dosage form, new acquisition, etc., the FDA is my third or fourth concern. They now regularly fall behind class action lawyers, FTC, state of California and retailers."

NEUTRAL: Manager/senior manager of ingredient supplier/producer
"You can see mislabeled illegal products on the shelf in almost every part of [the] U.S. So how effective can the FDA be?"

NOT AT ALL EFFECTIVE: CEO of consultancy
"Woefully inadequate resources have been given to the supplement industry regulation at FDA. Hundreds and hundreds of thousands of products are marketed—many on Amazon and websites—and no one has much of an idea what is in these products and who is responsible for marketing them."

REGULATIONS, YES, JUST NOT THOSE REGULATIONS

In summary, our survey findings underscored that industry professionals continue to have mixed opinions on mandatory product listing, though it's clear they favor legislative reforms ahead of FDA's proposal, including changes that would promote and expand access to dietary supplement products. It's also evident that many industry professionals remain convinced that FDA is not effectively enforcing its regulations and the law. Regardless of your views on the issues identified above, we are hopeful you will leverage this report as a guide in facilitating fruitful conversations with colleagues, FDA, trade association partners, members of Congress and others.

For additional perspective on FDA enforcement, this report features a four-part investigative series of articles focused on the NDIN requirement, previously published by Natural Products Insider, as well as a follow-up article to the series. We also included some key documents related to the investigation. If you take a deep dive into this series on FDA enforcement of the NDI provision in DSHEA, let us know your perspective on the events of recent years.

"When I assess a new ingredient, new claim, new dosage form, new acquisition, etc., the FDA is my third or fourth concern. They now regularly fall behind class action lawyers, FTC, state of California and retailers." (director/senior director of finished goods manufacturer/brand)

Finally, thanks for taking the time to read this report. Please drop us a line with your feedback and questions at josh.long@informa.com and sandy.almendarez@informa.com.

NDI APPENDIX, PART I:

Supplement industry, FDA clash over NDI enforcement

July 20, 2020 | by Josh Long

On Aug. 7, 2019, a former regulator who leads a dietary supplement trade group in Washington, D.C., emailed three FDA officials, attaching a document that acknowledged receipt of a shipment of beta-alanine from China. The shipment's consignee, or U.S. entity responsible for its receipt, was Armada Nutrition, a contract manufacturer in Spring Hill, Tennessee, that makes multi-ingredient powder solutions for nutrition brands.

The attachment was merely one document in a mountain of records shared with FDA that identified Chinese exporters of beta-alanine to the U.S. and American companies accepting the shipments, or U.S. supplement brands marketing the ingredient, an amino acid widely used in sports nutrition products.

Dan Fabricant, president and CEO of the Natural Products Association (NPA), and Kevin Bell, outside counsel to NPA, peppered FDA with documents in emails and during meetings over a period of more than a year. One of their chief objectives was to persuade the agency to detain U.S.-bound shipments of beta-alanine from China that had not gone through a premarket safety review by FDA. To date, their coordinated and extensive efforts have not resulted in an FDA import alert against forms of beta-alanine made in China that compete with one of Bell's clients—Natural Alternatives International Inc. (NAI), whose founder, Mark LeDoux, chairs NPA's board of directors.

'FUNDAMENTAL PROBLEM HERE'

This series of articles highlights a lingering—and perhaps growing—rift between FDA and some factions of industry over enforcement of a provision in a 26-year-old law intended to flag novel ingredients in supplements before they pose risks to consumers. Industry lawyers, former FDA officials and business executives suggested NAI's pleas reflect an agency reticent to enforce a key requirement in the Dietary Supplement Health and Education Act of 1994 (DSHEA), even when FDA is spoon-fed evidence that an ingredient may be adulterated.

At issue: The new dietary ingredient notification (NDIN) requirement, widely considered to be underutilized either intentionally or negligently, or through a "present in the food supply" exemption in the law that contributes to FDA's challenges in assessing novel ingredients in supplements. Lindsay Haake, an FDA spokesperson, said in a July 9 email that the Office of Dietary Supplement Programs (ODSP) has received approximately 1,140 NDINs since the program's inception.

Considering the sheer size of the industry, the math doesn't seem to add up. Nutrition Business Journal (NBJ), a publication owned by Informa, projects 2020 sales of dietary supplements to reach US$54.5 billion with growth of 12.1%, and FDA has estimated the market contains as many as 80,000 dietary supplement products.

New Dietary Ingredient Notifications (NDINs): BY THE NUMBERS

1,140 total received since inception of program

48% percent of acknowledged notifications (19) in FY19 without objection

15 Notifications filed with FDA through first half of FY20

Source: FDA through spokesperson and Freedom of Information Act request

"There's a fundamental concern here," said LeDoux, chairman and CEO of NAI, a publicly traded company in Carlsbad, California. "Either the system is broken or it's unenforceable. And if it's unenforceable, then it needs to be fixed legislatively and/or administratively. It begs the question: Why would you file an NDI if the agency isn't going to protect your efforts?"

An import alert, which NAI requested, could further its commercial interests. If FDA choked off the supply of beta-alanine coming into the U.S. from China, U.S. brands marketing beta-alanine in their nutritional products are more likely to license NAI's CarnoSyn beta-alanine, which is sourced from a manufacturer in Japan.

Bell, Fabricant and LeDoux stressed FDA enforcement action would promote its central mission of protecting the public health. NAI in 2018 submitted to FDA an NDIN for CarnoSyn beta-alanine, which disclosed manufacturing details and other data upon which the agency could assess the safety of the ingredient. By contrast, FDA has no way of knowing, for example, whether the processes used to manufacture beta-alanine in China are safe, the three men said in interviews.

"If other people are just going to copy you and not even bother to file, how does that help not only American business but the American consumer to know what they're getting is safe?" LeDoux asked. The issue of NDI enforcement is a challenging one; FDA bears the burden of proving an ingredient is "adulterated," and NAI and its advocates did not provide evidence to establish beta-alanine coming from China is unlawful, according to FDA representatives in an email and two interviews.

Among FDA's observations, an NDI is exempt from the notification requirement if—per Section 413(a)(1) of DSHEA—it's "been present in the food supply as an article used for food in a form in which the food has not been chemically altered." The NDIN "requirement exists except for where it doesn't," Steven Tave, former director of FDA's ODSP, said in an interview.

And in an emailed response to questions, FDA said through a spokesperson that some stakeholders take the view that "once an NDI has been the subject of one NDI notification and introduced to the market, other products containing that ingredient are excepted from the notification requirement."

CARNOSYN BETA-ALANINE

LeDoux founded NAI 40 years ago out of his home in San Marcos, California, when he was 25 years old. A prominent figure in the industry, he serves as chairman of NPA's board and speaks at industry events.

LeDoux shared that in 1986 the private company went public through a reverse merger acquisition when the prime rate—the rate banks use as a basis to set loans—exceeded 15%. NAI (Nasdaq: NAII) generated FY19 net income of $6.5 million—or 92 cents per diluted share—on sales of $138.3 million, a 4% increase from the prior year ($132.4 million).

The beginning of 2020 was a challenging one for NAI. For the quarter that ended March 31, the company reported a net loss of $4 million, or a loss of 61 cents per diluted share, on sales of $25.5 million. Its sales decreased

28.1%, or $10 million, from $35.5 million in the comparable prior-year period. In a press release announcing the results, LeDoux cited "several unforeseen challenges" in the quarter, "including the loss of a former customer and the COVID-19 global pandemic."

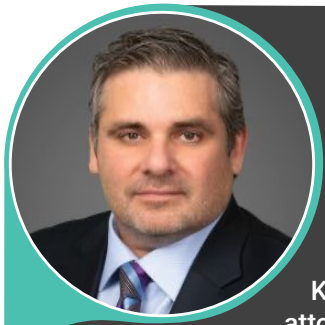
In part, NAI attributed waning sales to "certain customers discontinuing the use of our CarnoSyn beta-alanine in favor of generic beta-alanine and lower overall consumer demand for our customers' CarnoSyn products." In the nine months that ended March 31, CarnoSyn beta-alanine royalty, licensing and raw material sales revenue decreased $3.2 million, or 23.9%, from $13.5 million during the comparable period the prior year.

According to NAI's website, its CarnoSyn brands—CarnoSyn instant release beta-alanine and SR CarnoSyn sustained release beta-alanine—are patented ingredients "well known to deliver benefits for athletic performance: increased strength, enhanced endurance, faster recovery and greater mental focus."

Bell, NAI's outside counsel, has been in numerous communications with FDA officials over what he described in a letter to FDA as "adulterated beta-alanine" being imported into the U.S., in violation of federal law. He pointed out NAI successfully navigated the NDIN process for CarnoSyn beta-alanine.

In a letter dated Feb. 1, 2019, FDA advised Bell it filed NAI's notification for CarnoSyn beta-alanine at a total daily intake of 6.4 grams per day. The so-called good day or AKL (acknowledgment) letter is the best outcome for a manufacturer that submits a premarket dietary ingredient notification to FDA. The agency does not "approve" these notifications and reserves the right to take enforcement action against an acknowledged NDIN if the ingredient is found to be adulterated, unsafe or misbranded.

"NAI is the only company that has submitted an NDIN for beta-alanine to FDA," Bell wrote in a Feb. 24, 2020 letter to Tave. "The company spent hundreds of thousands of dollars to not only compile publicly available information about the ingredient's identity, manufacturing process and safety, but also to conduct its own commercially confidential, preclinical studies. The agency did not object to NAI's basis for concluding that CarnoSyn beta-alanine is reasonably expected to be safe, as manufactured, and under the conditions of use proposed in the notification."



KEVIN BELL

Kevin Bell, an attorney in Washington, D.C. representing Natural Alternatives International Inc., communicated with FDA officials for over a year in an effort to get them to detain beta-alanine manufactured in China and exported to the U.S. that has not gone through a pre-market safety review by FDA. FDA has yet to grant his request.

NAI sources CarnoSyn beta-alanine from an ingredient manufacturer in Japan known as Yuki Gosei Kogyo Co. Ltd (YGK). The identity and safety data upon which NAI relied in its notification were based on YGK's production method "and final product of commerce," wrote Bell, a partner with Arnall Golden Gregory LLP (AGG), who leads his firm's patent and dietary supplements practices.

CHINESE SUPPLIERS OF BETA-ALANINE

YGK doesn't control the production of beta-alanine imported into the U.S. In an attachment to the letter to Tave, Bell identified 24 Chinese manufacturers and exporters of beta-alanine between Feb. 1, 2019 and Jan. 31, 2020. Combined, the top three exporters alone shipped more than 1 million kilograms of beta-alanine, according to data in the attachment sourced from the PIERS TI import database—a subscription service maintained by IHS Markit. Of the more than 3.3 million kilograms of beta-alanine imported into the U.S. during the above time frame, NAI imported about 31% of the ingredient from Japan, while more than 2.3 million kilograms of the ingredient, or 69% of total beta-alanine imports, came from China, Bell advised Tave. (See chart below of Chinese suppliers in Bell's attachment B to Tave).

Beta Alanine Chinese Manufacturers / Exporters List

02/01/19 -01/31/20

COMPANY	HQ Address	Website	Total Kilograms Exported to the U.S. (1)	Total # of Shipments Exported to the U.S. (1)	Notes
Imports Brought In Under Confidential Status			634,774	35	Various unknown companies.
Anqing Xinfu Chemical Co., Ltd.	Phoenix Cyclic Economic Industrial Park Anqing, Anhui, China (Import record address) No.44, Wanhe Avenue, Daguan District Anqing, Anhui, 246005 (D&B address)	No company website found.	502,935	23	Can't confirm address.
Anhui Huaheng Bioengineering Co., Ltd.	No.32 Fengjin Road, Shuang Feng Industry Park, Hefei, Anhui, China	huahengbio.com/en/AboutUs/1039/1141.html	306,000	14	Address Confirmed.
Jing Jing Phramceutical Co., Ltd.	No. 88, Jingyi Road Dacaozhuang Management District, Ningjin County, Xingtai, 055550 China	www.hbjingjing.cn/about/show.php?id=96&lang=en	273,840	15	Address Confirmed.
"Suzhou Vitajoy Bio Technology Company"	"B13-102,NO.192 Tinglan Lane, SIP, Suzhou, China"	www.vitajoy-biotech.com	232,753	10	Address Confirmed.
Xinfa Pharmaceutical Co. Ltd.	"No.1, Tongxing Rd., Kenli County, Dongying, Shandong, 257599, China"	www.sdxinfa.cn/	69,690	4	Address Confirmed.
Nanjing Shining Import and Export	#8 906, Jinlun International Plaza Hanzhong Road Nanjing, China	No company website found.	39,960	2	Can't confirm address.
Zhangjiagang Chuangyuan Plastic Industry Co. Ltd.	Shuanglong Village, Fenghuang Town, Zhangjiagang, Jiangsu, China 215614	No company website found.	36,193	2	Can't confirm address.
Sichuan Tongsheng Amino Acid	Room 1-11-1, No. 19 of North Tianshan Road, Deyang, SiChuan, China 618000	www.aminoacid.cc/contact_en.html	27,560	2	Address Confirmed.
Shanghai Chemspace Co., Ltd.	Building B3, 218 Huashen Road, Shanghai, China	No company website found.	21,600	2	Can't confirm address.
Shandong Rongcheng Municipal Supply Ltd.	No.1666, Donghuan Road, Juancheng County, Shandong Province, China 274600	http://en.yangchengshengwu.com/comcontent_contact.html	19,440	1	The import address is for a Shandong Yangcheng Biotech Co., Ltd.
Yueqing Vancol Import and Export Co., Ltd.	"No.7,Yongxing Yi Road, Chengdong Industrial Zone, Yueqing, Wenzhou,China 325600"	www.vancol.cn/contactus.html	18,680	1	"The address on the import records is the same as Vancol Electric co. Ltd. in China."
New Life Chemical and Equipment	No company address found.	No company website found.	16,884	1	"Import address listed is incomplete. There is a company in the US with the same name."

COMPANY	HQ Address	Website	Total Kilograms Exported to the U.S. (1)	Total # of Shipments Exported to the U.S. (1)	Notes
Foodchem International Corporation	Building 9,2277 Zuchongzhi Road,Shanghai,201203, China	www.foodchem.cn/	12,510	1	Address Confirmed.
Nanjing Nutrabuilding Bio Tech Co. Ltd.	"Room 1504 Suning Huigu Building 1 No. 268 Jiqingmen Street, Nanjing 210000 CN"	No company website found.	12,375	1	Can't confirm address.
"China Sinopharm International Corporation (Shanghai) C., Ltd."	293 Jiangning Road, Jing'an District, Shanghai, 200041	www.sinopharmintlsh.com/	11,100	1	Address Confirmed.
Eumex Line Shenzhen Limited	"Room J 26F., International Trade & Commercial Building, 3005 Nanhu Road, Shenzhen,China 518001"	No company website found.	11,060	1	Address Confirmed.
"Hebei Changhao Metal Wire Product Ltd."		No company website found.	11,060	1	"Import address listed is incomplete."
Northeast Pharma Import and Export	"19th Floor, Block B, Chamber of Commerce head quarter Mansion. No.51, The Youth Str., Shenhe Dist., Shenyang, China. 110014"	No company website found.	10,368	1	The name of the company is possibly Northeast Healthcare Co., Ltd.
"Qingdao Samin Chemical Co.,LTD. wv1"	"B-3A20, Heda Plaza 179 Tailiu Road, Qingdao, China"	www.saminchemical.com	10,066	1	Address Confirmed.
CTS Logistics Corporation	Nanjing Anjing Branch Room 4202, NO.288 Zhongshan East Nanjing, China	No company website found.	8,800	1	"Cant' confirm address. The company may be CTS International Logistics Corporation Limited."
"Changzhou Meiang International Trade"	"2620,15 Huangshan Road, Changzhou, Jiangsu, China"	No company website found.	8,460	1	Can't confirm address.
Jinan Asia Pharmaceutical Co., Ltd.	"Xinshi Town, Jiyang County Jinan, Shandong 250014 China (Import record address) Zhonghong Plaza, Jiefang Est Road, Jinan, China (Website Address)"	hl- asia.net/AboutMe. aspx?t=4&la n=en	7,800	1	Address Confirmed.
Sun Chemical Trading Co. Ltd.	Room A, 7/F, China Overseas Building, 139 Hennessy Road Wanchai Honk Kong, China	No company website found.	4,810	1	Can't confirm address.
SYNMR Biotechnology (Shanghai) Limited	"Union Energetic International Tower,New Jingqiao Rd, Pudong.,Shanghai"	www.synmr.com	4,492	1	Address Confirmed.
		TOTAL	**2,313,210**	**124**	

Note (1) - Data was retrieved from PIERS TI import database

"None of the companies importing and selling generic beta-alanine made in China can rely on NAI's NDIN #1103, nor have they made the statutorily required premarket notification," Bell wrote to Tave. "Thus, there is no way to determine how, or if, the ingredients being imported into the U.S. and distributed as generic beta-alanine are quantitatively or qualitatively related to CarnoSyn beta-alanine—the only beta-alanine for which the required notification has been made. Because of this, FDA cannot assume that the basis for concluding that NAI's CarnoSyn beta-alanine is reasonably expected to be safe can be directly applied or assumed for any of the generic forms of beta-alanine."

Natural Products Insider reached out via email (in English and Mandarin) to eight of the Chinese exporters of beta-alanine, requesting they disclose their U.S. customers of beta-alanine, whether customers are using the ingredient in their dietary supplements, and their legal basis for concluding beta-alanine can be lawfully marketed in the United States. None of them returned multiple requests for comment.

Among those contacted were the second and third top-producing exporters, Anhui Huaheng Bioengineering Co. Ltd, which exported 306,000 kilograms of beta-alanine between Feb. 1, 2019 and Jan. 31, 2020 in 14 total shipments, and Jing Jing Pharmaceutical Co. Ltd., which exported 273,840 kilograms of the same ingredient during the above time period in 15 total shipments, according to the PIERS TI import database cited in Bell's attachment.

A few months after NAI received its AKL letter, Jing Jing Pharmaceutical emailed LeDoux, touting the production of various products, including beta-alanine. "If you have any inquiry, please come here," the April 11, 2019 email stated. "I will give you the competitive price." In a more recent email sent June 18 to NAI, Jing Jing reminded the company that it produced beta-alanine and several other ingredients and wanted the "opportunity to show you our superior products."

Other documents obtained by NAI show the consignees of beta-alanine shipments are often manufacturers of dietary supplements, or ingredient suppliers targeting the nutrition industry. For example, based on the search terms "beta-alanine" and "b alanine" for the time period Jan. 1, 2019 to June 10, 2019, Armada Nutrition was identified as the consignee of 13 different shipments at the U.S. port in Savannah, Georgia, according to data Bell retrieved from the PIERS TI import database. Armada Nutrition, which did not respond to multiple requests for comment, obtained all its beta-alanine from Anhui Huaheng Bioengineering. (While the database refers to "Anhui Huaheng Bioengineering," the company describes itself on its website as Anhui Huaheng Biological Engineering or Anhui Huaheng Biotechnology).

During a four-month period ending June 26, 2020, Armada Nutrition obtained beta-alanine from Anqing Xinfu Chemical as well as Anhui Huaheng Bioengineering, according to additional import data obtained by Bell. Other consignees of beta-alanine from China included, among others, Nutravative Inc., an Allen, Texas-based ingredient supplier for the food, health and nutrition industries; and Fifth Nutrisupply Inc., a Chino, California-based supplier of nutritional raw materials. Neither company returned a request for comment in response to questions about beta-alanine.

NDI APPENDIX, PART II: Supplement maker, FDA met several times over NDI enforcement

July 27, 2020 | by Josh Long

On the evening of Feb. 26, 2019, Mark LeDoux, the founder of Natural Alternatives International Inc. (NAI), sent an optimistic email to some colleagues after meeting with FDA officials. Just weeks earlier, NAI—a nutritional supplements maker in Carlsbad, California—received word that FDA had acknowledged its safety-related notice for a new dietary ingredient (NDI) manufactured in Japan, CarnoSyn beta-alanine.

It took NAI nearly a year to compile all the information for its beta-alanine NDI notification (NDIN) to FDA—with hundreds of pages of documents describing such matters as testing, manufacturing methods and safety, LeDoux explained in an interview. NAI spent a minimum of

around $1 million investing in the NDIN process, and the figure is more than twice that amount when including human clinical trials to support components of the submission, he reported in a follow-up email.

During the Feb. 26 meeting with FDA officials, LeDoux turned his attention to rival forms of beta-alanine. It would not be the last time NAI complained to FDA that beta-alanine coming into the U.S. from China was "adulterated" and possibly dangerous to consumers. Over a period of more than a year, NAI and its advocates communicated with FDA employees—including Steven Tave, former director of the Office of Dietary Supplement Programs (ODSP)—through emails, phone calls and in-person meetings.

NAI believed it was making headway with FDA, its representatives suggested in emails following meetings with the agency. In recent months, though, FDA has declined requests for additional meetings by the head of a trade group with close ties to LeDoux, and the agency has not issued an import alert for "generic beta-alanine," as NAI requested. FDA representatives suggested in an email and interviews that the agency was not provided sufficient evidence to justify enforcement action against the ingredients flagged by NAI.

This article highlights the substance of NAI's pleas to FDA, points at which NAI's advocates seemed encouraged by meetings with agency officials, and the conclusions of the two parties following more than a year of back-and-forth conversations.

2019 MEETINGS

On Feb. 1, 2019, FDA advised NAI's outside counsel, Kevin Bell, that it filed NAI's NDIN for CarnoSyn beta-alanine. The acknowledgment letter was welcome news for NAI, reflecting the culmination of a substantial investment and confirmation that the company had satisfied a requirement in the law to establish a supplement containing an NDI "will reasonably be expected to be safe."

Twenty-five days later, LeDoux—chairman and CEO of NAI—met with FDA officials, including Tave. The objective, he recalled for this story, was "to discuss policing those products that were piggybacking on our successful NDI to import their beta-alanine without submitting safety or process data."

The meeting had been productive, LeDoux suggested, at the time, to Corey Hilmas, a medical doctor and former FDA official working for the Natural Products Association (NPA), in a Feb. 26, 2019, email sent that evening.

"I think we set the table for some productive outcomes based on relationship and the mutual recognition that FDA needs a quid-pro-quo for the NDI in order to establish the intrinsic commercial value of the undertaking for those companies that want to play by the rules," LeDoux, who chairs NPA's board of directors, wrote to Hilmas, according to a partially redacted email Natural Products Insider obtained from Bell, a partner in Washington, D.C., with the law firm Arnall Golden Gregory LLP (AGG).

Hilmas, who now works for KGK Science and was not immediately available to comment for this story, also attended the meeting.

In an earlier email that day to LeDoux, Hilmas indicated FDA expressed interest in the men drafting an import alert—which authorizes the detention of products (that appear to violate the law) at U.S. ports without physical examination—to support an adulteration charge. "Dan and I can work on that," Hilmas said, referring to Dan Fabricant, president and CEO of NPA, who previously oversaw FDA's Division of Dietary Supplement Programs.

That spring, LeDoux capitalized on another opportunity to discuss NDIs at a public meeting hosted by FDA, "Responsible Innovation in Dietary Supplements."

During the May 16, 2019 meeting, Tave reminded industry that "an effective NDI notification process represents FDA's only opportunity to evaluate the safety of a new dietary ingredient before it becomes available to consumers."

FDA's "goal overall is not to [maximize] the number of notifications that we receive," he said, according to a transcript of the meeting. "Rather, our goal is to right-size the process to see that

appropriate notifications are submitted for the products for which they are required."

Several people from industry spoke during the meeting, including LeDoux, who said his company "spent millions of dollars" and entered FDA's "front door" by submitting an NDIN.

"Filing an NDI notification should not be considered too difficult; however, spending those kinds of resources as either a private or public company begs the question, 'We're a good citizen; now what?'" he stated.

"So by helping the government do its job, which is to promote the safety of consumer products in our space, we're looking at ways to work together with the agency to arrest those products that are in commerce that I believe are deficient in not only scope, content, but are, in fact, per se, adulterated because they have not gone through the front door of the FDA," LeDoux said.

NAI and its advocates would reiterate this "adulteration" theme in various correspondence with FDA. In support of their requests that FDA take enforcement action against beta-alanine, Bell and Fabricant provided records to FDA pertaining to the ingredient.

A month after the public meeting, Bell and Fabricant met again with FDA officials, providing "extensive data regarding imports of beta-alanine" between 2017 and May 2019, according to a timeline of events Bell prepared for this story.

During the June 14 meeting, FDA was asked to take action against entities violating the law, based on NAI's NDIN.

Bell and Fabricant made clear the "entire industry was taking a 'wait and see' approach on buying CarnoSyn to see if the FDA was going to do anything," Bell shared via email, in what he said reflected excerpts from a summary of the meeting. "If the FDA would take action, we believed it would have widespread effect on companies' actions in being compliant."

Later that year, in an email sent Oct. 4, 2019 to Tave and another ODSP employee, Sibyl Swift—now NPA's senior vice president of scientific and regulatory affairs—Fabricant attached an Excel spreadsheet of 10 supplement brands marketing beta-alanine and the beta-alanine products for each of the brands: Iovate, ProSupps, Redcon1, JNX Sports, MusclePharm, GHOST Lifestyle, Bulk Supplements, Old School Labs, Vital Pharmaceuticals and Bucked up.

Six of the companies began licensing CarnoSyn beta-alanine in either 2015, 2016 or 2017, though the last purchase by any of them (MusclePharm) was in March 2019, according to Bell. None of the brands responded to requests to comment for this story, whether on their legal basis for marketing beta-alanine in the U.S., or their reaction to NAI's requests that FDA target for enforcement action beta-alanine that hasn't been the subject of an NDIN.

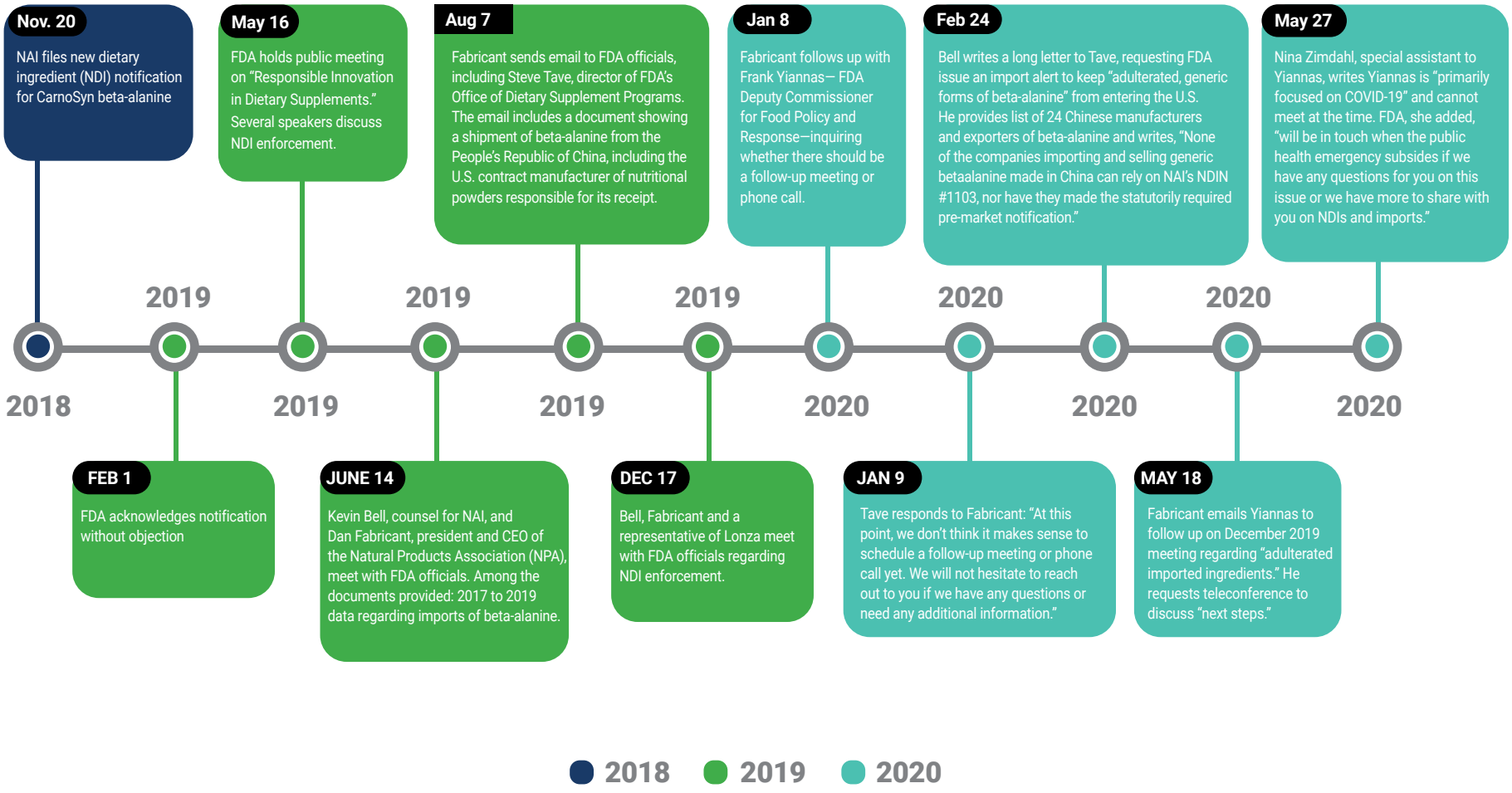
Also on Oct. 4, 2019, in a separate email addressed to Frank Yiannas, former FDA deputy commissioner for Food Policy and Response, Fabricant requested a meeting "to discuss the absence of enforcement on imported new dietary ingredients, which have failed to file an NDI notification." He advised FDA of an upcoming trade show (SupplySide West), where "the show floor is filled with imported knockoffs of NDIs."

"No one at FDA has seen the specifications behind such products or the underlying safety data as is required by statute," he wrote in the email, which also was sent to other FDA employees, including ODSP officials and Douglas Stearn, deputy director for regulatory affairs with the Center for Food Safety and Applied Nutrition (CFSAN).

"This creates a completely unbalanced playing field, effectively sending the message to U.S. companies that successfully submit an NDI that the agency is fine with someone claiming to have the exact same material as a company that submitted, without any evidence to show on that front."

Four days later in an email to Yiannas, Fabricant attached for FDA's consideration a draft import alert/bulletin for beta-alanine coming into the U.S. without an NDIN. It essentially proposed detaining products and bulk dietary ingredients containing beta-alanine that hadn't been subject to an NDIN.

Timeline Related to CarnoSyn Beta-alanine



Sources: FDA records, emails, Kevin Bell, Dan Fabricant

On Dec. 17, 2019, at FDA's campus in White Oak, Maryland, Bell and Fabricant met again with FDA officials to discuss NDI enforcement. According to the two men, Yiannas appeared by phone while several officials appeared in person, including Stearn, Tave and Cara Welch, now deputy director of ODSP, who prior to her tenure at FDA worked at NPA. Also present, according to Bell and Fabricant, was a representative of Lonza, the multinational company with a specialty ingredients segment. Melanie Disa, a spokesperson for Lonza, did not respond to multiple requests for an interview to comment on NDIs.

The conversation related to the broader issue of import alerts, as well as specific companies and NDIs including beta-alanine, Bell and Fabricant confirmed.

While FDA officials expressed interest in the issues, "Steve Tave told us to be patient," Fabricant said. "We had been sending information for over a year specific to the beta-alanine issue and longer than that in a broader context. I think we had demonstrated we had been plenty patient."

Fabricant followed up again with Yiannas on Jan. 8, and though the holiday season had recently ended, he said he "didn't want to lose any momentum on our [December 2019] meeting and addressing the import issue of adulterated NDIs."

"Does it make sense to have a follow-up meeting or phone call in early/mid-February on the matter?" Fabricant asked by email. "In the interim, if there's anything needed from us, please let us know what we can do on our end."

The next day, Tave advised Fabricant he was responding on Yiannas' behalf. "At this point, we don't think it makes sense to schedule a follow-up meeting or phone call yet," he wrote in an email. "We will not hesitate to reach out to you if we have any questions or need any additional information. We very much appreciate your collaboration on this important issue."

On Feb. 24, Bell sent Tave an eight-page letter, requesting FDA enforce against "adulterated" beta-alanine being imported into the U.S. The letter also included two attachments: FDA's Feb. 1, 2019 letter to Bell, acknowledging NAI's NDIN for CarnoSyn beta-alanine; and a list of 24 Chinese manufacturers and exporters of beta-alanine, which identified their addresses, websites, kilograms of beta-alanine exported to the U.S. and total shipments between Feb. 1, 2019 and Jan. 31, 2020.

"Despite being a responsible stakeholder in the dietary supplement industry for over 40 years, since receiving its AKL [acknowledgement without objection] letter from FDA, NAI continues to be negatively impacted by scofflaws exporting adulterated, generic forms of beta-alanine to the U.S. and FDA's lack of enforcement of NDIN requirements," Bell wrote to Tave.

Fabricant followed up again in May with Yiannas concerning "adulterated imported ingredients," requesting a teleconference to discuss "next steps." He also expressed interest in exploring what FDA actions would result from the May 2019 public meeting.

Nina Zimdahl, special assistant to Yiannas, responded Yiannas was "primarily focused on COVID-19" and could not meet at the time.

DANFABRICANT

• • •

Dan Fabricant, the president and CEO of the Natural Products Association, met with FDA officials in December 2019 to discuss new dietary ingredients—including beta-alanine—being imported into the U.S. whose evidence of safety hasn't been reviewed by FDA.

Fabricant said he was joined at the meeting by Kevin Bell, outside counsel to NPA, as well as a representative of Lonza.

She said FDA would "be in touch when the public health emergency subsides if we have any questions for you on this issue or we have more to share with you on NDIs and imports."

In a June 8 email to FDA officials, Fabricant forwarded them an email sent to LeDoux about a company in China selling beta-alanine.

"It's clear from the thread that this company is currently selling their adulterated ingredient made with 'advanced enzyme catalysis, metabolic engineering and biological fermentation technology,'" Fabricant wrote, suggesting such "chemical changes" would require an NDIN based on draft guidance published by FDA in 2016.

Tave thanked him for sharing the information with his agency. Fabricant confirmed this was his most recent correspondence with FDA regarding beta-alanine.

'JUST A RUSE'

Bell is disappointed FDA has not taken enforcement action against beta-alanine, despite all the conversations and records shared with the agency.

"We were made to believe that Director Tave and other senior FDA officials wanted to move forward on several forms of NDI enforcement," the lawyer said in an email. "That apparently was just a ruse."

Tave, FDA's supplements chief, expressed a considerably different perspective. While he acknowledged NAI and its advocates provided many records to FDA, he maintained the information shared with the agency was not tied to violations of law.

"We met with them multiple times whenever they asked to meet," he said in an interview. We reviewed what they sent whenever they asked us to review something, but we don't ave the capacity to do their job."

NDI APPENDIX, PART III: FDA, supplement manufacturer debate NDI import alert request

Aug. 3, 2020 | by Josh Long

About five months ago, attorney Kevin Bell made a written request to FDA on behalf of his client, Natural Alternatives International Inc. (NAI), a manufacturer of nutritional supplements: Issue an import alert for beta-alanine ingredients produced in China, whose identity and safety data has not been reviewed by FDA's Office of Dietary Supplement Programs (ODSP).

NAI, of Carlsbad, California, also supplies beta-alanine to its customers. It's manufactured in Japan and was the subject of a 75-day, premarket new dietary ingredient notification (NDIN) to FDA, based on a safety-related requirement in the Dietary Supplement Health and Education Act of 1994 (DSHEA).

> **"In 25 years, as far as I know, there has never been an import alert under the theory that since one ingredient received an acknowledgement without objection for notification, everybody else is adulterated."**
>
> **—STEVEN TAVE, DIRECTOR, FDA OFFICE OF DIETARY SUPPLEMENT PROGRAMS**

In a Feb. 24 letter, Bell advised an FDA official that several different methods are being used in China to produce beta-alanine, including the use of GMOs to synthesize the ingredient.

"As FDA is well aware, a manufacturing process that utilizes GMOs may cause or increase potential risks for creating contaminants and/or impurities—or worse," Bell wrote in the eight-page letter to Steven Tave, former director of ODSP. "Refusal by manufacturers to provide this information to FDA as required in a NDIN is indicative of a potential health risk."

NAI's lawyer requested the agency "issue an import alert to stop adulterated generic forms of beta-alanine from entering the U.S." An import alert would demonstrate FDA takes "seriously" the NDIN requirement, which would change the "risk profile" of companies in the supplement sector, according to Bell, a partner in Washington, D.C., with Arnall Golden Gregory LLP (AGG).
Robert Durkin is a former FDA official who now practices law at AGG in the nation's capital.
He said in an interview with Bell that an import alert would require making a charge that the ingredient—in this case, beta-alanine—appears to violate the law based on a "technical adulteration" for failure to provide FDA an NDIN.

"It's a much easier burden on the agency to make a technical adulteration charge than it is to make an actual adulteration charge based on safety and risk," said Durkin, who worked as deputy director of ODSP under Tave before leaving the agency in October 2019. Beginning in April 2015, Durkin also served as acting director of FDA's Division of Dietary Supplement Programs—and later the Office of Dietary Supplement Programs—before Tave came on board.

A technical adulteration charge is "just paperwork," Durkin added. "There's no science involved."

Section 801 of the Federal Food, Drug and Cosmetic Act (FD&C or Act) "explicitly authorizes FDA to refuse admission of articles that appear to violate the Act," according to an FDA regulatory procedures manual. "Detention without physical examination," the manual states, "properly places the responsibility for ensuring compliance with the law on the importer."
Commenting on import alerts through a spokesperson, FDA said a firm may be subject to "detention without physical examination" for various reasons, such as if the agency identified a microbiological pathogen in a product, a product contains pesticides that are not permitted or exceed tolerance levels, a firm refused to allow FDA to conduct a foreign inspection, or a product is an unapproved new drug.

FDA confirmed that over a recent 19-month period, it had not issued a new import alert for an imported product for which it did not receive an NDIN.

Marc Ullman, a lawyer in New York who started an FDA practice in 1999, agrees FDA should use an import alert to target novel dietary ingredients that have not gone through the NDIN process.

"FDA's powers at the border are at their greatest," Ullman, of counsel with Rivkin Radler LLP, said in an interview. The agency only must demonstrate "the product appears to violate the Act." He suggested FDA could detain beta-alanine ingredients for which there is no NDIN on file with FDA.

The process, Ullman concluded, is not "resource-intensive. You don't have to leave your desk."

An import alert requires a significant amount of analysis and FDA clearance, responded Tave, the agency's dietary supplements chief. Others involved, for example, include the Office of Compliance with the Center for Food Safety and Applied Nutrition (CFSAN), import authorities within the Office of Regulatory Affairs and Office of Chief Counsel.

"Like everything else at FDA, it's not like firing off a Tweet or a press release," he said in an interview. "That's not to say it's not a useful tool. It's just to say that it's not like flipping a switch."

If FDA detained a "copycat of an NDI" through an import alert, a manufacturer could get back its property by establishing its product doesn't violate the FD&C, Durkin said. Before products enter the market, he explained, manufacturers "should have a basis for knowing that their ingredient doesn't violate the Act and that their ingredient is reasonably expected to be safe."

FDA issued an import alert on kratom, a botanical from Southeast Asia that FDA considers an NDI, when the leader of the Natural Products Association (NPA), Dan Fabricant, directed FDA's then-Division of Dietary Supplement Programs.

Two import alerts currently apply to kratom, including one issued in 2019 (Import Alert 54-15) that remains in effect. Based on the agency's "review of the publicly available information regarding kratom, there does not appear to be a history of use or other evidence of safety

establishing that kratom will reasonably be expected to be safe as a dietary ingredient," FDA stated in Import Alert 54-15.

In advocating for an import alert, Fabricant said his division approached other parts of FDA, including the Office of Compliance and Office of Chief Counsel, explaining justification for the requested action. Unlike a request for an injunction, an import alert does not require involvement from the U.S. Department of Justice (DOJ) and its attorneys, stated Fabricant, who led FDA's supplement division from 2011 to 2014. (Late in 2015, the Division of Dietary Supplement Programs was elevated to an Office).

Is an import alert "the hardest thing the agency does?" asked Fabricant. "Hell no."

Durkin distinguished kratom from "counterfeit" NDIs that haven't been reviewed by FDA. While FDA possessed "information that showed kratom was dangerous," the agency lacks the documentation to demonstrate "these counterfeit ingredients are safe," he said.

An import alert on a copycat NDI, Durkin stated, "would have an exponential impact through the supply chain. If you stop it at the border, think of all the possible harm you're preventing right there."

Tave distinguished kratom from beta-alanine, the subject of an NDIN that FDA acknowledged without objection. By contrast, FDA has never acknowledged an NDIN for kratom, he said. "In 25 years, as far as I know, there has never been an import alert under the theory that since one ingredient received an acknowledgement without objection for a notification, everybody else is adulterated," Tave explained. "This would be unprecedented. It's not that it hasn't happened in six years … it has never happened before."

Fabricant countered that when he worked at FDA, his division brought cases that were unprecedented, including when FDA exercised its mandatory recall authority, pressuring USPlabs—a now-defunct dietary supplement manufacturer prosecuted by DOJ—to voluntarily recall supplements containing aegeline.

Durkin described his former employer as "extremely risk-averse when it considers taking new regulatory pathways."

As an "institution" and as "individuals," FDA is "afraid to lose a fight," he said in a recent interview. "Perfect has become the enemy of good."

L-TRYPTOPHAN CRISIS

Durkin questioned what other rules companies are breaking if they fail to notify FDA before marketing an NDI and don't have a legal basis for putting their ingredient into commerce. Are they violating cGMPs (current good manufacturing practices)—FDA regulations intended to ensure supplements are made to quality standards, contain what's declared on the label and are free of contaminants?

The intent of the FD&C is to "protect people up front, not just react" when consumers are harmed, said Bell, who argued he presented a compelling case to FDA of potential harm from an NDI. While NAI provided FDA evidence of safety at certain levels for its ingredient, that doesn't mean other manufacturers can rely on that evidence because it's unknown how they are producing the ingredient and what bacteria strains they're using, he added.

Tave agreed the NDIN requirement is intended to prevent harm, but he stated his agency must "establish every element of a violation" per DSHEA. Tave acknowledged Bell's letter to him shows firms besides NAI are importing beta-alanine into the U.S., and he conceded the ingredient is being sold in the U.S. However, he added, "The letter does not make a case that any specific firm is doing so unlawfully."

Bell and another attorney pointed to the L-tryptophan crisis in 1989 to highlight the potential harm to consumers if an ingredient undergoes a change in a manufacturing process. U.S. authorities traced an illness known as eosinophilia-myalgia syndrome (EMS) to contaminated L-tryptophan, an amino acid sold as a supplement.

The Japanese manufacturer likely responsible for the illnesses, Showa Denko K.K., produced its ingredient "through a fermentation process involving Bacillus amyloiquefaciens," according to a 1994 article published in the *Cornell Journal of Law and Public Policy*. "In December 1988, Showa Denko began to use a new, genetically-altered strain of Bacillus amyloiquefaciens called Strain V, and in 1989, reduced the amount of activated carbon in the purification process by one-half. Between October 1988 and June 1989, some batches bypassed a filter which removed heavier chemicals. These potentially contaminated batches went through the purification process with other batches."

In certain epidemiological studies, FDA said in a 2001 paper, the vast majority of EMS cases (more than 95%) were traced to L-tryptophan supplied by Showa Denko. The agency, however, suggested "L-tryptophan-associated EMS was caused by several factors and is not necessarily related to a impurity in a single source of L-tryptophan."

In his letter to Tave, Bell cited the L-tryptophan calamity to highlight the potential harm to consumers if ingredient suppliers do not disclose their manufacturing processes to FDA in an NDIN.

"It was later shown that changes to the manufacturing protocols made by this firm resulted in the production of many impurities that were not found in L-tryptophan manufactured using previously established protocols," Bell wrote to Tave, in his request for the agency to issue an import alert. "One of these contaminants, a dimer of amino acid L-tryptophan, was strongly related to the outbreak of EMS. NAI knows that similar, but slightly different, means of production for beta-alanine can result in the presence of both characterized and uncharacterized contaminants."

'CONNECT THOSE DOTS'

In response to questions for this article, FDA through a spokesperson said Bell neither specified the harmful manufacturing methods for beta-alanine nor identified the companies using them.

"And even though the Bell letter names a number of entities manufacturing and exporting beta-alanine from China to the United States, it does not offer any evidence to indicate where those ingredients are going—including whether they are destined for processing into dietary supplements over which FDA has jurisdiction," the agency wrote in an email.

Per the law, the burden of proof falls on FDA to establish a dietary supplement is adulterated, the agency added. "I can't bring charges against a product for violating the dietary supplement rules if there's no evidence that the product is being used in a dietary supplement," Tave explained in the first of two phone interviews.

STEVE TAVE

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Steven Tave oversees FDA's Office of Dietary Supplement Programs. A long-time FDA official, he was named ODSP's first permanent director in November 2016 after serving as acting director beginning in March 2016.

Addressing the level of detail FDA is seeking from an outside party that could support an enforcement action, Tave likened the process to writing a brief to a court in which the judge in her order essentially adopts verbatim the petitioning lawyer's motion. He practiced law as a litigator in FDA's Office of Chief Counsel and in the private sector.

"Give me all of the pieces of evidence," Tave said. "Connect those dots to show why these products are in violation and why that supports

the use of the agency's resources as a public health matter, where we need to prioritize to do something right now."

Bell and Fabricant asserted they provided FDA volumes of records over a period of more than a year—many of which are referenced in a previous article—and offered to share additional information.

Until a reporter shared FDA's comments for this story, Bell said he was unaware of its position that he had not provided the agency adequate information. "While FDA has more than enough data to meaningfully pursue NDI enforcement, we were consistently instructed not to inundate Director Tave with too much, but rather to 'spoon feed' him with limited amounts of information to avoid overwhelming ODSP and delaying any enforcement efforts," he explained by email. "Anything that was pared down was pared down at the request of FDA," Bell added in one of several interviews. "That wasn't our decision."

Among the information Bell said was provided to FDA:

- The identity of Chinese manufacturers of beta-alanine over several years, including their addresses, import records of individual shipments and the recipients of shipments in the U.S.;
- The names of U.S. ingredient suppliers, contract manufacturers and companies selling finished brands that incorporated generic beta-alanine into their supplements.

"These documents and information were provided in face-to-face meetings, telephone calls and numerous correspondence," Bell stated. "In meetings at FDA with Director Tave and other senior FDA officials, we described specific forms of manufacturing methods that included the use of unidentified bacterial strains being used at many Chinese facilities. These strains included E.coli and fermentation methods that FDA had no insight into. The very concept that the agency would not pursue enforcement of the FD&C because they didn't have every piece of information in advance is not true."

NAI, Bell added, doesn't have the authority to conduct a foreign inspection of a firm to demand disclosure of its production process, such as use of GMOs. "That is FDA's job," he said. "Our job was to 'lead the horse to water.'"

In a recent interview, Tave said no one at FDA "instructed" NAI's advocates to do anything. While he acknowledged FDA was given "mountains and mountains of information," he suggested the information could not help achieve "the result that they are demanding" because it did not show violations of the law.

"They know we have limited resources," he said. "We can't just spend all of our time combing through information, looking for a violation when the firm that's complaining hasn't taken the time to do that." He described the records given to FDA as "a document dump."

"Here are piles and piles of spreadsheets, bills of lading—things that we don't have the expertise to review—things that were not connected to a violation," Tave said. "We met with them multiple times whenever they asked to meet. We reviewed what they sent whenever they asked us to review something, but we don't have the capacity to do their job."

He added, "We work with industry and we will always work with industry. We do not work for industry."

'SECOND COMER' INGREDIENTS

In an interview, attorney Scott Bass explained why, in his opinion, a "second comer" or "follow-on product" to an NDIN must also notify FDA. "The law requires all follow-on manufacturers to file as well, and … the single reason is L-tryptophan," said Bass, a partner with Sidley Austin LLP, who heads the firm's Global Life Sciences team. "There can be two companies making the same ingredient, and one cheats on filtration. One uses a different chemical for extraction."

How can FDA know whether the second-comer is "using cheaper processes and manufacturing" in violation of cGMPs, Bass asked? "You don't unless you file an NDIN saying, 'Here's our basis for safety.'"

While a copycat compound may claim to be the same dietary ingredient as one successfully acknowledged by FDA, "have you shown it's the same?" Fabricant asked.

Frank Jaksch Jr. is co-founder and executive chairman of the board of directors of ChromaDex Corp., a nutraceutical company that on two separate occasions successfully navigated the NDIN process for Niagen, also known as nicotinamide riboside (NR)—a member of the vitamin B family promoted to boost nicotinamide adenine dinucleotide (NAD+). He agreed a "piggyback compound" poses many unanswered questions about the production of an ingredient, such as whether the two ingredients have different impurities.

"If something is not chemically identical, then all bets are off," he said in an interview.

Sibyl Swift, a former FDA official, concurred with that assessment. NPA announced in January that Swift joined the trade group as senior vice president of scientific and regulatory affairs.

"Unless you're following the exact same process with the exact same chemicals, reagents, then it's something different and it was manufactured differently," said Swift, whose last job at FDA was associate director for research and strategy within ODSP. "And you should come in and notify [FDA] for it—even if the end product looks the same."

SECTION 413(A)(1)—NDIN EXEMPTION

That doesn't mean FDA assumes NDIs in commerce that it hasn't reviewed are all adulterated. In its emailed response to questions, FDA cited a "novel misconception" in recent years that an acknowledged NDIN "entitles the notifier to market exclusivity via on-demand enforcement against potential competitors." The agency referenced Bell's letter, in which the lawyer concluded "NAI or its authorized agents are the only entities allowed to import and distribute beta-alanine without violating the FD&C Act."

"The law doesn't support the argument that having an acknowledged NDI notification is the only way to lawfully market a dietary supplement," Tave explained.

FDA, for example, cited Section 413(a)(1) of DSHEA. That section exempts an NDI from a premarket notification to FDA if the "supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered."

Dietary ingredients marketed before Oct. 15, 1994 in the U.S. are not considered "new" and also are exempt from the notification requirement.

The NDIN "requirement exists except for where it doesn't," Tave said in a second interview. "It doesn't say, 'Everybody must submit an NDI notification unless.' It says first that if you're an article present in the food supply, that satisfies Section 413."

And if FDA is going to move against a firm for violating the obligation in the law to file an NDIN, the agency must show the product is "in commerce unlawfully because it's subject to the requirement," Tave added. "And how can we show that it's subject to the requirement if we don't know if it's exempt or not?"

'FDA HAS RESOURCE' TO MAKE INQUIRIES

Addressing FDA's comments about "market exclusivity," Bell questioned how there could "be any misconception, novel or otherwise, centered around 'on-demand' enforcement when there has been no enforcement."

"What should a notifier with an AKL [acknowledgement] letter like NAI expect from FDA after investing millions of dollars to submit a quality NDIN and then trying to assist FDA in identifying the companies that knowingly choose to ignore the" FD&C, he asked. "Can they expect anything from FDA?"

Clearly, FDA is free to make inquiries to U.S. marketers of beta-alanine and Chinese exporters of the ingredient. If FDA believes an ingredient is an NDI, "it's perfectly appropriate" for the agency to fire off a letter to companies marketing that ingredient, Steve Mister, president and CEO of the Council for Responsible Nutrition (CRN), said, commenting generally on NDIs and not beta-alanine specifically.

The agency could ask questions, such as whether the ingredient was marketed before 1994, whether it's in the food supply and not chemically altered, and whether the company has submitted an NDIN to FDA or done a GRAS (generally recognized as safe) self-affirmation, he added in an interview. "At some point, my part of helping [FDA] had to

have a natural stopping point," and FDA needed to start its investigation, Bell said.

John Venardos is a global regulatory and government affairs consultant, who previously held high-level positions with Bodybuilding.com and Herbalife. Asked about the NAI case, he said FDA has an obligation "in this situation and in similar situations to make a determination" through cGMP inspections, for example, whether an ingredient is violative of the law or identical to a previously acknowledged NDI.

"To simply say they don't have enough information is not adequate," he said in an interview. "FDA has resource—both domestically and internationally, and through the customs authorities, to conduct inquiries."

While Tave acknowledged FDA could write letters letter to exporters of beta-alanine, he didn't disclose whether the agency has done so. "There's no requirement that a company answer a non-statutory demand from the agency," he said. "If we have sent letters like this, and received responses or not, we wouldn't be able to discuss those because we only discuss the compliance status of a firm with that firm."

NDI APPENDIX, PART IV:

FDA leaves open possibility of NDI enforcement against Chinese-produced beta-alanine

Sept. 29, 2020 | by Josh Long

An FDA official responsible for overseeing the dietary supplement market has not ruled out the prospect that his agency would take enforcement action against an ingredient manufactured overseas and incorporated in sports nutrition products. But he didn't commit to such action either.

The debate whether FDA should enforce against beta-alanine manufactured in China has sparked a war of words (see page 34) between Steven Tave, former director of the Office of Dietary Supplement Programs (ODSP), and some industry advocates, including former FDA officials who were once charged with his duties.

People close to supplement manufacturer Natural Alternatives International Inc. (NAI) have called for FDA to enforce against Chinese-produced beta-alanine, whose identity and safety has not been vetted by the agency through a new dietary ingredient notification (NDIN). In February 2019, FDA acknowledged without objection NAI's NDIN for CarnoSyn beta-alanine.

"We've never said that we wouldn't take action here," Steven Tave, former director of the Office of Dietary Supplement Programs (ODSP), said in an interview.

FDA COULD ISSUE IMPORT BULLETIN

For example, Tave said FDA has the authority to issue an import bulletin. Such a bulletin could advise field staff to collect samples of beta-alanine for review of labels and laboratory tests, according to former FDA officials familiar with import operations. If these reviews established an appearance of a violation of law, that could prompt FDA to detain the sampled products and issue an import alert to make it easier to identify such products coming into the U.S. Ultimately, FDA could refuse admission of the products found to be violative of the law, choking off the U.S. supply of beta-alanine sourced from China.

Tave, though, stopped short of saying his agency issued an import bulletin. Import bulletins are not public, he said; and, according to an FDA regulatory procedures manual, import bulletins are generally only valid for 90 days.

"It's entirely possible in this case that we've done something that we've been asked to do, but we're just not able to say that we've done it," Tave said. "I'm not saying that we have or haven't, but that's out there."

Even if FDA issued an import bulletin, it doesn't mean the agency will eventually issue an import alert for certain beta-alanine ingredients

produced in China. Products identified in an import alert on a "red list" are subject to detention without physical examination, based on FDA's determination that they appear to violate the law.

"FDA does not detain products simply because they are subject to an import bulletin," said Richard Chiang, a former FDA official, whose 13-year experience at the agency included working as a field investigator. "For FDA to legally detain an imported product, the agency must find an appearance of a violation of FDA law. FDA can detain a shipment without physical examination if the product has a history of one or more violations."

FDA hasn't said it won't issue an import alert in response to NAI's request, according to Tave. "The only fact on the record is that we haven't issued one yet," he explained.

According to FDA's response to a Freedom of Information Act (FOIA) request submitted by Natural Products Insider, the agency has not detained any products containing beta-alanine at the U.S. ports in recent years. Asked to identify such products detained between Jan. 1, 2018 and Aug. 31, 2020, a FOIA officer responded that FDA's "Office of Regulatory Affairs Division of Import Operations" could not "locate any records responsive" to the request.

People close to NAI have argued FDA should issue an import alert for beta-alanine, since Chinese manufacturers have not submitted an NDIN to FDA. The notification requirement is part of the Dietary Supplement Health and Education Act of 1994 (DSHEA), which amended the Federal Food, Drug and Cosmetic Act (FD&C).

FORMER ODSP OFFICIAL: FDA COULD DETERMINE IF EXEMPTION APPLIES

Tave said NAI has failed to establish beta-alanine produced in China is in violation of the law. An NDI, he explained, is exempt from the notification requirement in DSHEA if it had been present in the food supply as an article used for food in a form not chemically modified.

FDA need only show an appearance of a violation of law to detain products, some former FDA officials countered. If FDA detained a "copycat of an NDI" through an import alert, a manufacturer could get back its property by establishing its product doesn't violate the FD&C, said Robert Durkin, of counsel in the FDA and healthcare practices with the law firm Arnall Golden Gregory LLP (AGG). Durkin previously served as deputy director of ODSP under Tave. Before products enter the market, Durkin explained in a previous article for this series, manufacturers "should have a basis for knowing that their ingredient doesn't violate the Act and that their ingredient is reasonably expected to be safe."

Durkin said FDA could figure out whether the food supply exemption in Section 413(a)(1) of DSHEA applies to beta-alanine marketed in dietary supplements. In fact, FDA's own records show the agency routinely makes such determinations. For instance, in several warning letters related to substances FDA considers NDIs subject to the notification requirement—including DMBA (1,3-Dimethylbutylamine), DMHA (1,5-Dimethylhexylamine) and Acacia rigidula—FDA concluded the ingredients were neither old dietary ingredients nor met the 413(a)(1) exemption.

"To address 413(a)(1) requires checking various databases to ascertain if there is any indication that the NDI is present in the food supply as an article used for food in a form in which the food has not been chemically altered," Durkin explained by email. "If checking these databases and depending on the results is sufficient enough to support the agency issuing a warning letter or conducting a seizure, how can it not be sufficient enough to support a detention? To the extent a party feels their product has been improperly detained, there are well-established FDA guidelines for companies to follow in making that determination."

Asked to respond to his former colleague's remarks, Tave said AGG has neither identified specific beta-alanine-containing dietary supplements for FDA to review nor advised the agency that the beta-alanine manufactured in China is "materially different" than NAI's ingredient.

"We could do [database] searches," Tave said. "They're resource-intensive. They're time-intensive, but what would they show? They're not going to create a legal violation where we haven't seen one."

FDA HAS AMPLE 'LOW' AND 'MIDDLE-HANGING FRUIT'

Rick Collins is a partner in Mineola, New York, with the law firm Collins Gann McCloskey & Barry PLLC. Collins, who often counsels sports nutrition companies, said FDA could take enforcement action against beta-alanine ingredients that don't meet the food supply exemption in Section 413(a)(1). But he noted "countless products" are on the market "that could be the subject of NDI notifications or should be the subject of NDI notifications."

"In an age when marketers are making claims that their supplements will prevent or cure COVID-19, and when some CBD marketers are making disease claims right and left … there's so much low-hanging and middle-hanging fruit that by the time FDA got around to looking at beta-alanine—or many other ingredients that are not causing deaths and destruction on a widescale basis—they're probably not so worried about it," the lawyer explained via email. "But that feeds into the perception by many in industry that FDA's resources are not sufficient to go after other than the most egregious offenders."

In a letter dated Feb. 24, NAI requested FDA issue an import alert for generic forms of beta-alanine manufactured in China. Kevin Bell, a partner with AGG who wrote the letter on behalf of NAI, attached a list of companies manufacturing beta-alanine in China and exporting the ingredient to the U.S. Tave said FDA received the letter before COVID-19 materialized in the U.S., but at a time when public health agencies were already aware of the emerging global pandemic.

NAI "sent us a letter at the end of February," Tave said. "They didn't immediately get the exact response that they wanted while there's a worldwide pandemic going on. And then they ran to the press to put pressure on us."

Asked to respond to Tave's comments, Bell said it's been over 18 months since FDA acknowledged NAI's NDIN for its ingredient, CarnoSyn beta-alanine. He also pointed out NAI and its reps corresponded with FDA numerous times over a period of more than a year. But in 2020, communications cooled between FDA officials and people close to NAI.

Beginning in January, Tave, Frank Yiannas, former deputy commissioner for Food Policy and Response, "and other senior FDA officials have refused to have any further meetings with us and quit returning phone calls," Bell said via email. "I believe NAI is entitled to know if FDA has taken or intends to take action and when."

Dan Fabricant, president and CEO of the Natural Products Association (NPA), also has requested FDA take action against so-called copycat ingredients to successfully notified NDINs, including beta-alanine manufactured in China. He addressed the prospect that FDA may ultimately take action against beta-alanine, as NAI requested.

"It's one thing to say government's bureaucratic," said Fabricant, who previously served as director of the Division (now "Office") of Dietary Supplement Programs, in an interview. "You're talking years here. You can do a lot in years."

FDA NOT AWARE OF ACUTE SAFETY CONCERNS

FDA has received many adverse event reports (AERs) linked to supplements containing beta-alanine, including CarnoSyn beta-alanine, according to FDA records obtained by Natural Products Insider. But consumers who ingested the supplements may have underlying health conditions, and products associated with AERs typically contain multiple ingredients.

For example, a consumer using a GNC sports nutrition product reported in April 2015 that his "face was on fire." But according to the AER, doctors disclosed the patient was "borderline diabetic." The label disclosed the product contained well over 30 ingredients, including beta-alanine. AER records don't prove a specific product or ingredient caused an illness, according to FDA and other experts.

"If we saw something that concerned us from a safety perspective, we would be acting as quickly as we could," Tave said, when asked about a reporter's presumption that FDA would have acted against beta-alanine if it identified a major safety concern.

He added he's not "aware of any" acute safety concerns with beta-alanine. "Based on what we have looked at, I haven't seen anything that rises to the level of a safety concern that would cause us to take action," Tave said.

NAI for years did not raise safety concerns about beta-alanine in patent infringement lawsuits against competitors that cost the company millions of dollars, according to Tave. The company only raised the issue in 2019—after obtaining its acknowledgement letter from FDA for CarnoSyn beta-alanine—and even then, NAI failed to identify a "tangible safety concern," he contended.

NAI provided "innuendo like 'genetically modified' and 'coming from China,' but never actually gave us any information about how a product was manufactured and what it is about a product that renders it unsafe," Tave said. "It's quite possible that these products are on the market lawfully." Bell disagreed with Tave's assessment. For starters, he said a company suing for patent infringement isn't required by the U.S. Constitution to raise a safety issue. "I find it curious that Director Tave has spent so much time reviewing prior patent infringement lawsuits filed by NAI … as opposed to the job he is paid to do," Bell said.

The lawyer reiterated his previous observations in this series that FDA does not know how generic forms of beta-alanine are manufactured in China, posing risks that could lead to a health crisis. He highlighted the 1989 outbreak of eosinophilia-myalgia syndrome (EMS) among users of L-tryptophan, an amino acid sold as a supplement, and linked to a company using "recombinant technologies." "Similar technologies deployed by Chinese firms making beta-alanine without going through the NDI process is rife with unnecessary risk," Bell cautioned.

NAI MAKING 'CORNER-THE-MARKET MONOPOLY PLAY'

For this series of articles, Natural Products Insider reached out to several Chinese manufacturers of beta-alanine, as well as U.S. marketers of the ingredient—none of whom responded to requests for comment on the record.

A senior executive of a U.S.-based marketer of beta-alanine in supplements, who spoke on condition of anonymity, argued the ingredient isn't subject to an NDIN because it's a grandfathered substance under DSHEA. An ingredient marketed in the U.S. before Oct. 15, 1994 is not considered an NDI and presumed safe.

"You don't need to go through all that extra work with the government to do an [NDIN] when this is an old dietary ingredient clearly," the source proclaimed.

A book ("Pre-DSHEA List of Old Dietary Ingredients") developed by NPA identifies old or grandfathered dietary ingredients, but beta-alanine is not on the list. Fabricant wrote the book and compiled the list, along with an NPA colleague at the time, Corey Hilmas, a medical doctor and former FDA official who now works at KGK Science. The book, which NPA announced in December 2017, contains 850 old dietary ingredients, based on such documentation as catalogs and bills of lading, Fabricant said.

"Could there be other sources?" he asked. "Sure, but someone put it forward."

NAI is attempting to leverage federal regulations to monopolize the supply of an ingredient, according to another senior executive with a U.S.-based company that markets beta-alanine in sports nutrition products. This person only agreed to speak on condition of anonymity.

"Just looking at it from a business perspective, it seems like the typical corner-the-market monopoly play," said the executive, commenting on NAI's request for FDA enforcement action against the Chinese companies. "Basically, you can't sell this ingredient unless you come through us. And we're going to try to use the regs as our legal basis for doing so."

Bell and Fabricant countered other ingredient manufacturers are free to submit an NDIN to FDA for their beta-alanine. The senior executive, however, questioned whether Chinese manufacturers need to submit an NDIN to FDA if their ingredient is made the same way as NAI's.

"The whole purpose of the NDI process is to notify FDA of the new ingredient, show its safety and acceptable levels of use in humans," said the source, who added requiring other companies to invest in the process for the same ingredient is "nothing more than a duplicative process" if the NDI can be shown safe.

On the other hand, people close to NAI emphasized without FDA's review, there is no way to ascertain how beta-alanine is being produced in China and whether it poses potential safety concerns.

MAJOR CHINESE MANUFACTURERS OF BETA-ALANINE NOT INSPECTED BY FDA

FDA does conduct foreign inspections for compliance with its regulations, including cGMPs (current good manufacturing practices) applicable to dietary supplements. Based on Tave's remarks and an analysis of FDA inspection records, there is no indication the agency has identified significant problems with beta-alanine produced in China. In fact, none of the major Chinese exporters of beta-alanine have been inspected by FDA in recent years, Natural Products Insider learned through a review of FDA inspection records and U.S. import records involving beta-alanine.

Over roughly the last 2 ½ years ending Aug. 31, 2020, FDA has inspected 17 firms in China for compliance with cGMPs, according to FDA records obtained through a FOIA request. None of the inspections were conducted in the first half of 2020.

In an attachment to the Feb. 24 letter to Tave, Bell identified 24 Chinese manufacturers and exporters of beta-alanine between Feb. 1, 2019 and Jan. 31, 2020. Combined, the top three exporters alone shipped more than 1 million kilograms of beta-alanine, according to data in the attachment sourced from the PIERS TI import database—a subscription service maintained by IHS Markit. However, none of those top producers were inspected by FDA in recent years for compliance with cGMPs, FDA inspection records show. Based on import records he reviewed, Bell only recognized one of the firms on the list, Innobio Corp. Ltd., which he said was responsible for a few imports of beta-alanine in 2016-2017. FDA inspected the firm in August 2018 and issued a document known as a Form 483 for alleged regulatory violations, according to FDA records. However, Natural Products Insider was unable to immediately obtain a list of the alleged infractions since they were issued in paper form, and the company could not be reached through its website for comment.

TAVE: NAI VIOLATED THE LAW ITSELF

In the last of several interviews conducted for this series of articles, Tave seemed to find irony in NAI's pleas that FDA enforce against other manufacturers of beta-alanine that have not submitted an NDIN to FDA. He said CarnoSyn beta-alanine was on the market for years before FDA received its notification from NAI.

"If you believe the legal theory that the Arnall Golden [Gregory] law firm has put forward to us, if you agree with their proposition, then their client was marketing an unlawful ingredient for multiple years," Tave said. "So either their client was engaged in prohibited behavior under the Food, Drug and Cosmetic Act—at least from 2016 and likely before until early 2019—or there's no basis for the action that they're insisting that we take right now."

Bell acknowledged that as of April 2015, NAI imported and sold CarnoSyn beta-alanine. However, he noted FDA's objection rate to NDINs at the time was immense—around 75%. Industry complained at the time "there was not enough communication or back-and-forth with the FDA," he explained.

NAI filed its NDIN with the agency in November 2018, a little over two years after FDA published its second draft NDI guidance in August 2016. "This is not some 20 years of violating the Food, Drug and Cosmetic Act," Bell said. "There was no NDI for beta-alanine until CarnoSyn came around … [and] the FDA acknowledged it."

He dismissed the notion that NAI's request has no basis in the law. "We have an NDI," he said. "We've identified entities that the FDA doesn't even know about using speculative—at best—methods for manufacturing beta-alanine. And yet the FDA seems to fight against doing anything.

"At this point," NAI's lawyer added, "I feel there's an active fight against NDI enforcement."

'STATUTE TIES OUR HANDS'

Tave suggested enforcing the NDIN requirement in DSHEA is a priority for his office.

"Increasing our ability to enforce the NDI provisions is definitely a focus for us," he said. "There's been a lot that we've been working on both publicly and privately behind the scenes, but the reality … is that the statute ties our hands. It's just not fair to tie both of our hands behind our back and then have people complain that we're not punching hard enough." Tave concluded, "We're playing the hand we're dealt."

NDI APPENDIX, SIDEBAR:

Former FDA officials clash with supplement chief over NDI enforcement

by Josh Long

In this four-part series of articles, Steven Tave, former director of FDA's Office of Dietary Supplement Programs (ODSP), has come under fire for not enforcing against generic forms of beta-alanine manufactured in China, whose identity and safety has not been reviewed by FDA. Two of the people quoted frequently in this series, Robert Durkin and Dan Fabricant, were previously charged with carrying out the agency's supplement oversight duties now handled by Tave.

Durkin currently works for a law firm that has represented supplement manufacturer Natural Alternatives International Inc. (NAI), whose new dietary ingredient (NDI), CarnoSyn beta-alanine, was successfully acknowledged by FDA in 2019 after the agency reviewed its safety profile. The NDI notification (NDIN) requirement is a crucial component of the 26-year-old Dietary Supplement Health and Education Act of 1994 (DSHEA).

In an interview, Tave questioned why Durkin and Fabricant, while overseeing the market for dietary supplements, didn't enforce against so-called copycat ingredients to successfully acknowledged NDIs.

"If this is such an obvious and easy outcome, if it's so easy for us to take action against anybody as soon as one party has an NDI notification acknowledged, if it doesn't involve anyone lifting a finger, why didn't it happen during Fabricant's four-year tenure at FDA?" Tave asked. "Why didn't it happen when Durkin was here four years?"

From 2011 to 2014, Fabricant served as director of FDA's Division of Dietary Supplement Programs. Since then, he has been president and CEO of the Natural Products Association (NPA), a trade association whose board chairman, Mark LeDoux, founded NAI and is the company's CEO.

In April 2015, Durkin began serving as acting director of the Division of Dietary Supplement Programs. Following FDA's creation of an "Office of Dietary Supplement Programs," he served a stint as acting office director. After Tave came on board, Durkin became the permanent deputy director until leaving FDA in the fall of 2019 to join Arnall Golden Gregory LLP (AGG).

Tave observed Durkin and Fabricant held leadership roles at FDA's supplement division and/or office for nearly a decade after the agency published its first NDI draft guidance in 2011.

If enforcement against copycat NDIs is "straightforward" and "easy, what's their excuse for not doing it during that decade?" Tave asked, referencing Durkin and Fabricant. "You can't take both sides of the issue and now say, 'Oh, it's simple. FDA should do this.' This law has been around for 25 years. Again, we're talking about something that's never been done. There's a reason for that.

"If they were so good at their jobs and this is such an easy thing to do, one of those things can't be true," Tave added. "Either, it's not that easy, or they weren't that effective."

Asked to respond to Tave's remarks, Fabricant said, "I'll take my track record over his track record any day."

During his tenure, Fabricant explained, he issued NDI guidance in response to a mandate imposed by the Food Safety Modernization Act (FSMA). The supplement division also took actions against the sports nutrition stimulant DMAA, which culminated in litigation between FDA and Hi-Tech Pharmaceuticals Inc. And FDA moved against USPlabs LLC—a now defunct supplement manufacturer successfully prosecuted by the U.S. Department of Justice—in response to an outbreak of hepatitis linked to supplements containing potentially hepatotoxic aegeline.

Tave "hasn't faced nearly the public health threats that I faced in the office and had to handle," Fabricant said. "He has an office. I had a division."

Asked whether he considered enforcing against copycat ingredients, and if so, why he didn't,

Fabricant responded FDA issued an import alert on kratom—an NDI—while he was at the agency. Unlike beta-alanine, FDA has not acknowledged an NDI notification (NDIN) for kratom.

DAN FABRICANT

Dan Fabricant, the president and CEO of the Natural Products Association, served as director of FDA's Division of Dietary Supplement Programs from 2011 to 2014.

"This is a straight up-and-down violation of the law," Fabricant proclaimed, referring to the information shared with FDA regarding beta-alanine. That's not how Tave sees it. According to him, NAI hasn't demonstrated manufacturers of beta-alanine are in violation of the law. What's more, he said, FDA has never issued "an import alert under the theory that since one ingredient received an acknowledgement without objection for a notification, everybody else is adulterated."

Fabricant suggested Tave's role is to evolve the office program.

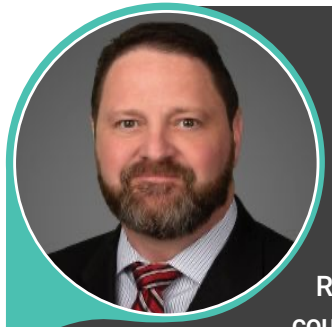
"His job, he thinks, is to give his opinion on the statute, not to exercise the authorities he has at his disposal and find a way to make them work," he said. "As a citizen of the United States, in terms of protecting the public health, that should scare people."

Durkin also addressed Tave's remarks. He said he became acting director of the Division of Dietary Supplement Programs at a time when the program was under criticism by the media, including prominent U.S. newspapers, for failure to oversee dietary supplements.

"To make matters even worse, relationships with outside stakeholders were just about nonexistent, if not adversarial," Durkin said via email. "To be blunt, this [was] a pretty dark time for the program."

He said he was enlisted to "quickly fix a part of FDA that was failing to adequately protect the public health."

"We immediately began mending relationships with outside stakeholders and supporting enforcement actions," Durkin said, citing as examples injunctions, seizures and warning letters. Addressing Tave's specific remarks, he rejected the idea that the action requested of FDA—specifically an import alert for forms of beta-alanine that have not been subject to an NDIN—is "easy" or "obvious." However, Durkin said "more than enough information was provided to make a decision one way or another," and he didn't "understand why it took so long for stakeholders to receive meaningful, honest feedback."



ROBERT DURKIN

Robert Durkin is of counsel in the FDA and healthcare practices of Arnall Golden Gregory LLP. He previously served as deputy director of FDA's Office of Dietary Supplement Programs.

The requested import alert "should be a relatively low drain on agency resources while having the potential for dramatic and positive downstream impacts on the quality and safety of dietary supplements," Durkin concluded. "I'd like to think that if an external stakeholder brought something like this to me while I was making the decisions, that I would have done something positive with it."

NDI APPENDIX, SIDEBAR:

GRAS self-affirmation poses challenges to NDI enforcement

FDA suggested the prevalence of a regulatory pathway known as GRAS (generally recognized as

safe) self-affirmation complicates its efforts to enforce compliance with a new dietary ingredient notification (NDIN) requirement in the Dietary Supplement Health and Education Act of 1994 (DSHEA).

Manufacturers of conventional food have an option to inform FDA of their determination that an ingredient is GRAS, which provides the agency an opportunity to review the materials and raise issues that question the firm's conclusion. On the other hand, the GRAS self-affirmation process does not involve agency review.

Marianna Naum, an FDA spokeswoman, said, "[T]he use of a dietary ingredient in a dietary supplement is not eligible for GRAS." In reality, though, manufacturers may add an ingredient to conventional food through GRAS self-affirmation, then incorporate the substance into a dietary supplement without notifying FDA.

By following the regulatory pathway above, a supplement manufacturer may conclude a new dietary ingredient (NDI) is not only safe but exempt from a notification requirement in DSHEA. The exemption in Section 413(a)(1) of DSHEA covers NDIs that "have been present in the food supply as an article used for food in a form in which the food has not been chemically altered."

During a 2017 public meeting hosted by FDA, the leader of the United Natural Products Alliance (UNPA), Loren Israelsen, estimated the ratio of GRAS affirmations to NDINs at 6 or 7 to 1, following the passage of DSHEA.

FDA's Office of Dietary Supplement Programs (ODSP) has received approximately 1,140 NDINs since the program's inception, according to Lindsay Haake, an agency spokeswoman, in a July 9 email. The notification requirement is intended to give FDA the opportunity to review the identity and safety of an NDI.

A proposal from Washington, D.C.-based attorney Scott Bass and physician Pieter Cohen of Harvard Medical School would largely gut the exemption in Section 413(a)(1)—what the authors described as a "loophole" that has "swallowed the law." Manufacturers of supplements have used the exemption "to justify not submitting safety data to the FDA," according to Cohen and Bass, a partner with Sidley Austin LLP, who helped negotiate DSHEA.

DSHEA "was written with the expectation that this exemption would be used infrequently, but its language is not sufficiently clear," the two men wrote in a paper published in December 2019 in the *New England Journal of Medicine*. "The exemption was not meant to apply to new chemicals, combinations or synthetic compounds. Nonetheless, the FDA has appeared to condone the use of this loophole to permit countless substances to be introduced in the absence of submitted safety data."

NAI GRAS AFFIRMATION

Firms reliant on GRAS self-affirmation don't have to "notify FDA that they are doing so or share the basis for their conclusion," FDA noted in an email to Natural Products Insider. But some manufacturers that go through the process publicize the information. For instance, on April 11, 2017, Natural Alternatives International Inc. (NAI), a manufacturer of nutritional supplements, announced receiving GRAS affirmation regarding its SR CarnoSyn beta-alanine.

On its website, NAI described the ingredient as "an advanced delivery form of CarnoSyn, which delivers higher dosing levels of beta-alanine, and is proven to provide benefits for both wellness and healthy aging." The company said the GRAS affirmation would allow it to broaden its "product offerings beyond the sports nutrition space and focus on the food and beverage industries, including medical and other fortified food products."

The announcement was made more than 18 months before NAI submitted its NDIN (Nov. 20, 2018) for CarnoSyn beta-alanine, which is distinguisable from SR CarnoSyn beta-alanine.

NAI used the GRAS self-affirmation process for SR CarnoSyn beta-alanine, confirmed Kevin Bell, outside counsel to NAI and a partner with Arnall Golden Gregory LLP (AGG) in Washington, D.C. Naum, the FDA spokeswoman, verified the agency had no records of a GRAS submission for beta-alanine in its database.

In a letter to Steven Tave, former director of ODSP, Bell requested FDA issue an import alert, detaining beta-alanine manufactured in China that hasn't been subject to an NDIN. But FDA suggested some manufacturers of beta-alanine may have established the safety of their ingredient through a GRAS self-affirmation—as NAI did with SR CarnoSyn beta-alanine.

"But notably, unlike with the NDI notification requirement, there is no requirement that firms relying on this exception notify FDA that they are doing so or share the basis for their conclusion," the agency stated via email. "There is also no requirement that they notify FDA that these ingredients are marketed as foods. Therefore, in the absence of a product listing requirement for dietary supplements, there is no systematic way for FDA to know when products relying on this exception are introduced to the market in order to even inquire as to whether they have satisfied the requirements for marketing."

If beta-alanine is being used in "dietary supplements, it could be under self-GRAS," Tave said in an interview. "It might not. We don't know."

Attorneys, consultant and firms "view GRAS as an alternative to the NDI notification," he added. "We can't just assume that products out there are unlawful."

NDI APPENDIX:

FDA denies request to enforce against beta-alanine in supplements

Jun 25, 2021 | by Josh Long

Fourteen months after requesting in writing that FDA stop the importation into the U.S. of "adulterated generic forms of beta-alanine," nutritional supplements manufacturer Natural Alternatives International Inc. (NAI) received an answer met with disdain from former FDA officials.

Cara Welch, the acting director of FDA's Office of Dietary Supplement Programs (ODSP), essentially denied the request in an April 28 letter to NAI's outside counsel, Kevin Bell, a partner in the nation's capital with Arnall Golden Gregory LLP (AGG).

"FDA needs to make the best use of agency resources, and we typically prioritize those issues for which there is a known safety risk for consumers," Welch concluded in the letter to Bell. "At this time, we do not have concerns about beta-alanine that warrant the further investment of FDA's limited resources."

Bell and two former FDA officials with whom he is associated blasted the public health agency. Welch's letter, the men proclaimed, highlights FDA's unwillingness to enforce a provision of the Dietary Supplement Health and Education Act of 1994 (DSHEA) intended to protect consumers from potentially harmful ingredients.

"This fight is far from over," Bell promised in an interview. "Now that they've given us this final agency action, [the] law permits the next things to happen."

At the tiff's core: a premarket notification requirement for new dietary ingredients (NDIs), which the law defines as a dietary ingredient not marketed in the U.S. before Oct. 15, 1994. Subject to an exemption, a manufacturer or distributor of an NDI must provide FDA evidence that a "supplement containing such dietary ingredient will reasonably be expected to be safe," based on the conditions recommended or suggested in the product's labeling.

The NDI notification (NDIN) provision is crucial, FDA officials have said, because it represents the agency's only chance to review the safety of a novel dietary ingredient in a supplement before it reaches consumers. The requirement is perhaps more important than ever, considering the industry's extraordinary growth since 1994, when Congress estimated annual sales of $4 billion. Nutrition Business Journal estimated sales of dietary supplements in the U.S. grew 14.5% to $55.75 billion in 2020.

NAI, a public company (NASDAQ: NAII) based in Carlsbad, California, followed the NDIN

requirement for its ingredient, CarnoSyn beta-alanine.

It took NAI nearly a year to compile all the information for its beta-alanine notification to FDA—with hundreds of pages of documents describing such matters as testing, manufacturing methods and safety, according to the company's founder, chairman and CEO, Mark LeDoux. NAI spent a minimum of around $1 million investing in the NDIN process, and the figure is more than twice that amount when including human clinical trials to support components of the submission, he said.

In 2019, FDA responded to the notification with an acknowledgement or "good day" letter. Other manufacturers of beta-alanine for use in supplements have not followed the same regulatory pathway.

Enter Bell, who requested FDA essentially block "generic forms" of beta-alanine from entering the U.S. from China via an import alert. In a Feb. 24, 2020 letter, he remarked these forms of beta-alanine had not been the subject of NDINs and posed potential hazards to consumers. The lawyer noted different manufacturing processes could, for instance, introduce a contaminant or impact a substance's purity.

FDA'S BURDEN OF PROOF

In the April 28 letter to Bell, Welch stated "FDA bears the burden of establishing that the requirement to submit an NDIN applies."

She continued, "Importantly, to meet this burden, FDA would need to demonstrate that beta-alanine is not present in the food supply as an article used for food in a form in which the food has not been chemically altered."
Welch suggested it's possible other forms of beta-alanine are in the food supply in a form not chemically modified, which would make the ingredients exempt from the NDIN requirement under Section 413(a)(1) of the Federal Food, Drug & Cosmetic Act (FDCA). She noted, for instance, beta-alanine is present in energy drinks.

"The presence of beta-alanine in the food supply raises significant questions that would need to be answered before FDA would be in a position to demonstrate that certain imported beta-alanine appears to be adulterated," Welch wrote to Bell.

While manufacturers of a food ingredient have a duty to ensure its safety, they may do so through a process known as GRAS (generally recognized as safe) self-affirmation, which several consultants said is subject to a rigorous and thorough analysis by experts. On the other hand, critics argue GRAS self-affirmation avoids public input and FDA review, while leaving room for conflicts of interest to undermine the integrity of the safety analysis.

Companies also have the option to voluntarily notify FDA of a conclusion that a substance is GRAS under the conditions of its intended use. Marianna Naum, an FDA spokeswoman, confirmed FDA has not received any GRAS notices for beta-alanine.

It's unclear whether China-based manufacturers of beta-alanine targeted in Bell's 2020 letter have taken steps to comply with FDA rules. In a four-part series of articles on this topic reported by Natural Products Insider, several manufacturers of beta-alanine—as well as sports nutrition brands marketing the ingredient in the U.S.—did not respond to requests for comment.
Some industry veterans have characterized the NDIN exemption in Section 413(a)(1) as a "GRAS loophole" that wasn't the intent of Congress when it passed DSHEA.

"You hear about this GRAS loophole," said Dan Fabricant, who leads the Natural Products Association (NPA), whose chairman of the board of directors is NAI's LeDoux. FDA has "effectively created it here or double-downed on it."

PUBLIC HEALTH RISKS

FDA, though, cited other reasons for denying NAI's request. Welch advised Bell that FDA is unaware "of any evidence to support an assertion that beta-alanine manufactured by others presents a risk to the public health."

"Your communication speculated as to potential reasons that beta-alanine manufactured by other entities could be adulterated, but it did not provide any specific evidence that other beta-alanine currently being imported into the United States is adulterated," Welch stated. "While we acknowledge that differences in manufacturing could potentially change the safety and suitability of the ingredient for certain conditions of use, or even change the identity of the ingredient, FDA is not aware that such differences are at issue here."
In a 2020 interview, ODSP's then-director Steven Tave acknowledged FDA was given "mountains

and mountains of information" by Bell and his allies, but he suggested the information could not help achieve "the result that they are demanding" because it did not show violations of the law. Bell suggested FDA's recent letter to him would encourage "bad actors" and sends the following message to industry: "You haven't shown enough people got hurt yet or died. Those are the things we [FDA officials] take an interest in."

'KNOCK-OFF INGREDIENTS'

Welch denied Bell's request for NDI enforcement through an import alert about a week after a member of Congress wrote to her about related issues.

"My concern pertains to the lack of consumer protection regarding the new dietary ingredient notification (NDIN) process, which appears to lend itself to knock-off ingredients that 'piggy-back' off a valid NDIN submitters' information," Rep. Jeff Van Drew, a Republican from New Jersey, wrote to Welch in an April 20 letter. "American companies invest significantly in research and development to maintain compliance and appropriately introduce new dietary ingredients."

The congressman added, "Knockoff or 'copycat' ingredients not only undermine the scientific, financial and regulatory investment of companies that submit an NDIN, but also erode the integrity of the NDIN process, which the FDA publicly states is critical to the dietary supplement industry."

Van Drew requested Welch explain every action taken by FDA "to conclude generic beta-alanine entering our country from China was expected to be safe—and how they will be in the future."

CRITICISM BY FORMER FDA OFFICIALS

Welch's letter to Bell drew a strong rebuke from former FDA officials with whom he is aligned, including Robert Durkin, an AGG attorney who previously served as ODSP's deputy director. It was Durkin who signed the acknowledgement letter to NAI in 2019.

Asked what message FDA's letter conveys to the broader marketplace, Durkin responded he wouldn't spend a "dime" on an NDIN, and he advised supplement firms protect their intellectual property.

"Spend the money you need to spend to make sure your ingredient's safe under the conditions of use, but instead of taking the time to write an NDIN or any of that, get yourself a patent. Get yourself a trademark," Durkin said in a conference call interview, where he was joined by Bell and another former FDA official, Fabricant.
He added, "[It's] obvious that FDA has no intention to enforce the NDIN requirements."

FDA had no immediate response for this article to some of the criticisms leveled by former FDA officials. And in a follow-up email after this article was published, an FDA spokesperson declined to comment "on the agency's enforcement deliberations" outside its April 28 response to Bell. Durkin, who once held the same position as Welch—acting director of ODSP—argued FDA has taken inconsistent positions regarding its burden of proof. For example, while the agency has noted it bears the obligation to show an ingredient like beta-alanine is subject to an NDIN, Durkin said FDA has put the placed the burden of proof on industry to establish NAC (N-acetyl-L-cysteine) is not precluded from the definition of a dietary supplement.

In 2020 warning letters, FDA asserted NAC was first approved as a drug in 1963, and therefore cannot be lawfully marketed in a supplement. FDA, however, is open to receiving evidence from industry that could change its mind.

"It just seems like the agency sways back and forth when it determines what it's going to do and not do and what burden it has to meet," Durkin said. FDA is "horribly inconsistent, and it almost seems like, in this case [involving beta-alanine], it's an excuse to not do something."

FDA "might not have liked the idea of pursuing beta-alanine, but it doesn't mean it was incorrect" or "outside the scope of the law," according to Fabricant, who previously directed what was then called FDA's Division of Dietary Supplement Programs.

He suggested FDA has spent a lot of taxpayer time and money "to just avoid doing the right thing versus doing it."

"And here we are," he added. "Has it made the industry and … FDA's regulation of the industry better? I think it's a resounding 'no.'"

February 24, 2020

Steven J. Tave
Director
Food and Drug Administration
Office of Dietary Supplement Programs
Center for Food Safety and Applied Nutrition
5001 Campus Dr.
College Park, MD 20740

Re: Request for Immediate Enforcement Action to Stop Adulterated Forms of Beta-Alanine from Being Imported Into the U.S.

Dear Mr. Tave:

We are writing on behalf of Natural Alternatives International, Inc. (NAI), to follow-up on our prior meetings with the Food and Drug Administration (FDA or Agency) and reiterate NAI's request that FDA take swift and appropriate enforcement action against companies that are importing adulterated beta-alanine into the United States in clear violation of the Federal Food, Drug & Cosmetic Act ("FD&C Act"). The laws of the United States do not allow for such willful disregard for public safety. NAI respectfully requests that FDA issue an Import Alert ("IA") to stop adulterated generic forms of beta-alanine from entering the U.S.[1] It has become imperative that FDA take this action to protect the public health, as well as the integrity of its own laws and regulations as provided by the FD&C Act for dietary supplements and dietary ingredients. This action will not only serve public interests, but also protect responsible dietary supplement brand owners that invest the resources necessary to submit a NDIN to FDA.

NAI is a publicly-traded company and the sole importer and distributor of beta-alanine sold under the well-known and respected brand name, CarnoSyn® beta-alanine. In November 2018, NAI submitted a New Dietary Ingredient Notification (NDIN) to FDA for CarnoSyn® beta-alanine, to which it received an acknowledgement letter without objections (AKL letter) from FDA on 1 NAI's request for an IA is a proposed action that it believes FDA could take to stop a verified, widespread violation of the FD&C Act at the border, while minimizing the burden on Agency resources. It is not meant to be viewed as the only action FDA could take regarding this issue. If the Agency believes an import bulletin is a more effective action, then NAI would, of course, be supportive of FDA's decision and provide any further information necessary. February 1, 2019.[2] (See Attachment A, AKL letter for NDIN #1103). As described during meetings at FDA in 2019 and in further detail below, NAI diligently monitors import records and has identified millions of kilograms of adulterated, generic forms of beta-alanine being imported into the United States from companies in China that blatantly refuse to submit an NDIN and comply with U.S. laws. These entities instead choose to use various unidentified and potentially harmful methods of manufacturing to produce large quantities of generic forms of beta-alanine that are subsequently imported into the U.S., used in the manufacture of dietary supplements and sold to American consumers. NAI respectfully submits that it presents an undeniable case for enforcement by FDA that is straightforward, consistent with U.S. laws and regulations, does not overburden agency resources and will result in the best interest of American consumers.

BACKGROUND

Under Section 201(ff)(1) of the FD&C Act, a dietary ingredient is any one of 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 the total dietary intake; or (F) a concentrate, metabolite, constituent, extract or combination of any ingredient described in (A), (B), (C), (D), or (E). A New Dietary Ingredient ("NDI") is defined as a dietary ingredient that was not marketed in the United States (U.S.) before October 15, 1994 (21 U.S.C. § 350b(d)). Under Section 413 of the FD&C Act (21 U.S.C. § 350b), a dietary supplement that contains a NDI shall be deemed adulterated under section 402(f) of the FD&C Act (21 U.S.C. § 342(f)) unless it meets one of two requirements:

1. the dietary supplement contains only dietary ingredients that have been present in the food supply as an article used for food in a form in which the food has not been chemically altered; or
2. there is a history of use or other evidence of

safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the FDA with information (in the form of an NDIN), including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe. [See Section 413 of the FD&C Act (21 U.S.C. § 350b) and section 402(f) of the FD&C Act (21 U.S.C. § 342(f)].

A NDIN submitted to the Agency must contain detailed and specific information related to the safety and identity of the product. See FDA Final Rule, Premarket Notification for a New Dietary Ingredient, 62 Fed. Reg. 49886 (Sept. 23, 1997). If a manufacturer fails to submit the required NDIN to the FDA, a dietary supplement containing a NDI is deemed to be adulterated under Section 402(f).

NAI is the only company that has submitted a NDIN for beta-alanine to FDA.[3] NAI's notification was extensive. The company spent hundreds of thousands of dollars to not only compile publicly available information about the ingredient's identity, manufacturing process and safety, but also to conduct its own commercially confidential, pre-clinical studies. The Agency did not object to NAI's basis for concluding that CarnoSyn® beta-alanine is reasonably expected to be safe, as manufactured, and under the conditions of use proposed in the notification.

NAI's NDIN for CarnoSyn® beta-alanine included information and data concerning NAI's ingredient manufacturer, Yuki Gosei Kogyo Co., Ltd. ("YGK"), located in Japan. The safety and identity data relied upon in NAI's NDIN was based on that specific manufacturer's method of production and final product of commerce. NAI only imports CarnoSyn® beta-alanine from YGK.

IMPORTATION OF BETA-ALANINE INTO THE UNITED STATES

NAI procures and imports CarnoSyn® beta-alanine for sale to its customers, including other contract manufacturers and branded dietary supplement companies. No third parties are authorized by NAI to rely on its NDIN, unless they purchase CarnoSyn® beta-alanine from the company.

NAI previously informed FDA that substantial amounts of generic beta-alanine continue to be manufactured in China and imported into the U.S., for use as a dietary supplement or a component of a dietary supplement. NAI has gathered data that shows 3,362,622 kilograms of beta-alanine were imported from February 1, 2019 through January 31, 2020. Of this total, NAI imported 1,049,412 kilograms (31% of total beta-alanine imports) from Japan and the remaining 2,313,210 kilograms (69% of total beta-alanine imports) were imported from China by other companies.[4] Thus, the majority of beta-alanine coming into this country is generic and does not rely on a NDIN, and as such is adulterated under Section 402(f). (See Attachment B, List of companies importing adulterated, generic beta-alanine into the United States from China on page 17-18).
None of the companies importing and selling generic beta-alanine made in China can rely on NAI's NDIN # 1103, nor have they made the statutorily required pre-market notification. Thus, there is no way to determine how, or if, the ingredients being imported into the U.S. and distributed as generic beta-alanine are quantitatively or qualitatively related to CarnoSyn® beta-alanine—the only beta-alanine for which the required notification has been made. Because of this, FDA cannot assume that the basis for concluding that NAI's CarnoSyn® beta-alanine is reasonably expected to be safe can be directly applied or assumed for any of the generic forms of beta-alanine.

RISKS TO PUBLIC HEALTH

There are numerous inherent and unnecessary risks to the public health by continuing to allow the use of generic beta-alanine in dietary supplements. Manufacturers and distributors are knowingly evading important federal laws and regulations by denying FDA its statutorily mandated opportunity to evaluate the identity and production methods for these generic forms of beta-alanine. Without the required

NDIN submissions, there is absolutely no way—short of forcause-inspections of each of these manufacturing facilities in China—for FDA to know if any of the generic forms of beta-alanine are manufactured in a manner that does not also produce dangerous contaminants or impurities. In fact, NAI has obtained information that some manufacturers and distributors that import generic forms of beta-alanine into the U.S. utilize manufacturing processes very different from the one utilized by Yuki Gosei, NAI's Japanese manufacturer of beta-alanine. This is concerning because the manufacturing process utilized by NAI's manufacturer is the only one that FDA has had the opportunity to evaluate and determine whether it will produce a product of commerce reasonably expected to be safe under the proposed conditions of use. Instead, by violating the FD&C Act, companies refusing to submit NDINs intentionally place FDA in the untenable position of being unable to (i) know the identity and manufacturing process for any generic beta-alanine being imported into the U.S. from China, (ii) assess and prevent risks to the public health, and (iii) immediately address any health emergency that may arise.

As the Agency expressly noted throughout its 2016 draft guidance on NDINs, varying manufacturing practices may affect the purity of a food substance, introduce contaminants, and alter the physicochemical structure or biological properties, such as bioavailability or toxicity.[5] Through investigation, NAI is aware that there are several different methods used in China to manufacture generic beta-alanine. One or more of those methods appears to include the use of genetically modified organisms ("GMOs") to synthesize the ingredient. As FDA is well aware, a manufacturing process that utilizes GMOs may cause or increase potential risks for creating contaminants and/or impurities – or worse. Refusal by manufacturers to provide this information to FDA as required in a NDIN is indicative of a potential health risk.

The FDA need go no further than the well-known L-Tryptophan crisis in 1989, to see the similarity for unnecessary public harm. In that case, FDA took action to limit the availability of dietary supplements containing the amino acid L-Tryptophan "because of the association between dietary supplements containing L-Tryptophan and the 1989 epidemic outbreak of eosinophilia myalgia syndrome (EMS) in the United States."[6] Epidemiological studies conducted following the outbreak revealed that 95% of the cases could be traced to one L-Tryptophan supplier.[7] In 1988, that supplier of the L-Tryptophan dietary supplements made changes in manufacturing protocols and produced L-Tryptophan through a fermentation process using a new genetically modified strain of a bacteria. It was later shown that changes to the manufacturing protocols made by this firm resulted in the production of many impurities that were not found in L-Tryptophan manufactured using previously established protocols. One of these contaminants, a dimer of the amino acid L-Tryptophan, was strongly related to the outbreak of EMS. NAI knows that similar, but slightly different, means of production for beta-alanine can result in the presence of both characterized and uncharacterized contaminants. In fact, NAI knows that one of the contaminants characterized can be a dimer of beta-alanine. It should be pointed out that, like tryptophan, betaalanine is an amino acid and it is possible that a dimer of beta-alanine may have toxicities similar to those of other amino acid dimers. The use of GMOs in the L-Tryptophan case illustrates that a change or difference in the manufacturing process can alter a product and result in serious injury to consumers. The NDIN process is designed to provide FDA an opportunity to review the adequacy of the manufacturing process and the manufacturer's conclusion that said process produces a safe NDI. Simply put, without appropriate NDIN submissions for the various forms of generic beta-alanine and outlining the associated manufacturing processes, the FDA cannot evaluate the risk of using dietary supplements containing this or any other NDI. Moreover, FDA will not have a record on file about the NDI in the event a safety problem does arise and the Agency needs to identify the root cause of the problem.

IMPORT ALERTS AS A NDIN ENFORCEMENT TOOL

The purpose of an import alert is to (i) prevent potentially violative products from being distributed in the United Stated, (ii) free-up agency resources to examine other shipments, (iii) provide uniform coverage across the country, and (iv) place the responsibility back on the importer to ensure that the products being imported into the United States are in compliance with the FDA's

laws and regulations. NAI's request satisfies all of the criteria the FDA considers when issuing an IA. Given the wide range of risks to the public health that could result from imported ingredients that are adulterated, an opportunity to enforce the NDIN requirement at the border through issuance of an IA would have an exponential impact in preventing such dietary ingredients from making their way into domestic commerce, while freeing up agency resources to address other issues. It is estimated that approximately 77% of Americans take dietary supplement regularly.[8] With many, if not most, dietary ingredients being imported from other countries. As noted by you Import at the May 16, 2019, Responsible Innovation in Dietary Supplements Public Meeting hosted by FDA, the dietary supplement industry has experienced remarkable growth since the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994. Then Acting Commissioner Sharpless stated that the industry has grown to include an estimated 80,000 products with the industry estimated to be worth over $40 billion dollars.[9] The frequency of unscrupulous companies exporting violative 'copycat' ingredients to the U.S. is likely significant, presenting a concerning, yet controllable, risk to the public health. Companies that knowingly violate the FD&C Act should not be allowed to benefit from marketing products in U.S. commerce at the expense of diligent companies such as NAI. NAI respectfully requests that the FDA issue an IA effective to stop importation of violative ingredients by those entities breaking U.S. laws for economic gain and to avoid FDA regulations. An effective IA would serve as an effective enforcement tool to encourage companies to submit statutorily required NDINs to the Agency. Considering that the NDIN process is essentially the Agency's only real opportunity to evaluate the safety of a NDI before it becomes widely available to consumers, an opportunity to strategically enforce the FD&C Act by issuing an IA while encouraging companies to make required NDIN submissions, should not be overlooked. Moreover, an IA is an effective enforcement tool that does not require significant resources for the Agency to enforce once it is established.10 Despite being a responsible stakeholder in the dietary supplement industry for over 40 years, since receiving its AKL letter from FDA, NAI continues to be negatively impacted by scofflaws exporting adulterated, generic forms of beta-alanine to the U.S. and FDA's lack of enforcement of NDIN requirements. However, NAI recognizes that for FDA enforcement to be effective, it will also need to bear some of the burden and provide FDA with the necessary information to allow the Agency to take immediate action. To that end, we are providing FDA, not only with information on NAI's NDIN, but also identification of the specific companies manufacturing and importing adulterated generic forms of beta-alanine into the United States.

NAI respectfully submits that the following information should be sufficient to facilitate FDA's prompt issuance of an appropriate IA without imposing significant burden on Agency resources:

1. NAI submitted the statutorily required NDIN for CarnoSyn® beta-alanine on November 20, 2018. NAI's NDIN was assigned NDIN #1103 by FDA.
2. NAI received an AKL letter from the Agency dated February 1, 2019. (See Attachment A).
3. To date, there are no other NDIN's for beta-alanine on FDA's List of Submitted 75-Day Premarket Notifications for New Dietary Ingredients. (See fn. 3).
4. There are no third parties authorized to rely on NAI's CarnoSyn® beta-alanine NDIN.
5. List of the companies that are exporting generic beta-alanine from China, and the amounts exported into the country by these companies. (See Attachment B).

CONCLUSION

NAI is currently the only company that has submitted a NDIN for beta-alanine. Therefore, NAI or its authorized agents are the only entities allowed to import and distribute beta-alanine without violating the FD&C Act. However, the majority of beta-alanine being imported into the U.S. from China is from companies that have not submitted the required NDIN. FDA must take action to not only enforce the NDIN requirements set forth by the FD&C Act, but also to protect consumers and reputable dietary supplement manufacturers and distributors, such as NAI, that are committed to complying with all applicable laws and regulations. NAI respectfully reiterates its request that FDA issue an IA to keep adulterated, generic forms of beta-alanine out of the country and domestic

commerce. NAI believes this type of enforcement action will be highly effective and may lead other reputable companies to submit the required NDINs. It will also ensure that American consumers are exposed to new dietary ingredients that have been shown to be safe.

Please let me know if there is any additional information we can provide the agency that would be useful.

Respectfully submitted,

Kevin M. Bell
Counsel for Natural
Alternatives International, Inc.

Attachments

cc: Douglas Stearn

William Correll

Scott McIntyre

Cara Welch, Ph.D.

Footnotes:

1 NAI's request for an IA is a proposed action that it believes FDA could take to stop a verified, widespread violation of the FD&C Act at the border, while minimizing the burden on Agency resources. It is not meant to be viewed as the only action FDA could take regarding this issue. If the Agency believes an import bulletin is a more effective action, then NAI would, of course, be supportive of FDA's decision and provide any further information necessary.

2 To date, NAI's CarnoSyn® beta-alanine is the only beta-alanine for which the statutorily required NDIN has been submitted, and as such, is the only form of beta-alanine that is compliant with the FD&C Act. NAI also owns and maintains a worldwide intellectual property portfolio related to its CarnoSyn® beta-alanine that includes patents, trademarks and copyrights.

3 See The FDA's List of Submitted 75-Day Premarket Notifications for New Dietary Ingredients, available at https://www.fda.gov/food/new-dietary-ingredients-ndi-notification-process/submitted-75-daypremarket-notifications-new-dietary-ingredients.

4 Import data for Chinese beta-alanine imports was retrieved from PIERS TI, a well-known, third-party import database.

5 See generally, The FDA's Draft Guidance entitled "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry" (August 2016), available at https://www.fda.gov/media/99538/download

6 See FDA's Information Paper on L-Tryptophan and 5-hydroxy-L-tryptophan (February 2001), available at http://www.nemsn.org/Articles/FDA-Info.pdf

7 Id.

8 See CRN's Press Release, entitled "Dietary Supplement Use Reaches All Time High," Available-for-purchase consumer survey reaffirms the vital role supplementation plays in the lives of most Americans," available at https://www.crnusa.org/newsroom/dietary-supplement-use-reaches-all-time-high-availablepurchase-consumer-survey-reaffirms

9 See Speech by Norman E. "Ned" Sharpless, MD at the FDA Public Meeting on Responsible Innovation in Dietary Supplements (May 16 2019), available at https://www.fda.gov/news-events/speeches-fdaofficials/fda-public-meeting-responsible-innovation-dietary-supplements-05162019

10 This is particularly true here. NAI's CarnoSyn® beta-alanine is made in Japan by YGK using the same manufacturer and method disclosed in NDIN # 1103 Generic forms of beta-alanine made in China and imported into the U.S. is not covered by any NDIN and is adulterated.

ATTACHMENT A

February 1, 2019

Dear (b) (4),

This letter is to inform you that the Food and Drug Administration (FDA) filed your notification that you submitted to FDA on behalf of Natural Alternatives International, Inc., pursuant to 21 United States Code (U.S.C.) § 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)), on November 20, 2018. Your notification concerns a new dietary ingredient that you call "CarnoSyn® Betaalanine" that you intend to market as a bulk dietary supplement ingredient.

According to your notification, the "[r]ecommened directions for daily use are using one to two tablets of CARNOSYN® Beta-alanine (i.e. 800 mg to 1.6 g/serving) taken four times daily (maximum CARNOSYN® Beta-alanine daily intake of 6.4 g per day) following meals with water. This dietary ingredient is not intended to

be used in children or pregnant women. It is intended to be used in adults (less 18 years of age). Total daily intake of 6.4 g per day [of CARNOSYN® Beta-alanine]." Under 21 U.S.C. § 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or rustributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C. § 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the condition recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. § 342(f)(l)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury. In accordance with 21 CFR 190.6 (c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date, your client must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains the new dietary ingredient that is the subject of this notification. Please note that acceptance of this notification for filing is a procedural matter, and thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ngredient is safe or is not adulterated under 21 U.S.C. § 342.
FDA is not precluded from taking action in the future against any dietary supplement containing your new dietary ingredient if it is found to be unsafe, adulterated, or misbranded.

Your notification will be kept confidential for 90 days after the filing date of November 20, 2018. After the 90-day date, the notification will be placed on public display at www.regulations.gov as new dietary ingredient notification report number 1103. Prior to that date, you may wish to identify in writing specifically what information you believe is trade secret or confidential commercial information and include an explanation of the basis for this belief.

If you have any questions concerning this matter please contact Dr. Fred Hines, Consumer Safety Officer, Evaluation and Research Staff, at (240) 402-1756 or by email: Fred.Hines@fda.hhs.gov.

Sincerely,

Robert J. Durkin, Esq., M.S., R.Ph.
Deputy Director
Office of Dietary Supplement Programs
Center for Food Safety and Applied Nutrition

JEFFERSON VAN DREW
SECOND DISTRICT, NEW JERSEY

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April 20, 2021

Acting Director Cara Welch, Ph.D.
Office of Dietary Supplement Programs
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Director Welch,

We must continue to look for innovative ways to protect our dietary supplement supply chain. That includes advocating for enforcement of the laws and regulations enacted by Congress that are overseen by the Food and Drug Administration (FDA). I have serious concerns over the lack of action and enforcement at our nation's borders and ports by the FDA.

As you know, the Federal Food, Drug, and Cosmetic Act (the FD&C Act) requires that manufacturers and distributors who wish to market dietary supplements that contain "new dietary ingredients" notify the FDA about these changes. The notification must include information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing a new dietary ingredient will reasonably be expected to be safe under the conditions of recommended use.

My concern pertains to the lack of consumer protection regarding the new dietary ingredient notification (NDIN) process, which appears to lend itself to knock-off ingredients that "piggy-back" off a valid NDIN submitters' information. American companies invest significantly in research and development to maintain compliance and appropriately introduce new dietary ingredients. Knockoff or "copycat" ingredients not only undermine the scientific, financial and regulatory investment of companies that submit an NDIN, but also erodes the integrity of the NDIN process, which the FDA publicly states is critical to the dietary supplement industry. Furthermore, a failure by the FDA to stop manufacturers and distributors from circumventing the NDIN process only to intentionally avoid agency review of their manufacturing processes poses unnecessary safety risks to consumers.

Until very recently, the administration had not published an import alert for dietary supplements in several years. As you know, this is the administration's opportunity to review the safety profile of most new ingredients imported into the United States before they reach consumers. Issuing and actively enforcing an import alert for new dietary ingredients that have failed to comply with the NDIN regulations would provide the FDA with the ability to police the market in a way that is resource efficient and consistent with the goals of protecting the public's health, while also providing the intellectual property protection the industry desperately needs.

I recently came across a series of articles published by Natural Products Insider detailing discrepancies between the FDA and industry stakeholders over enforcement of a provision in a 26-year-old law intended to flag novel ingredients in supplements before they pose risks to consumers. It seems to me that the NDIN requirement is considerably underutilized, and I request more information as to how FDA uses the NDIN process to verify that imports coming into the U.S. market are safe for consumption. Additionally, I request an explanation as to every action the FDA took to conclude generic beta-alanine entering our country from China was expected to be safe – and how they will be in the future.

I would greatly appreciate it if you joined my staff and me for a conference at your earliest convenience to discuss this important matter. To that end, I will have my office reach out to inquire about your availability. I am sure you will agree that there has never been a more critical time in our nation's history for us as public servants to protect the citizens we serve.

Sincerely,

Jeff Van Drew
Member of Congress

April 28, 2021

Mr. Kevin M. Bell
Partner
Arnall Golden Gregory LLP
1775 Pennsylvania Avenue NW, Suite 1000
Washington, DC 20006

Dear Mr. Bell:

We are writing to respond to your February 24, 2020, letter (February 2020 letter) to Steven Tave, former Director of the Office of Dietary Supplement Programs (ODSP) at the Food and Drug Administration (FDA or the Agency), "request[ing] that FDA take swift and appropriate enforcement action against companies that are importing adulterated beta-alanine into the United States in clear violation of the Federal Food, Drug & Cosmetic Act." In your February 2020 letter, you assert that (1) " . . . the majority of beta-alanine imported into the United States is generic and does not rely on a [new dietary ingredient notification] NDIN, and as such is adulterated under Section 402(f)," and (2) "[t]here are numerous inherent and unnecessary risks to the public health by continuing to allow the use of generic beta-alanine in dietary supplements." We appreciate your continued engagement with FDA as we have evaluated this issue.[1] We have carefully considered the information you provided as well as other information available to the Agency, and we do not agree that there is clear evidence to support either assertion. With regard to your first assertion that " . . . the majority of beta-alanine imported into the United States is generic and does not rely on a [new dietary ingredient notification] NDIN, and as such is adulterated under Section 402(f)," for purposes of this response, we interpret your use of "generic" to mean that the beta-alanine that you assert is adulterated is not the same beta-alanine that is the subject of the NDIN submitted by Natural Alternatives International, Inc. (NAI). We do not dispute your assertion that beta-alanine is being imported into the United States that is not the subject of NAI's NDIN; however, the fact that a dietary ingredient is not covered by NAI's NDIN, or any NDIN, does not automatically render the dietary ingredient adulterated under section 402(f) of the Federal Food, Drug & Cosmetic Act (FD&C Act).

For a dietary supplement to be deemed adulterated under section 402(f) of the FD&C Act for failure to meet the requirements in section 413(a) of the FD&C Act, the dietary supplement must, as a threshold matter, contain a "new dietary ingredient" as defined in section 413(d) of the FD&C Act, and it must not be exempt from the requirement to submit a new dietary ingredient notification under section 413(a)(1) of the FD&C Act. Section 413(a)(1) of the FD&C Act exempts from the new dietary ingredient notification requirement a "dietary supplement which contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered." While the NDIN process set forth in section 413(a) provides a powerful tool to FDA to be able to evaluate the safety of certain new dietary ingredients contained in dietary supplements, before asserting that a dietary supplement containing a new dietary ingredient is deemed adulterated under sections 413(a) and 402(f), FDA bears the burden of establishing that the requirement to submit an NDIN applies.

Importantly, to meet this burden, FDA would need to demonstrate that beta-alanine is not present in the food supply as an article used for food in a form in which the food has not been chemically altered. In reviewing NDINs, FDA focuses on confirming that the information submitted demonstrates the safety of the ingredient when used under the conditions recommended or suggested in the labeling. 21 CFR 190.6(b) specifies the information that must be included in the notification, but such information does not necessarily include information demonstrating whether the dietary ingredient has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered (see section 413(a)(1) of the FD&C Act). FDA has reviewed and intends to continue reviewing voluntarily submitted notifications for NDIs that may be exempt from the notification requirement under section 413(a)(1) of the FD&C Act. [2] While our review of the safety information included with NAI's NDIN did not raise any safety concerns, our response should not be interpreted as a conclusion about whether beta-alanine generally is

subject to the requirements in section 413(a)(2) of the FD&C Act.

While FDA has not reached a definitive conclusion as to whether beta-alanine would be excepted from the NDI notification process on the grounds that it is present in the food supply as an article used for food in a form in which the food has not been chemically altered, FDA is aware of evidence suggesting that beta-alanine is present in the food supply as, for example, an ingredient in energy drinks. The presence of beta-alanine in the food supply raises significant questions that would need to be answered before FDA would be in a position to demonstrate that certain imported beta-alanine appears to be adulterated.

With regard to your second assertion that "[t]here are numerous inherent and unnecessary risks to the public health by continuing to allow the use of generic beta-alanine in dietary supplements," we are not aware of any evidence to support an assertion that beta-alanine manufactured by others presents a risk to the public health. Your communication speculated as to potential reasons that beta-alanine manufactured by other entities could be adulterated, but it did not provide any specific evidence that other beta-alanine currently being imported into the United States is adulterated. While we acknowledge that differences in manufacturing could potentially change the safety and suitability of the ingredient for certain conditions of use, or even change the identity of the ingredient, [3]FDA is not aware that such differences are at issue here. To the extent you have specific evidence of particular risks of safety or other evidence of adulteration, we welcome the opportunity to review such information. However, speculation about differences in the manufacturing process or about potential contaminants is generally not sufficient to support an enforcement action. Additionally, while we agree that requiring additional information about the manufacturing process for a particular new dietary ingredient prior to its marketing would be more helpful in helping to ensure the ingredient's safety, your February 2020 letter essentially sets forth an argument for why the NDI notification requirement should be broader than it currently is, rather than explaining what the law currently requires. As explained previously in this letter, we have not identified evidence that FDA could use to demonstrate that beta-alanine generally is subject to the NDI notification requirement in section 413(a)(2). In the absence of such evidence, FDA bears the burden of demonstrating that betaalanine is adulterated—for example, that it is a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. See section 402(f)(1)(B) of the FD&C Act.

Based on the NDIN we have received as well as other information FDA has reviewed pertaining to beta-alanine generally, we have not identified any information that is sufficient for the Agency to demonstrate that any imported beta-alanine presents a risk to public health or that the safety information available does not also demonstrate the safety of beta-alanine more generally. As you noted in your February 2020 letter and in our March 31 call regarding this issue, FDA did not object to NAI's basis for concluding that its beta-alanine is reasonably expected to be safe. As such, it is unclear on what basis FDA could prove that there is not a reasonable assurance that beta-alanine more generally does not present a significant or unreasonable risk of illness or injury. If a particular beta-alanine were sufficiently different from NAI's beta-alanine such that the prior safety assessment no longer translated, then it might be possible to demonstrate that such beta-alanine would be adulterated under section 402(f)(1)(B) of the FD&C Act. However, this would require affirmative evidence of how this beta-alanine differs, and why those differences alter the safety analysis. We have seen no such evidence here.

To be clear, we are not today asserting definitively that certain imported beta-alanine for use as a dietary ingredient in dietary supplements is not adulterated. However, as noted above, we have significant questions about whether it is. Even assuming that imports of beta-alanine, or certain imports of beta-alanine, were unlawful, FDA makes regulatory and enforcement decisions on a case-by-case basis, recognizing that it is unable, as a practical matter, to take enforcement action against every violative product. FDA needs to make the best use of Agency resources, and we typically prioritize those issues for which there is a known safety risk for consumers. At this time, we do not have concerns about beta-alanine that warrant the further investment of FDA's limited resources.

If you have additional information to provide that might change our current thinking, please let us know. We will continue to monitor the marketplace and, whenever we identify violations of the law, we will take action as appropriate to protect the public health.

Sincerely,

Cara Welch, Ph.D.
Acting Director Office of Dietary Supplement Programs Center for Food Safety and Applied Nutrition

Footnotes:

1 This response also captures the substance of, and addresses some of the issues raised during, a March 31, 2021, call between you and Dr. Daniel Fabricant from the Natural Products Association and FDA representatives from the Center for Food Safety and Applied Nutrition's Office of the Center Director, Office of Compliance, and ODSP, as well as FDA's Office of the Chief Counsel.

2 See FDA, Draft Guidance for Industry, Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; August 2016, at 25, Available at https://www.fda.gov/media/99538/download.

3 See, e.g., FDA, Draft Guidance for Industry, Dietary Supplements: New Dietary Ingredient Notifications and Related Issues; August 2016, at 20-21, Available at https://www.fda.gov/media/99538/download; FDA, Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives; June 2014 Available at https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents/guidance-industry-assessing-effects-significant-manufacturing-processchanges-including-emerging.