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Via E-Filing and FedEx

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

Re: Docket No. FDA-2017-N-4625; Jarrow Formulas, Inc. Comment on Issues and Problems in Development of a List of Pre-DSHEA Dietary Ingredients ("ODIs"): New Strains of Probiotics; Probiotic Manufacturing; a Fast Track System for Certain Ingredients; and Synthetic Dietary Ingredients

Dear Sirs and Madams:

We are writing on behalf of Jarrow Formulas, Inc. ("Jarrow" or "JFI"), a 40-year old dietary supplement company headquartered in Los Angeles, California. This letter Comment expands on the brief oral presentations of the undersigned, JFI's two food law regulatory attorneys at the FDA's Public Meeting to Discuss Development of a List of Pre-DSHEA Dietary Ingredients, held in College Park, MD on October 3, 2017. A further detailed discussion of a number of our positions are contained in JFI's December 12, 2016 Comment on the New Dietary Ingredient ("NDI") Revised Guidance and in a second May 15, 2017 Comment specifically devoted to issues concerning probiotics, and we incorporate those comments by reference.

Introduction and Threshold Issues

As we stated at the October 3, 2017 meeting and in our previous Comments, there are no provisions of DSHEA and/or any other applicable federal legislation that impose an affirmative duty on the seller of an ODI to show evidence of marketing prior to October 15, 1994 to confirm the ODI status of that ingredient, i.e., that a dietary ingredient is not an NDI. Sec. 8 of the Dietary Supplement Health and Education Act ("DSHEA") in no way demands the compilation of a list of "grandfathered" ingredients—by either the FDA or the supplement industry or both—but rather envisions consideration of ingredient status on a case-by-case basis by the manufacturer or developer of a new dietary ingredient or new supplement. In this regard, JFI agrees. Nonetheless, if there is to be such a list, JFI is concerned with the content and limitations of such a list of ODIs, and with FDA's restrictions on the type of evidence and documentation that are acceptable, and submits the following Comment.

A. The requirements for specific proof that an ingredient was marketed as a dietary ingredient in a dietary supplement before October 15, 1994 have been augmented in the NDI Revised Draft Guidance to include documented proof that the ingredient was sold as part of a dietary supplement, at what amount, and the daily intake. The Revised Guidance also requires that the manufacturer have evidence that the current manufacturing method of the pre-DSHEA dietary ingredient is identical to the historical manufacturing method that predates DSHEA. This ex post facto requirement is an historic and scientific impossibility: such records were not maintained before October 1994. Further, it is a fact that neither the industry nor the Agency has the resources for submissions by industry or review by the Agency of tens of thousands of formulas. Congress never intended this exercise and the American people would not understand or appreciate the waste of time and money. Finally, most of the requested information, such as exact amounts and formulation, is of no use other than to hinder and obstruct. It would be overreaching makework.

We note that this new requirement in the 2016 Draft Guidance (being treated as required, not merely as a "non-binding recommendation") is found nowhere in Sec. 8 of DSHEA, or in 21 C.F.R. Sec. 190.6. In this area (and others) the Revised Draft Guidance attempts to create new law. Many companies, due to past procedures on record retention, will not have the designated documentation. State and/or Federal government do not require record retention to this degree (23 plus years back). It is necessary to limit the stipulations on documentation only to those matters that affect the safety of the product. Indeed, JFI believes that the type of documentation for an ODI be at the discretion of, and the responsibility of, the individual manufacturer (as also addressed below).

B. Because DSHEA placed dietary supplements under the food umbrella, the sale of a dietary supplement or dietary ingredient outside the United States, in a category that would fall under the food umbrella in the U.S., should constitute presence in the food supply. Accordingly, when this same ingredient is to be sold in the U.S. in a form that is not chemically altered, it should be eligible for the exemption from a notification. The applicable statute in DSHEA did not link the presence in the food supply to a specific category, place, or date.

C. Consumption of these ingredients outside the U.S. as a food and/or as a dietary supplement should qualify as presence in the food supply, since supplements are considered a sub-set of the food category in the U.S., and more importantly, since safety of these ingredients is established by the fact of past consumption alone.

I. <u>New Probiotics, including New Strains, are not always New Dietary Ingredients</u>

A. If finalized, a pre-DSHEA/ODI list should not be considered exhaustive and exclusive, and we are pleased that FDA agrees with this stance. Were any ODI list to be exclusive, such a list could become similar to the EU Commission's list of 121 ingredients for nutritional supplements or reminiscent of the original GRAS list of 1958 that failed to contain all substances generally recognized as safe and thus was inappropriate.

B. For the history of use and safety of probiotics, FDA should look to the species and not the strains. As of 1994, some 23 years ago, there was a relative lack of sophistication and

accuracy of testing available: tools were more primitive, and scientists did not know exactly which strains were on the market. The question of species within a genus—for instance, the Bacilli—presents another matter as to safety. However, to call every new strain an NDI, even if the strain belongs to a well-recognized and historically safe species, would be technology overkill. Just because something can be done, does not mean it should be.

C. A statement by FDA in the 2016 NDI Revised Draft Guidance suggests that the Agency agrees with the role of the species in determining the safety of the strain and its status as new or not, and also suggests that FDA recognizes the distinction between species belonging to genera that contain both species with established safety and those known to contain pathogens (Page 65 and 66, Section VI, Part A. Article 17). However, FDA makes a contradictory statement when it further reasons: "FDA regards all members of a species containing pathogens as potentially harmful to human health and therefore, inappropriate for use as dietary ingredients, because of the absence of a consensus that there are valid scientific ways to distinguish between pathogenic and non-pathogenic members of a single species or to prevent horizontal transfer of genes for pathogenic traits between members of the same bacterial species."

JFI does not agree with this conclusion, and believes there are scientific ways to distinguish pathogenic from non-pathogenic species; thus, a comprehensive safety profile for every member within these particular species is unnecessary. Jarrow is aware of no precedents that would justify such an elaborate (yet restrictive) approach other than verification of the lack of antibiotic resistant plasmids**.** Agreeing with the reasoning of the International Probiotics Association ("IPA"), Jarrow's position is that horizontal transfer of any gene cannot be prevented. Accordingly, once a strain is proven as safe, and has demonstrated safety appropriately according to genomic mining for evidence of virulence factors or toxin production, or the absence of antibiotic resistance profile and transfer potential, then it should be considered for use as a safe dietary ingredient. Thus, only two simple tests need be done, not the full 10 tests and studies recommended in the Draft Guidance and the Revised Guidance: (i) Antibiotic Plasmids test ("ABP"), to test for antibiotic resistance; and (ii) a test for any contamination.

D. Jarrow concurs with the list of over 40 well-established species that IPA provided to FDA in its Comment to the 2016 NDI Draft Guidance—a list of grandfathered species known to have a long, safe history of use in foods. After being screened for toxins and antibiotic resistance, a strain belonging to such a species would be considered as safe. Contrary to FDA's position, any strain of a grandfathered species should be considered safe as well with no need for a New Dietary Ingredient Notification ("NDIN").

Such a list would be based on those genera and species that are globally recognized as used historically in foods, and as safe and suitable for continued use in foods. Because all of these species have been used in foods, any new strain derived should be identified unequivocally as within a genus and species on this list by using whole genome sequencing alignment. Once the species is confirmed, safety of the strain can be readily established. As detailed above, such safety criteria can include: history of use, assessment of antibiotic resistance profiles and lack of transferability, and mining the genome to demonstrate a lack of toxin production and virulence factors. For the purpose of inclusion to the grandfathered or exempted from NDI notification list, the data about identifying the strain as belonging to a species that is grandfathered and the supportive safety evidence may be submitted in the form of a Master File

within a procedure that is appropriate for the type and grade of the particular dietary ingredient status, as discussed further in Sections II and III, and the Conclusion.

E. Fermentation processes that do not chemically alter or change the genetic identity of a strain should not require an NDIN. In its NDI Guidance, FDA should revise its list of physical changes that are not chemical or identity changes; and thus it should read as follows: *Dehydration, lyophilization, or making a tincture, solution in water, or slurry can be said to change the composition of the ingredient, but only by changing the amount of water (or ethanol, in the case of a tincture). FDA regards such a minor change in composition as extremely unlikely to change the safety profile of an ingredient used in a conventional food or a supplement. Another example would be a minor loss of volatile components. These are all physical changes without chemical changes, and thus do not produce an NDI. Similarly, a change in the fermentation media will not affect the genetic identity or the safety profile of the probiotic or other ingredient, and thus will not change the genome necessitating an NDI.*

F. A new fermentation medium does not create a new Probiotic. There are well-justified reasons for altering manufacturing processes for microbial food cultures. These can vary from removing allergens, to adapting to market demands, improving stability, improving yields, and (more importantly) the continuous improvements to process optimization as technology advances. However, these improvements and changed media do not change the identity of the microbial food culture or alter its safety profile. As we have written in our Comment on Probiotics and NDI Guidance, filed on May 15, 2017, and as we stated at the October 3 Public Meeting, by analogy, if an Italian woman starts eating Japanese food, that does not change her into a Japanese woman.

Science has shown us that genetic changes resulting from media changes are very rare but can be considered normal. Some examples from the research have concluded the following outcomes: Long-term evolution surveys determined that it took 31,500 generations to accumulate natural mutations to permanently adapt to media changes.[1] Changes are not due to media changes, but are due to normal heterogeneous populations of cells in any culture.[2] And finally when cultured in different media—glucose, lactose, glucose and lactose—it took 2,000 generations to see a change, and only after extensive screening.[3] From the published scientific articles, we recognize that genetic drift potential during fermentation might temporarily change gene expression with a low calculated risk[4] to no permanent change to the genetic code, medium components are consumed from the organisms during fermentation, and safety is maintained during the fermentation stage with extremely low calculated risk of genetic change. JFI appreciates the willingness of FDA to consider arguments supported by evidence—as the agency

[1] Blount et al., (2008) Historical contingency and the evolution of a key innovation in an experimental population of Escherichia coli. PNAS, 105(23), 7899-7906.

[2] Kussell, E. (2013). Evolution in microbes. Biophysics, 42.

[3] Quan et al. (2012). Adaptive evolution of the lactose utilization network in experimentally evolved populations of Escherichia coli PLoS Genet, 8(l), e1002444.

[4] Drake J. W., A constant rate of spontaneous mutation in DNA-based microbes, Proc. Natl. Acad. Sci. USA Vol. 88, pp. 7160-7164, August 1991 Genetics.

should, since it has prided itself on being a "science-based agency" for over 15 years. (See JFI Comment on Probiotics and NDIs, dated May 15, 2017.)

G. Combining two probiotics that have a reasonable expectation of safety individually does not produce additional safety concerns. The same principle applies across the dietary supplement industry and was clearly Congressional intent. Applying the same principle, combining two foods creates a novel food? Combining two GRAS ingredients creates a new non-GRAS ingredient? GRAS should be granted only one use at a time?

H. The idea of preventing horizontal gene transfer is unrealistic. What is relevant is not whether the strain will accept foreign DNA *in-vivo*, but instead, how that strain acts in a safe manner, to supplement the diet. Therefore, we request that this proposition be considered on a case-by-case basis. It is a scientific fact that certain Clostridia, for instance, are non-pathogenic and beneficial. Clostridia butyricum is one such example. This species might have the potential to reduce colorectal cancer risk; and that application if submitted with substantiation at the proper level of significant scientific agreement could be a lawful Health Claim under the 1992 Nutrition Labeling & Education Act ("NLEA"). Once determined to be safe, FDA should allow this probiotic ingredient to be marketed as a dietary ingredient/supplement like any other probiotic. The joint FAO/WHO group of 2001 published general probiotic safety characterization tests to include antibiotic resistance, metabolic activities assessment, side effects assessment, epidemiological surveillance and adverse events post-market monitoring, toxin production, and hemolytic potential.

I. Similar to the lyophilization process, a change in the fermentation media does not genetically alter the identity of the strain or affect its safety profile, and therefore should not be considered a chemical alteration—even though FDA considers it an intrinsic part of the identity of the microorganism. (See above.) JFI agrees that each strain must be individually identified and its safety evaluated, as well as the determination of whether the notification requirement applies or not. However, JFI strongly believes that if the strain is identified to belong to those genera and species that have a long history of use either in dietary supplements prior to DSHEA in the U.S. or in foods—anywhere in the world at any time—the strain is not an NDI unless it is genetically modified. Jarrow agrees with the IPA proposal for an expansion of the scope of the 'grandfathered list' to capture not only pre-DSHEA ingredients, but also to consider the established safety of use of bacterial strains that have been marketed in foods and can be generally presumed safe.

II. A Proposal for Fast-Track Notifications for "Middle-Aged" Ingredients

As we presented at the October 3 Public Meeting, Jarrow Formulas, indeed Mr. Jarrow Rogovin personally, has a modest proposal for what we lawyers called "middle-aged" ingredients, neither old nor new, defined as on the market five years or more. For post-DSHEA dietary ingredients with a history of safe use in any country, the full procedure of the Notification—with 10 safety and toxicology tests being recommended in the Revised Guidance—should not be required. Instead, a much more streamlined procedure, but one still providing the statutory (per Sec. 8 of DHSEA) safety standard for the new supplement, should be permitted by the FDA. And we must continuously keep in mind that the safety standard for a

successful NDI is "a reasonable expectation of safety" of the new supplement, and not the higher GRAS standard of Generally Recognized As Safe. This proposed Abbreviated Procedure, perhaps analogous to the Fast-track procedure for some drugs, would include:

- Disclosure of the category of the dietary ingredient ("DI")
- Full and detailed description of the DI
- Description of the manufacturing process
- Being on the market in any country for a minimum of 5 years
- Evidence for safety conclusion, based on history of safe use
- Documented absence of any serious AERs during this period
- If a Probiotic, it should be screened for the ability to produce antibiotic resistance.

We would be especially appreciative to hear back from the Office of Dietary Supplements as to the response of the Office as to this specific Proposal.

III. Self-Affirmed GRAS Procedure is more Appropriate than NDI Notifications for Certain Food-based Ingredients

Notification of a GRAS determination to FDA is voluntary under the GRAS Final Rule. Self-affirmed GRAS is allowed and lawful under FDA regulations, and therefore must be considered. See: 81 FR 54959, published August 17, 2016; effective October 17, 2016. It is still FDA's position that in an assessment of whether or not a substance is GRAS, "common knowledge" can be based on either "scientific procedures" or on experience based on common use of a substance in food prior to January 1, 1958. FDA may not disregard the fact that all categories of foods, conventional and non-conventional, should qualify provided that safe history of use is established. Molecules, such as specific amino acids, that occur in foods and are extracted and purified or concentrated, should be allowed to utilize self-affirmed GRAS status. This is a common sense approach, which is explored further in our Conclusion.

IV. FDA's Inconsistent Position for Supplements vs. Foods re. Synthetic Plant-derived Ingredients: Example of the Impossible Burger

The FDA's current position on dietary supplements that contain synthetic ingredients is inconsistent with the Agency's policy on food products that contain synthetic ingredients. More specifically, the Agency's treatment of the novel "Impossible Burger," which contains a synthetic (indeed GMO) ingredient derived from a plant, widely diverges from the Agency's regulation of dietary supplements containing synthetic plant ingredients. The discrepancy is not only demonstrated in the Agency's varying responses concerning the Impossible Burger and "bioequivalent" synthesized dietary supplements, but extends to the Agency's policy on synthetic steroid supplements and in other realms, as well. For example, the Agency also abides by a hands-off approach in its policy on genetically modified organisms ("GMOs"), which

necessarily include synthesized ingredients. By contrast, dietary supplement products containing plant-based synthetic ingredients are outlawed altogether (precluded from being deemed a dietary ingredient)—as stated in both the 2011 Draft Guidance on NDI Notifications, and on the 2016 Revised Guidance. Also in contrast to synthetic vitamins, synthesized botanicals are proscribed.[5]

The Impossible Burger

Recent newspaper and magazine articles have explored the regulatory controversy surrounding a synthetic meat product created and marketed by Impossible Foods, Inc. *See* Matt Simon, *The Impossible Burger: Inside the Strange Science of the Fake Meat that Bleeds*, WIRED, Sept. 20, 2017; Stephanie Storm, *Impossible Burger's 'Secret Sauce' Highlights Challenges of Food Tech*, N.Y. TIMES, Aug. 8, 2017; *FDA Casts Doubt on Safety of Impossible Burger's Key GMO Ingredient*, HUFFINGTON POST, Aug. 11, 2017; David Gelles, *The 'Impossible' Veggie Burger: A Tech Industry Answer to the Big Mac*, N.Y. TIMES, Jan. 13, 2017. As discussed in these articles, as well as in the Agency Response Letter to Impossible Food's GRAS Notice, the Impossible Burger contains soybean leghemoglobin ("SLH") derived from *Pichia pastoris*. SLH is a genetically engineered yeast. Synthetically-produced SLH also results in the production of 46 unexpected additional proteins, some of which remain unidentified, and none of which have been assessed for safety in this product.

Importantly, SLH is a synthetic copy of heme—apparently an ancient molecule found in every living organism—which causes the Impossible Burger to resemble and taste like meat. In a letter dated August 10, 2017, Pat O. Brown (CEO and Founder of Impossible Foods) described the production of the Impossible Burger in this way: "[w]e used yeast cells, into which we introduced a plant gene encoding a protein called [SLH] that is naturally found in the roots of soy plants. The heme in the Impossible Burger is atom-for-atom identical to the heme found in meat, fish, plants and other foods." The Huffington Post described the Impossible Burger by focusing on the synthetic nature of its production: "[t]he Impossible Burger is made using a genetically engineered form of a protein [] SLH or 'heme' that is found in the root nodules of soybean plants. Impossible Foods adds an SLH gene to a yeast strain, which is then grown in vats using a fermentation process." Thus, the Impossible Burger is a GMO food—for which no set of laws or regulations exist, and on which scientists are divided as to safety issues.

Impossible Foods submitted an application to seek GRAS status for SLH from the FDA in September of 2014. Specifically, the Impossible Food's GRAS Notice stated that SLH is "[i]ntended for use as a **flavor** in meat analogue products." (emphasis added). In his August 2017 letter, Pat O. Brown declared that because SLH is a synthetic copy of naturally-occurring heme, it should be "by default presumed to be safe," and that scientific testing of the Impossible Burger was not necessary. But out of "deep respect" for the FDA and the safety of Impossible Burger consumers, Mr. Brown stated that his company undertook a "deep scientific study of its [product's] safety." The company's conclusion that SLH is safe for human consumption was based, in part, on a study that fed rats SLH every day for a month at levels more than 200 times

[5] Amy Povinelli, Esq. and Holly Stewart, Esq., of Ryley Carlock and Applewhite, both contributed to this Section IV.

what an average American would consume if all ground beef in their diet came from Impossible Food's meat product.

However, Impossible Foods withdrew its GRAS notice in late 2015, after documents produced under a Freedom of Information Act ("FOIA") request revealed that the FDA had circulated an internal memorandum in preparation for a phone call with Impossible Foods that indicated SLH would not meet the requirements for GRAS status. Namely, the Agency's position was that the "FDA believes that the arguments presented, individually and collectively, do not establish the safety of SLH for consumption, nor do they point to a general recognition of safety." Nonetheless, no enforcement action was taken against Impossible Foods (i.e., no warning letter or consumer alert was issued) when its novel product with a synthetic GMO ingredient became publicly available in 2016. Today, the Impossible Burger continues to be marketed and sold in 43 restaurants nationwide, which means that millions of novel burgers are being consumed.

Notably, Impossible Foods identified SLH as a "flavor" in its GRAS notice. But the description of the Impossible Burger also leads to the interpretation that SLH is, instead, a food ingredient. Thus, because the Agency has yet to formally comment on the Impossible Burger it remains unclear whether SLH is a flavor or food ingredient. If SLH is a new flavoring, then it falls within the statutory category of a food additive. The FD&C Act states that food additives require premarket approval based on data demonstrating safety. Any food additive that has not been approved for its intended use in food is deemed to be unsafe and causes the food to be adulterated under Sec. 402(a)(2)(C)(i) of the Act. Yet the Agency has permitted the company to withdraw its unsuccessful GRAS notice and has never required Impossible Foods to even file a food additive petition, despite the Agency's safety concerns. Thus, we currently have the disharmony that synthetic botanical supplements would be banned as adulterated, yet novel burgers with this questionable synthetic ingredient are not banned.

Inconsistent Treatment of Supplements Containing Plant-Based Synthetic Ingredients

In stark contrast to the laissez-faire approach taken by the Agency to the plant-based synthetic meat product of the Impossible Burger, the 2011 NDI Draft Guidance, in place at the time of the Impossible Burger's submission of its 2014 GRAS notice, takes a significantly different position regarding plant-based synthetic substances. Specifically, the 2011 Draft Guidance states that "[a]ltering the chemical structure of a dietary ingredient . . . creates a new substance that is different from the original dietary ingredient [and that] the new substance is not considered to be a dietary ingredient merely because it has been altered from a substance that is a dietary ingredient." (Jarrow concurs with the FDA position on DMAA because there is no basis to claim that DMAA is a component of food or even of a recognized herb.)

Both the 2011 and 2016 Draft Guidance on NDINs notifications state that dietary supplements containing plant-based synthetic ingredients (particularly synthetic herbs or botanicals) are deemed adulterated under § 402(f) of the FD&C Act. Namely, the Draft Guidances issued in 2011 and 2016 point out that according to the FD&C Act, synthetic herbs or

botanicals cannot be dietary ingredients at all.[6] The 2016 Draft Guidance states that "a substance that has been synthesized in a laboratory or factory has never been part of an herb or other botanical and, therefore, is not a dietary ingredient." The FD&C Act delineates that an herb or botanical includes only plants, algae, fungi, their exudates, and their physical parts. 21 U.S.C. § 321(ff)(1)(C). The Draft Guidances issued in 2011 and 2016 conclude, then, that a synthetic copy of an herb or botanical is necessarily excluded from the definition of a dietary ingredient, and that any dietary supplements containing such synthetic ingredients are deemed adulterated. The ban on biosynthetic equivalents fails to take into consideration the impact on rare or endangered species or the availability of substances from slow growing flora.

Interestingly, the Agency has yet to explain why dietary supplements containing synthetic botanical or plant ingredients should receive such vastly different treatment from a food product containing a synthetic plant ingredient other than the notion that supplements must be food derived which is hardly the case otherwise, viz, amino acids. Historically, the Agency has permitted synthetic food products to enjoy marketability in spite of substantial health concerns surrounding their consumption. For instance, various artificial sweeteners have been approved as new food additives, despite dubious safety evidence; the most notable example is aspertame, on the market and ubiquitous in diet sodas for over 40 years. Its categorization as "food additives" is an arbitrary distinction in light of the likely comparative serving size amounts.

Inconsistent Treatment of Genetically Modified Organisms

Furthermore, it is clear from the company's own description of the Impossible Burger's processing that SLH is a GMO, which brings to the fore yet another apparent discrepancy in the Agency's policy on laboratory-made food products as opposed to synthetic dietary ingredients. The *Huffington Post* article discussed above echoes the letter written by the Impossible Foods Founder and CEO by stating that the SLH in the Impossible Burger is "genetically engineered." It is significant that the Agency has also taken a laissez-faire approach to GMOs despite the fact that they are essentially brand new molecules. The FD&C Act does not mention GMOs at all, and the Agency has issued no regulations pertaining to GMOs, even though GMO foods and seeds have been on the market for over twenty years.

Apparently, the Agency's only official documents on GMOs have been the Statement of Policy it issued in 1992 entitled, "Foods Derived from New Plant Varieties" and the Guidance it issued in November of 2015 entitled, "Voluntary Labeling Indicating Whether Foods Have or Have Not Been Derived from Genetically Engineered Plants." The former announced the general policy that the Agency has abided by from the early 1990s until today: "foods . . . derived from plant varieties developed by [. . .] new methods of genetic modification are

[6] The 2011 Draft guidance mentions that "in rare instances" a new substance created from the chemical alteration of a dietary ingredient may "independently qualify for one of the dietary ingredient categories listed in section 201(ff)(1) of the FD&C Act." The 2016 Draft Guidance expands upon this notion by explaining that, under certain circumstances, a synthetic copy of an herb or botanical may qualify as a dietary ingredient under the provision's subsection of substances used "'to supplement the diet by *increasing* the *total* dietary intake.'" Therefore, a synthetic plant-based ingredient does not qualify as "an herb or other botanical" under the FD&C Act but it may qualify as a dietary ingredient under this alternative subsection so long as it is a "substance commonly used as human food or drink" and "has been used as a lawfully marketed ingredient in the conventional food supply."

regulated within the existing framework of the Act." Also in 2015, the Agency determined that AquaBounty Technologies' genetically engineered salmon was safe for human consumption. But there are a number of genetically engineered plants being marketed and sold which the Agency has yet to review for safety. For example, over the past several years, GMO corn and soy have had a pervasive presence in our food supply—because they are extensively used in animal feed. Even if such products are not directly ingested by consumers, GMO corn and soy are routinely fed to livestock, such as cows and pigs, which in turn comprise a large part of our country's supply of conventional meat.

The United States Department of Agriculture ("USDA") has taken the logical position that genetically engineered plants cannot be deemed organic because, by definition, they are not naturally-occurring. *See Organic Standards*, USDA (last visited Nov. 19, 2017), https://www.ams.usda.gov/grades-standards/organic-standards (stating that "organic operations must demonstrate that they are protecting natural resources, conserving biodiversity, and using only approved substances"). The USDA's position is that "[t]he use of genetic engineering, or GMOs, is prohibited in organic products," and that organic products cannot come "in contact with [genetically engineered] substances from farm to table." *Id.* Likewise, the first regulation issued from the National Organic Program, which governs organic food and was finalized in 2000, prohibits the use of GMOs during the production or handling of any organic product. *See* 7 CFR 205.1.

In contrast with the USDA's policy, the FDA declares that the same regulatory framework that applies to any non-synthetic food product similarly applies to food products containing genetically engineered substances. Specifically, the Agency states that it regulates human food from "genetically engineered ('GE') plants like we regulate all food. . . . We encourage producers of new foods and food ingredients to consult with the FDA when there is a question about an ingredient's regulatory status, [including] foods produced using genetic engineering techniques." (Emphasis added: Note that there is no requirement for pre-market consultation.) In the 1990's the Agency created the Plant Biotechnology Consultation Program to "cooperatively work with GE plant developers to help them ensure foods made from their new GE plant varieties are safe and lawful." But, significantly, "the consultation program is **voluntary**." (Emphasis added).

Thus, similar to a voluntary GRAS notice, GE plants in food products are only monitored by a voluntary compliance mechanism. In contrast, dietary supplements containing new "dietary ingredients" that fall within the scope of the FD&C Act's definition of such substances must file a notification 75 days pre-market, with very rigorous notification requirements, evidencing a reasonable expectation of safety, with FDA in the 2016 Revised Guidance (as well as in the 2011 Draft Guidance) still recommending 10 safety and toxicology tests. Thus, non-synthetic NDIs must meet the demanding requirements of pre-market notification and may not enter the market until the NDI is acknowledged by the FDA, while GMOs (which are new and novel by definition) do not face any pre-market requirements, and manufacturers may choose whether to voluntarily consult with FDA pre-market. Moreover, synthetic botanicals and herbs are outlawed altogether from qualification as dietary ingredients while genetically engineered plant ingredients in food products are (and have been for 15 years) permitted on the market with no Agency regulation or interference. Again, this discrepancy appears quite contradictory since the core material of dietary supplements containing synthetic plant ingredients are often produced in

nearly identical ways as genetically engineered plants. Thus, the Agency should seriously consider further revising the 2016 Revised Draft Guidance in light of this contradiction in regulatory and enforcement policy it presents.

V. Concurrence with Positions of the American Herbal Products Association ("AHPA")

JFI agrees with the following positions of AHPA, which were presented by Michael McGuffin at the October 3, 2017 Public Meeting.

A. Any substance or compound that was part of the food chain on the DSHEA "grandfather" date in 1994 (and not thereafter chemically changed) should be included by reference in any Pre-DSHEA List as such substances or compounds are "grandfathered" by the explicit terms of the Statute. In addition, any authoritative list should include any traditionally processed ingredient derived from a pre-DSHEA botanical ingredient, since it should be assumed that every botanical raw material that was marketed in the U.S. pre-DSHEA was also marketed in an extract form manufactured through traditional processing (e.g., tinctures, oils, vinegars, etc.).

B. The agency must accept records that are currently widely available, modified as needed to make corrections or to remove a few specific listed ingredients. These include the lists submitted by industry in the years just after the enactment of DSHEA, AHPA's two editions of Herbs of Commerce, and the numerous other publications like herb books, farmer's almanacs, herbal ingredient catalogs, and pharmacopoeial references. While the AHPA list constitutes a comprehensive list of plant species putatively sold in the United States prior to October 15, 1994, the list must not be considered as exhaustive; it is conceivable that it overlooked plants that could be recognized subsequently as ODIs, if evidence of marketing exists to support such a classification.

C. Thus, FDA should abandon any quest for absolute proof of pre-DSHEA marketing and move toward exercising enforcement discretion for dietary ingredients that are acknowledged as very likely to have been marketed in the U.S. as of October 15, 1994. This suggestion is consistent with FDA's statement in its September 6, 2017 Federal Register notice that the agency should "better focus our enforcement efforts in alignment with our strategic priorities of consumer safety, product integrity, and accurate information."

D. The FDA should move away from its prior position that only pre-DSHEA use of an ingredient in a product that would today be identified as a dietary supplement actually demonstrates an ingredient to be a pre-DSHEA ingredient. Congress intended the mere presence in the marketplace of any orally consumed dietary ingredient—whether in a conventional food, a supplement-form product, or an ingredient used in a traditional therapeutic product other than a new drug—to be sufficient to establish the ingredient as an existing, or old, dietary ingredient. The separate adulteration provisions of the law protect against any use of such ingredients unless reasonably expected to be safe.

E. The Agency should clearly communicate that there is no requirement for a dietary supplement company to document that pre-DSHEA ingredients used in their dietary supplements

are ODIs. Jarrow believes that the intent of Sec. 8 is that the individual manufacturer handles NDI issues on a case-by-case basis.

F. FDA should abandon its prior position that only pre-DSHEA use of an ingredient in a product that would today be identified as a dietary supplement actually demonstrates an ingredient to be a pre-DSHEA ingredient. Congress clearly intended the mere presence in the marketplace of any orally consumed dietary ingredient—whether in a conventional food, a supplement-form product, or an ingredient used in a traditional therapeutic product other than a new drug—to be sufficient to establish the ingredient as an existing, or old, dietary ingredient. The separate adulteration provisions of the law protect against any use of such ingredients unless reasonably expected to be safe.

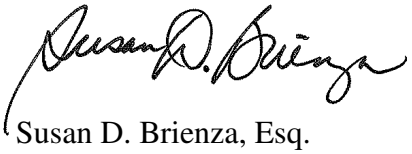
Conclusion

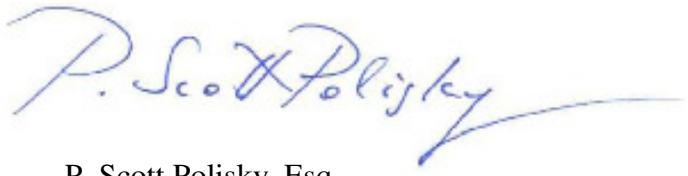
Rather than strict ODI vs. non-ODI distinctions, the Agency should adopt a graded process appropriate to the particular dietary ingredient. As discussed in Section I of this Comment, if the ingredient is a probiotic, there are numerous endemic issues FDA should evaluate in any conclusion as to status, e.g., after safety screening for toxins and antibiotic resistance, a strain belonging to a "grandfathered" probiotic species should not be classified as an NDI; and a new fermentation medium does not create a new probiotic. For the majority of dietary ingredients, in determining status and the appropriate level of scientific documentation, FDA should consider the specific source and type of the ingredient, as well as the number of years it has been on the market. A simple extraction of a naturally-occurring constituent or component of a food should not bear the same NDIN burden as a non-food derived molecule, with the manufacturer of the ingredient extracted from a food freely able to avail itself of the Self-Affirmed GRAS process. For example, Jarrow's position is that an ingredient such as Lycopene, a naturally-occurring constituent of the tomato, should not require an NDIN. With a substance such as Astaxanthin, the status and thus regulatory burden would hinge on its origin, with the conclusion depending on whether it is sourced directly from algae, or from an indirect source, e.g., salmon which eat algae. By contrast, a substance not naturally-occurring in any food, but rather, a product of human metabolism, such as Melatonin, in most cases should require an NDIN if not on the market prior to October 15, 1994. In addition, constituents of GMO foods would certainly be NDIs, similar to F DA's position on nanotechnology foods and compounds.

Finally, as we recommended in Section II of this Comment, FDA should also consider our Proposal for "fast track", simpler notifications for "middle-aged" ingredients—neither old nor new—defined as on the market for five years or more. For post-DSHEA middle-aged dietary ingredients with a history of safe use in any country, the FDA should not require a full-blown NDIN with the attendant burdensome and expensive panoply of safety and toxicology tests currently recommended in the Revised Guidance. Instead, a much more streamlined procedure, but one still providing the statutory (per Sec. 8 of DSHEA) safety standard for the new supplement ("reasonable expectation of safety") should be permitted by FDA.

Thank you for your serious consideration of this Comment. If there are any questions regarding this letter, please contact Susan Brienza at 602-440-4885 or sbrienza@rcalaw.com, and Scott Polisky at 917-837-9600 or Poliskylaw@aol.com.

Sincerely,





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cc: Jarrow L. Rogovin, founder of Jarrow Formulas, Inc.

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