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May 15, 2017

Via 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Re: Docket No. FDA-2011-D-0376: "Revised Draft Guidance for Industry; Dietary Supplements: New Dietary Ingredient ("NDI") Notifications and Related Issues"; Jarrow Formulas, Inc.'s Supplement to its December 12, 2016 Comment with an Expanded Discussion of Probiotics

> **Dr. Gottlieb:** *"As someone who uses dietary supplements every day, I believe they serve an important role in health promotion for millions of Americans and I support consumer access to these products. I believe the regulatory framework established under DSHEA is the right one, and if confirmed, I would commit to enforcing DSHEA, as intended by Congress."*
>
> At Senate Committee Hearings, in "FDA nominee strongly affirms DSHEA during hearing," *NutraIngredients-USA*, by Hank Schultz, April 25, 2017.

Dear Sirs and Madams:

We are writing on behalf of Jarrow Formulas, Inc. ("Jarrow" or "JFI"), a 39-year old dietary supplement company headquartered in Los Angeles, California. This letter Comment is to supplement the December 12, 2016 Comments of Jarrow Formulas, Inc. ("Jarrow" or "JFI") concerning FDA's 2016 Revised New Dietary Ingredient ("NDI") Draft Guidance, here with an expanded discussion of the segment of the dietary supplement market well known as probiotics. We note that the FDA itself stated in its August 12, 2016 Notice announcing its Revised Guidance, that stakeholders "can comment on any guidance at any time (see 21 CFR § 10.115(g)(5))," and we used this further time to explore, analyze, and cover the multitude of issues on probiotics, in particular new probiotic ingredients. As we stated at the conclusion of our original Comments, there are myriad and legal, scientific, and technical issues raised in this Guidance as to live microorganisms. Thus, we have elected to prepare and submit this supplemental, separate Comment on the Revised Draft Guidance solely as to Probiotics in the

context of NDIs. (Hereafter, the Revised Draft Guidance of August 2016 is also referred to as "the Guidance" or "the Revised Guidance.")

As detailed in our first Comment, the Guidance is at odds with DSHEA, with the applicable regulation, and with prior FDA policy. In particular, as to probiotics and prebiotic supplements, the Guidance is inaccurate on many issues and raises more questions than it answers. Significantly, during the most recent April 4, 2017 webinar on the subject, both legal and scientific experts questioned the contradictory nature of the Guidance and its treatment of probiotics. *See* "Probiotics – Challenges and Opportunities from Legal to Lab," webinar sponsored by the Council for Responsible Nutrition and *Natural Products Insider*. These unanswered questions, and a change in policy and treatment of probiotics, leave the supplement industry concerned about the overall impact the Guidance will have if implemented in its present form.

Again, as with the earlier Draft, FDA's 2016 Guidance does not merely guide the industry in the filing of more complete NDI Notifications; instead it attempts to undermine DSHEA, go well beyond the one regulation on NDI Notifications, and in essence impose a new and unauthorized pre-approval scheme—as to new Probiotics as well. Yet with the recent election, the voters have elected executive and legislative branches of government that disfavor further regulatory burdens on business that discourage, threaten and destroy jobs, and that inhibit American innovation. The proposed Revised Guidance is contrary to this expressed will of the public, and to the first executive actions of this new administration *to reduce the number of regulatory burdens* on business in general.

The dietary supplement industry is a multi-billion dollar enterprise in the U.S. This Guidance will severely affect formulators, researchers, R & D, manufacturers, factory workers, ingredient suppliers, marketers, retailers, sales people, and consumers. These points above are especially true for the segment of the supplement market well-known as Probiotics.

I. Introduction and Definition of "Probiotic"

After reviewing both the July 2011 Draft Guidance on NDI Notifications and the August 2016 Revised Draft Guidance, one notices a curious omission: the terms Probiotic and Prebiotics do not occur, despite the fact that probiotics (also termed "live cultures") were discussed in detail, including in the 2011 Draft Guidance a focus on possible risks from "harmful pathogens" --though that "risk" was neither defined nor explained. It was hypothetical since the category of Probiotics is a well recognized, safe, and growing sector within the dietary supplement industry. The market for probiotic dietary supplements is increasing at a CAGR of 11%; and *Euromonitor* estimates that this sector will be worth $5 billion globally by 2021. The U.S. is the leading market for probiotic dietary supplements, computed at a value of $1.9 billion in 2016. (Source: Presentation of Stephen Daniells, Ph.D., Webinar sponsored by United Natural Products Association (UNPA) on November 17, 2016.)

We confirmed the absence of those words Probiotic and Prebiotics with simple searches using the Find function—absent in both the 2011 and the 2016 Draft Guidances. Instead, the FDA uses such terms as: bacterial microorganism, live cultures, fermented foods, and live or viable microorganisms. Such terms obviously need further clarification as "bacterial

microorganisms" also describes B. anthracis aka anthrax. Yet there are clear and well-established definitions for the term "Probiotic," formulated by international groups of experts, notably in 2001.

A 2014 paper provides the background in this summary:

> In 2001, an Expert Consultation of international scientists working on behalf of the Food and Agriculture Organization of the United Nations (FAO) and the WHO debated the emerging field of probiotics. One output was a reworking of the definition of probiotics to the following: "live microorganisms which when administered in adequate amounts confer a health benefit on the host." [citation from 2001 omitted] Since then, this definition has become the most widely adopted and accepted version worldwide. [Emphasis added.]

Then this definition was referenced as accepted by others in the field 13 years later, in 2014, in a paper significantly entitled "Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic."[1] (Emphasis added.) The same definition is repeated in many later scientific papers: for example, Mary Ellen Sanders, Ph.D., writes in "Probiotics in 2015: Their Scope and Use": "Probiotics are defined as live microorganisms that, when administered [ingested] in adequate amounts, confer a health benefit on the host."

These definitions have been much debated and widely accepted by scientific bodies; and it is significant to note that while there continue to be scientific discussions and publications concerning the efficacy of various strains, there is no question among experts that probiotics occur in foods, supplements, drugs, and medical foods, and generally have beneficial effects.

It is also clear that historically the FDA has considered Probiotics to be a sub-category of dietary supplements. For example, in the Preamble to the Final Rule on Claims for Dietary Supplements, 65 Fed. Reg. 1000 (January 6, 2000), the FDA) gave the following claim as an example of an acceptable claim, permissible for dietary supplements: "Helps maintain intestinal flora." This at least implies that FDA recognizes that probiotics are used to supplement the diet, and that they confer a health benefit—echoing the accepted definition above unless FDA was referring only to prebiotics. But then, a "prebiotic" for what? Just "micro-organisms."

In this Comment, we discuss the history, safety, benefits, and science of Probiotics; and in various ways we disagree with FDA's handling of new products in this important sector of the dietary supplement market within the Revised Guidance. Avoidance of the term "Probiotics" comes across as bureaucratese for its own sake, because literate Americans know what a probiotic is.

II. Probiotics are Clearly Dietary Ingredients within the Dietary Supplement Definition

It is important in this Comment to revisit specific areas of DSHEA that play a role when creating a guidance document to interpret the statute (Sec. 8 of DSHEA) and the regulation (21 C.F.R. §190.6) as to the content of NDI notifications. The intent of Congress when a statute is

[1] Hill C, Guarner F, Rei G, *et al.* in *Nat Rev Gastroenterol Hepatol.* 2014; 11: 506-514.

enacted should be a paramount when drafting implementing regulations and guidance documents. The statute and Congressional intent is supposed to control all follow on documents. In turn, the statute, Congressional intent, the regulations, and guidelines generally determine resulting case law.

By looking back at DSHEA we see under §2. Findings:

Congress found that –

(1) improving the health status of United States citizens ranks at the top of the national priorities for the Federal Government;

(2) the importance of nutrition and the benefits of dietary supplement to health promotion and disease prevention have been documented increasingly in scientific studies; […]

(5) preventative health measures, including education, good nutrition, and appropriate use of safe nutritional supplements will limit the incidence of chronic diseases, and reduce long-term health care expenditures; …

(6)(B) reduction in health care expenditures is of paramount importance to the future of the country and the economic well-being of the country; […]

(8) consumers should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements; […]

(12)(A) the nutritional supplement industry is an integral part of the economy of the United States; […]

(13) although the Federal Government should take swift action against products that are unsafe or adulterated, the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers;

(14) dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare; and

(15)(A) legislative action that protects the right of access of consumers to safe dietary supplements is necessary in order to promote wellness; …".

From these findings, it is clear the intent of Congress was to make safe dietary supplements readily available to Americans for the purpose of improving their health and well-being, while decreasing overall health care expenditures, and increasing economic gains for the nation through this rapidly expanding industry sector, while also reducing certain healthcare costs.

Section 413 (b) allows for a petition, stating that "Any person may file with the Secretary a petition proposing the issuance of an order prescribing the conditions under which a new dietary ingredient under its intended conditions of use will reasonably be expected to be safe." (Emphasis added.) This clearly defines what is considered an NDI and what is not. It also clearly established that the required standard of safety is "reasonably be expected to be safe," and not the higher food additive standard or the GRAS standard of Generally Recognized As Safe.

Section 13 of DSHEA establishes the Office of Dietary Supplements, where the purpose of this office is stated to be "(b) (1) to explore more fully the potential role of dietary supplements as a significant part of the efforts of the United States to improve health care; and (2) to promote scientific study of the benefits of dietary supplements in maintaining health and preventing chronic disease and other health-related conditions." Yet the Guidance actually discourages scientific research and R & D investment for beneficial supplements. Reclassification of probiotics as "biologics" would be a devastating blow to any further investment in the field. It would put prebiotics into a class with insurmountable economic and regulatory hurdles and no discernible reason to invest. It would be a dead-end for no valid reason and opposed by the Public and Congress.

Probiotic supplementation is more relevant and important now than possibly at any other time in human evolution. Due to developments in sterilization, excessive use of cooking, and reduced intake of fresh produce and fermented foods, the daily dietary intake of healthful organisms and their metabolites has been reduced by many logs. Probiotic supplements and increased intake of well formulated and probiotic-fortified fermented and non-fermented foods is the reasonable course. The recklessly risky course is further exacerbated by the negative shift by modern humans away from their natural microbial ecology. The situation is particularly acute now that most infants in developed countries are currently born in pathogen-ridden hospital environments, and frequently by Caesarian birth and fed sterilized formulas. The exposure to probiotics and beneficial live microbes today occurs later in life and in fewer numbers and variety.

FDA's implied proposed reclassification away from the term and category of "probiotics" will only worsen an already undesirable situation. It is scientifically established that increasingly germ-free childhoods lead to more asthma and immune insufficiencies. These compelling health reasons require a more reasonable approach to the regulation of probiotic ingredients and encouragement–not stifling–of innovative new ones.

III. The appropriate classification of probiotics is clear under the plain reading of the dietary supplement statute.

It is inexplicable for the Agency to suddenly pose a dilemma for probiotics by deeming them as anything other than dietary supplements. Clearly, probiotics meet the "23-year" rule, except now the agency is moving the goal posts; on the market, yes, but never as probiotics. The notion is mind-boggling and argues against the adoption of any new scientific terms post-DSHEA. The regulatory scheme is being defenestrated – or, in this case, "evacuated."

To go so far as to now attempt to argue that any microbe from the generally recognized genera of probiotics is anything other than a dietary supplement is without scientific justification,

contrary to long-accepted understanding and practice, and a blatant attempt to "disembowel" Congressional intent and even long-established regulatory practice. As to the Agency's position that it does not recognize probiotics as a category, manufacturers, marketers, and consumers will not cease using the term.

In this context, the Agency is attempting to act more as a censor of cultural customs and as a linguistic monitor than as a food safety authority. In the process of doing so, it is not only usurping the role of Congress, but infringing on fundamental rights recognized in the Preamble of the Declaration of Independence, which were deemed to be part of the Constitution by the first Supreme Court Justices.

The Agency's "questioning" of the categorization of probiotics as dietary supplements has no basis in law. DSHEA states, *inter alia*:

> §3. Definitions.
>
> (a) Definition of Certain Foods as Dietary Supplements**.** Section 201 (21 U.S.C. 321) is amended by adding at the end the following:
>
> (ff) The term "dietary supplement" -
>
> (1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
>
> (A) a vitamin;
>
> (B) a mineral;
>
> (C) an herb or other botanical;
>
> (D) an amino acid;
>
> (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or [Emphasis added.]
>
> (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

Probiotic organisms are known to be acquired by their host – the human body – through various conventional (food) and unconventional (birth canal, hand-to-mouth transfer, breast feeding, the environment) routes. What is lacking here is not whether probiotics are "dietary" but the agency's understanding of the subtlety of what constitutes "dietary." Probiotics are permanent residents of their human hosts. They are not an artificial imposition. One example would be Lactic Acid Bacteria (LAB) and their historical background:

> Lactic acid bacteria (LAB), including species of Lactobacillus, Streptococcus, Pediococcus and Leuconostoc have been used for preservation of food by fermentation for thousands of years. People of Eastern Europe, Southern

Asia and Northern Africa have consumed yogurt and kefir for thousands of years. Fermentation of milk by LAB has permitted its preservation, improved its palatability and digestibility. Ancient people regarded these fermented milks as "divine" foods and as indispensable remedies for various illnesses.

Fermentation of food provides characteristic taste profiles and lowers the pH, which prevents contamination by potential pathogens. Fermentation is globally applied in the preservation of a range of raw agricultural materials (cereals, roots, tubers, fruit and vegetables, milk, meat, fish etc.). L. plantarum frequently occurs spontaneously, in high numbers, in most lactic acid fermented foods of plant origin, for example, in brined olives, capers, and sauerkraut. Thus, humans have in this way consumed large numbers of live LAB, and presumably those associated with plant material were consumed before those associated with milk based foods.

A century ago, Elie Metchnikoff (Russian scientist, Nobel laureate, and professor at the Pasteur Institute in Paris) postulated that LAB offered health benefits leading to longevity. He considered yogurt to be one of the most effective means of inhibiting intestinal infections, intoxications and putrefactions, which he thought were the cause of a great number of conditions such as premature senility and lack of vitality.[2] [As noted on page 9 of this Comment, the findings of Nobelist Metchnikoff (also spelled Metchnicov) were also praised by Dr. O'Sullivan, a key participant at FDA's 2000 Food Advisory Committee meeting on probiotics.]

In sum, the species found in the food supply that have a long history of safe use are also the same species found in probiotic products, and these same species are also residents of the human host. Further, it is as reasonable to supplement the body's probiotic population as it is to supplement, for instance, mineral intake.

When section 301 is taken into account in this light, there is no basis for the Agency to consider transfer of probiotics into the category of drugs and biologics. Doing so will have detrimental effects on the industry and on future products. More fundamentally, such reclassification is also scientifically and logically indefensible. Again, neither Congress nor the American people would tolerate such irrational overreach, particularly in light of the fact that probiotics are healthful, not harmful, organisms and resident in the human body for its benefit. In particular, probiotic supplements are well-recognized as beneficial by registered dietitians, and have won the approval and recommendation of many GI doctors as well as OB-GYNs.

IV. FDA's Long-Standing Recognition of the Worldwide Historical Use and Safety of Probiotics

In the same year as FDA issued its Final Rule on Claims for Dietary Supplements (2000), with claims about good bacteria or beneficial intestinal flora referenced as acceptable supplement "structure/function" statements, the Agency's Food Advisory Committee convened

[2] Peilin Guo, MS. RD & Silvano Arnoldo B.Sc., "Probiotics: The Foundation for Total Well Being," internal brochure for Jarrow Formulas, Inc.

for an important summit on probiotics. The September 26-27, 2000 meeting in Arlington, Virginia included a focus on two major topics: the long history of probiotics in fermented foods, and the safe use of probiotics in dietary supplements. From the Transcript of Proceedings, we find the following excerpts and quotations quite relevant and significant for the themes and arguments of our Comment. Apparently, in 2000, the FDA knew how to use and discuss the term and concept "Probiotic." What happened in the interim?

Dr. Bob Buchanan (FDA-CFSAN, Senior Science Advisor and Dir. of the Office of Science):

> Fermented foods have long been an integral part of the diets of various regions. One of the things that is unique as you travel around the world is that you get to sample the different fermented foods that all unique and interesting and are part of the character of the country. While these products have been an integral part of our diet, it hasn't been until the last half of the twentieth century that a scientific effort to study the organisms that are being ingested in fermented foods or as part of the normal contaminants of the diet, and their impact on the health of the consumer. (Page 10; all page references refer to the Report from this 2000 Symposium on Probiotics.)
>
> As we enter the twenty-first century FDA is increasingly being called upon to look at the whole area of probiotics in terms of both its safety and its efficacy, two areas for which we have responsibility both in terms of foods themselves and for dietary supplements. (Page 11)
>
> Probiotic means "for life." (Page 16) [Cf. The FDA accepting that the claim "good flora" is an acceptable structure/function claims for supplements, above.]

Dr. Douglas Archer (former FDA-CFSAN official with 20 years tenure):

> In 76 B. C., Plinio advocated the use of fermented milk to treat GI infections. In 1906, Tissier recommended the use of bifidobacteria for infants with diarrhea. (Page 27)
>
> Again, thinking about safety as an issue, populations consuming lactic acid bacteria worldwide –I mean, virtually everyone does if you go to various countries, certainly infants, children, adults, people of all health statuses -- and I know you will hear some clinical studies later that were done on some severely ill people and, yet, there are virtually no infections caused by the probiotic strains themselves. (Page 30)
>
> "In the area of probiotics, the U.S. is behind the world in their acceptance in common use. Clearly, the E.U. countries and Japan are light years ahead. In Japan, there are vending machines as common as Coca Cola or Pepsi Cola that dispense probiotic formulas. In the E.U., there are many products on the market, such as infant formulas containing probiotic cultures. (Page 34)

Dr. Mary Ellen Sanders, PhD. (Founding President and Current Executive Science Officer for the International Scientific Association for Probiotics and Prebiotics):

> I would say that in the U.S. if you asked people if there are bacteria in their intestinal tract they would probably say no. I don't think people are aware … there, so there is none of an inherent understanding. (Page 119)
>
> I would say there is a much greater inherent sense of GI tract health and the role of micoflora in the Asian culture than there is here. What you have in Europe is that they like their dairy fermented products there, and we have been very slow to copy that. … They are very trusting of fermented dairy products. (Page 120)

Dr. Daniel J. O'Sullivan (Department of Food Science and Nutrition, University of Minnesota):

> We all know what probiotics essentially are and, as we have heard this morning from Dr. Archer, it is a live microbial food supplement, so it beneficially affects the host's intestinal microbial balance. (Page 121; emphasis added)
>
> The concept of probiotics … is not brand new. The terminology may be quite new but the concept has been around for approximately a hundred years … at the turn of the century we had Metchnikov, a Nobel Prize winner, essentially promoting the use of lactobacilli cultures, fermented dairy products, and Tissier promoting the ingestion of bifidobacteria. (Pages 124-125; emphasis added)

V. Examples of the Agency's Use and Acceptance of the Term "Probiotic"

For years, FDA has received and acknowledged numerous 30 Day Notifications pursuant to Section 6 of DSHEA listing structure function statements that companies have made related to probiotics. These Notifications are of course then publically posted. This is significant because through this process, FDA has repeatedly been made aware of and acknowledged these claims and therefore the validity of probiotics as a class of dietary supplement products. Below is a selective, non-exhaustive list of Notifications for dietary supplement products submitted with statements related to probiotics.

- New Chapter, Inc. (May 2000) All-Flora Probiotic Live Cells: "Supports immune function"; "Supports intestinal detoxification and promotes normal bowel function"

- Weeks & Leo Co., Inc. (March 2003) Acidophilus with Pectin Capsules: "Helps reinforce intestinal flora"

- PhytoPharmica (November 2003) Probiotic Pearls: "Oral ingestion of probiotics produces a stabilizing effect on the gut flora."; "Probiotic Pearls is a probiotic dietary supplement designed to help support digestion and a healthy intestinal system."

- SLC Sweet, Inc. (November 2003) Somersize Living Active Activated Multi-Vitamin Dietary Supplement: "Is your multi-vitamin active.3 Somersize Activated Multi-Vitamins introduce a new experience in nutritional supplements with the maximum activity, digestibility and stability. By adding the value of "probiotic" nutrients, vitamins and minerals can increase your vitality and well-being like never before. Just as milk is biotransformed into yogurt, becoming one of nature's most powerful healing foods,

vitamins and minerals can be transformed to probiotic nutrients and become many times more effective in restoring balance and generating energy. Start Living Active, naturally!"

- CNS, Inc. (February 2005) FiberChoice: "Inulin assists in resorting and maintaining intestinal flora."; "Inulin found in FiberChoice assists in restoring and maintaining intestinal flora."; "Soluble fiber found in FiberChoice assists in restoring and maintaining intestinal flora."; "FiberChoice assists in restoring and maintaining intestinal flora."; "Inulin is a prebiotic which helps grow beneficial bacterial for good digestive balance."; "Inulin found in FiberChoice is a prebiotic which helps grow beneficial bacteria for good digestive balance."; "FiberChoice contains a prebiotic (inulin) which helps grow beneficial bacteria for good digestive balance."; "Inulin provides prebiotic nutrients that help grow the beneficial bacteria and prevent harmful bacteria."; "Inulin found in FiberChoice provides prebiotic nutrients that help grow the beneficial bacteria and prevent harmful bacteria."; "FiberChoice provides prebiotic nutrients that help grow the beneficial bacteria and prevent harmful bacterial."

- SCD Probiotics (March 2014) SCD Essential Probiotics: "Supports healthy digestion"; "Promotes regularity"; "Supports intestinal health"

- Country Life (February 2015) Power-dophilus Dairy Free Probiotic: "Supports digestive health."; "Helps to support microflora balance."; "Country Life's Power-dophilus provides a targeted blend of 12 billion CFUs per serving of four probiotics to support digestive health."; "Power-dophilus is formulated to help support microflora balance in both the small and large intestines, providing a wide array of support."

- Perrigo Company of South Carolina (February 2015) Perrigo – in sync promotional: "Probiotics are good bacteria that may help promote digestive system balance."

- Sotru, LLC (April 2015) Sotru Fermented Digestive Greens: "For your optimal health and vitality"; "Supports healthy gastrointestinal health"; "Fermented Greens for maximum nutrient absorbtion"; "With Tegrical an immunoglobulin-rich colostrumextract clinically-shown to support mucosal immune protection, healthy gut integrity and well being"; "Digestive enzymes and herbs, probiotics and prebiotic fiber for balanced intestinal microflora"; "To Support Optimal Digestion, Assimilation, and GI Health"; "Supports Healthy Gut"; "Enhances Digestion"; "Supports Immune Health"; "Supports Optimal Body Alkalinity"

- FoodScience Corporation (April 2015) Mega Probiotic-ND with Digestive Enzymes Chewable: "A Dietary Supplement to Support Digestion and G.I. Tract Health"

- Garden of Life, LLC (August 2015) Once Daily: "Daily Support for Digestive & Immune System Health"

In addition, many Warning Letters have been issued including references to probiotics, showing further that FDA itself uses and accepts the term of "Probiotics" to refer to a class of supplements:

- Warning Letter, James G. Cole, Inc. dba Maxam Nutraceutics (September 28, 2012): "For example, your firm used the component "(b)(4)" to manufacture "PCA Enzyme Supplement With Probiotics," but you failed to establish component specifications for this ingredient." "Specifically, your firm uses **"**(b)(4)" to manufacture "PCA Enzyme Supplement With Probiotics," but you did not perform an identity test or examination of this dietary ingredient."

- Warning Letter, Hillestad Pharmaceuticals USC, Inc. (April 17, 2013): "As previously stated, you use (b)(4) for all identity testing but you have not demonstrated that this is an appropriate test to identify probiotic species. We note that the (b)(4) is limited in its capability to adequately identify live strains of organisms."

Further, several 75-Day Premarket Notifications have been submitted to the FDA in support of new dietary ingredients for use as or in probiotics. In an August 2013 response letter from the FDA to Global Suppleceutical Formulations regarding its Notification related to the "7 AM **Probiotics**" product, the FDA thoroughly discusses the new dietary ingredient that is intended to be marketed in a dietary supplement product. The letter details further information needed, citing FDA guidance documents for the submitter to review that discuss what should be submitted to demonstrate the identity of a live microbial dietary ingredient as well as the safety of a microbial NDI. But not at any point does the FDA dismiss the proposed product as a probiotic, nowhere stating that a supplement or a dietary ingredient may not be a probiotic at all. Thus, our conclusion is that FDA itself uses and accepts the term "probiotic" in the context of dietary supplements and of supplement claims.

VI. Probiotics are safe, in both foods and dietary supplements

The intent of Congress in DSHEA was predicated on a presumption of the safety of dietary supplements. Yet, the burden of proof of safety for dietary supplements is a major issue in the Guidance that is at conflict with the original intent of Congress. Clearly this burden is placed on FDA as defined in 21 CFR Section 402(f)(1) "Adulteration of Foods" which states, "…In any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated." As is common knowledge, and--as we discussed on pages 3-4 of this letter--duly observed by many during FDA's internal 2000 discussion, probiotics have been used in foods and for supplements, and have been naturally-occurring in foods for decades, in some countries, for over a century.

It is significant to note that several probiotics have achieved the GRAS level of safety. In a letter dated November 18, 2008, concerning GRAS Notice No. GRN 000254, FDA had no questions regarding BioGaia AB's conclusion that Lactobacillus reuteri strain DSM 17938 is GRAS under the intended conditions of use (an ingredient in processed cheeses, yogurt, ice cream, fruit juices, fruit drinks, processed vegetables, processed vegetable drinks, beverage bases, energy bars, energy drinks and chewing gum at up to 10E9 colony forming units (cfu) per serving and in a drinking straw at a level of 10E9 cfu per straw).

In a letter dated July 8, 2009, concerning GRAS Notice No. GRN 000268, FDA had no questions regarding Morinaga Milk Industry Co., Ltd.'s conclusion that Bifidobacterium longum strain BB536 is GRAS under the intended conditions of use--an ingredient in breads/baked

goods, cereals, dairy products/dairy-based foods and dairy substitutes, fruit products, candy, chewing gum, cocoa powder, condiment sauces, flavored beverage syrups, fruit flavored powder beverage mixes, gelatin desserts, gravies, margarine, peanut and other nut butter/spreads, snack foods, weaning foods at a maximum level of 1x10E10 colony forming units (cfu) per serving and in milk based powdered infant formula at a level of 1x10E10 cfu per gram of infant formula powder that is intended for consumption for term infants aged 9 months and older.

In a letter dated April 19, 2011, concerning GRAS Notice No. GRN 000357, FDA had no questions regarding Danisco USA, Inc.'s conclusions that Lactobacillus acidophilus NCFM is GRAS under the intended conditions of use (an ingredient in ready-to-eat breakfast cereals; bars; cheeses, milk products; bottled water and teas; fruit juices, fruit nectars, fruit "ades," and fruit drinks; chewing gum; and confections at a level to provide for 109 cfu/per serving). NCFM was on the market long before 1994.

In a letter dated September 29, 2011, concerning GRAS Notice No. GRN 000377, FDA had no questions regarding Cargill Incorporated's conclusion that B. animalis subsp. lactis strain Bf-6 is GRAS under the intended conditions of use (an ingredient in dairy foods such as fluid milks, yogurt, milk-based desserts and gravies and cheeses; dry seeds, nuts and nut butters; grain products such as flour, yeast breads, quickbreads, cakes, cookies, pies, pastries, crackers, pancakes, waffles, French toast, crepes, pasta, cooked and ready-to-eat cereals, grain mixtures and meat substitutes; fruit and fruit beverages; dark-green vegetables, olives, pickles, relishes, and vegetable soups; salad dressing; sugars and sugar substitutes, syrups, honey, molasses, jellies, jams, preserves, gelatin desserts, ices and popsicles, candies, and chewing gum; and carbonated soft drinks, sports drinks, energy drinks, and water at a maximum level of 1011 cfu/ per serving).

In a letter dated May 29, 2008, concerning GRAS Notice No. GRN 000231, FDA had no questions regarding Mead Johnson & Company's conclusion that Lactobacillus casei subsp. rhamnous strain GG is GRAS under the intended conditions of use (an ingredient in hypoallergenic infant formula powder with extensively hydrolyzed casein and oils containing docosahexaenoic acid and arachidonic acid and without medium-chain triglyceride oil at a level of 108 cfu per gram that is intended for consumption for term infants from the time of birth).

In a letter dated August 31, 2009, concerning GRAS Notice No. GRN 000281, FDA had no questions regarding Fonterra Co-operative Group's conclusion that Lactobacillua rhamnosus strain HN001 is GRAS under the intended conditions of use (an ingredient in milk-based powdered term infant formula that is intended for consumption from the time of birth, as well as in milk-based powdered follow-on formula, at a level of 108 cfu per gram).

In a letter dated July 28, 2008, concerning GRAS Notice No. GRN 00236, FDA had no questions regarding Friesland Foods Domo's conclusion that galacto-oligosacharides (GOS) is GRAS under the intended conditions of use (an ingredient in term infant formula at a level of 5 grams per liter and other food categories, bars, yogurt, frozen dairy desserts, fruit drinks and energy drinks, fitness water and thirst quenchers, fruit pie filling, fruit preparation, jelly/jam, baby juice, baby yogurt drink, baby dessert, baby snack, milk, milk drinks, syrup flavorings for milk, meal replacement drinks, meal replacement drinks, meal replacement drinks for children and milk substitutes.) Even though technically this substance at issue is a Prebiotic, the fact that

it promotes the growth of beneficial organisms in the gut means that in essence it is a precursor to a probiotic, and it too has attained the Generally Recognized As Safe status. It's well known, bifidogenic effect raises no alarms for collateral risk of pathogen promotion. The guidance's "concern" contradicts the Agency's own prior GRAS position.

Finally, there are several recent (2016 and 2017) FDA no questions letters allowing GRAS status for various probiotics. For example, DuPont Industrial Biosciences received a no questions letter from the FDA on GRAS Notice No. GRN 000664 for an a-amylase enzyme preparation produced by *Bacillus licheniformis*. DuPont plans to use this enzyme in the production to obtain various glucose-rich syrups which in turn will be used in the manufacture of dextrose and high fructose corn syrup—clearly with widespread use in the food supply. On November 28, 2016, Keller and Heckman LLP received a no questions letter from the FDA on GRAS Notice No. GRN 000649 for an enzyme preparation produced by *Bacillus subtilis.* The sponsoring company, GenoFocus plans to use this enzyme preparation in a variety of food applications, including foods consumed by children less than one year of age. It is clear that this GRAS status even applies to foods for infants and even newborns, as the FDA letter includes this sentence: "This data supports that the intact enzyme and its metabolized products are not expected to be toxigenic, in case of the possibility of only partial digestion of protein by newborn babies as a result of their immature digestive systems.

We observe that the GRAS status for these probiotics in certain foods not only attests to their safety (with no questions even concerning the use of certain probiotics in infant formulas). Furthermore, we want to point out that the GRAS standard achieved by many probiotics--"*generally recognized* as safe"-- is a much higher safety standard than "reasonably expected to be safe," which is the safety standard for an NDI. Based on the foregoing, raising general safety concerns about probiotic ingredients in the Guidance deviates radically from logic and from prior practice, from FDA's own official safety assessments (in the GRAS letters above), and creates enormous uncertainty for industry.

VII. Regulatory and enforcement actions are inconsistent with safety concerns related to probiotics.

It has been 23 years since the passage of DSHEA, and thirteen years since FDA held a public hearing on developing this Guidance. In those years, with no specific guidelines, while FDA rejected numerous NDINs, the industry adopted and established practices in response to the prevailing situation. These industry practices, after 23 years of use, are well established and, as shown by the minimal number of adverse event reports for dietary supplements over the past several years, are also working well. In addition, there have been only approximately six Warning Letters sent by FDA as to improper NDIs on the market—none pertaining to probiotics. Most of all the earlier Warning Letters pertained to a steroid precursor, androstendione, which is not a dietary supplement at all. Again, by limiting the stipulations suggested in this Guidance to true NDIs with little or no history of safe use (as is proper under the law), this would limit notifications to those ingredients that need to show a reasonable expectation of safety, and would thus lessen the time and financial burden on both industry and the Agency, and avoid the risk of creating an unnecessary backlog in processing or inhibiting introduction of formulations containing ingredients that have a solid presumption of safety.

VIII. The existing "Grandfathered" lists are accurate and promote uniformity regarding NDIs.

To dismiss all industry "grandfathered" lists is inconceivable. Many industry lists are backed by evidence that the ingredients were actually marketed prior to October 15, 1994, and otherwise could be supported by affidavit. Some industry lists were, in fact, created for the purpose of having substantiated dates of use and the intended use, for their ingredients. The industries creating these lists invested time, money and resources to make sure these lists were accurate and complete. These lists, for lack of any guidance, have been used and are being used, as established industry standards, as "grandfathered" lists. Without these lists, the "grandfathered" status of many dietary ingredients marketed prior to October 15, 1994 would be eliminated through unachievable documentation requirements to prove prior marketing. The Agency needs to review and approve these lists, and to completely rethink its stance toward grandfathered ingredients.

The food industry, like most other industries, uses various ingredient suppliers to create a final product. The Guidance as drafted requires information on both the dietary ingredient and the dietary supplement. This will cause logistical and privacy problems when filing a notification, as proprietary information from both the manufacturer and the distributor will likely need to be included in one single notification. This process would deny a supplement manufacturer the freedom to change suppliers-- which in turn would prevent free competition.

To keep proprietary information confidential, it is suggested that FDA implement a system that would allow the manufacturer to submit information independent of the distributor's information. A dual system with an ingredient manufacturer master file, supported by a distributor notification of the supplement–if needed–is recommended by JFI.

The requirements for proof that the ingredient was marketed as a dietary ingredient in a dietary supplement before October 15, 1994, have been augmented in the Guidance to include documented proof that the ingredient was sold into a dietary supplement, at what amount, and the daily intake. The 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 which predates DSHEA. 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. Neither would Congress nor the American people tolerate such a waste of time and money. Further, most of the requested information such as exact amounts and formulations are of no use other than to hinder and obstruct.

We note that this new requirement is found nowhere in Sec. 8 of DSHEA, or in Sec. 190.6. In this area (and others) the Guidance attempts to create new law. Many companies, due to 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 only to those matters that affect the safety of the product. This is especially the case given that FDA's own estimate for the number of NDINs per year was quite low, but that the economic impact on the industry would be many times greater than FDA's estimate in the Final Rule announcing the regulation 21 C.F.R. sec. 190.6: According to the "Benefit-Cost Analysis" FDA included as part of the DSHEA Final Rule (21 CFR 190.6; Federal

Register, Sept. 23, 1997), "FDA estimated the number of new ingredients to be 0 to 12 per year and the cost per notification to be $410, for an annual cost range of $0 to $4,920 per year. In the most recent year [1996], the industry introduced six new ingredients for an estimated cost of $2,460. FDA received no comments on these estimates and consequently concludes that the actual costs of this rule will not be significant." (Emphasis added.)

In fact, the costs of the 1996 notifications were based on a vastly lesser level of documentation than that required in the Guidance. *Please see the detailed section on costs in the JFI December 12, 2016 Comment.* It is clear at this point—under the requirements of the Revised Guidance--that an NDIN costing $500,000 would be a "bargain." Five million dollars may be a likelier number, if not higher. Multiplied out, the cost of the industry would be equivalent to the gross sales of an entire year. It is a bankrupting number. It seems likely many companies could be put out of business.

Although an ingredient has been on the market as a dietary ingredient in a dietary supplement, or in food, the unachievable documentation requirements set forth by the Guidance have eliminated this ingredient from the "grandfathered" status it has enjoyed for the past 23 years. It is now the subject of an NDI notification. In submitting an NDIN to the Agency, it is, in fact, telling the Agency that the ingredient subject to the notification has not been on the market as a dietary ingredient in a dietary supplement or in food. Many of these "grandfathered" dietary ingredients now have published clinical studies – consistent with the purpose of the Office of Dietary Supplements -- "to promote scientific study of the benefits of dietary supplements…." In a broader view, the concept of "probiotics" itself must be deemed "grandfathered"; and transfer of the category to drugs or biologics would be contrary to the applicable law.

IX. Concurrence with the Position of IPA at the November 2, 2016 Workshop with FDA and the Views of Others in the Supplement Industry

Jarrow Rogovin, founder of Jarrow Formulas, Inc., was also one of the co-founders of the International Probiotics Association (IPA). Hence Jarrow Formulas was pleased that recently IPA took the initiative to plan a joint Workshop with the FDA to discuss the Probiotics category. That Workshop was held on November 2, 2016, in College Park, MD, and included presentations and discussion on when Probiotics are NDIs.

One issue presented and discussed at the November 2 IPA Workshop was: It is not clear what 'chemically altered' means for live microorganisms. For example, what is the manufacturing process that would sufficiently change the strain identity to affect its safety profile? Dr. Cara Welch's response to 3. above, was: "Manufacturing process changes are what will make the NDI draft guidance evergreen because any change [in the manufacturing process] puts an ingredient back in play" [meaning that the ingredient thereby becomes an NDI]. However, we believe that this rule is much too general and restrictive.[3]

An alarming example of this new rule displayed in the Revised Guidance is that each new fermentation medium will produce a new Probiotic, and thus an NDI requiring a Notification.

[3] Legal and scientific experts at the April 4, 2017 CRN webinar on probiotics expressed the same view.

The IPA's Comment, filed on Dec. 9, 2016, also took issue with FDA's position, and referenced scientific papers to refute this: Changing the fermentation medium does not change the genetics of the microorganism, and thus does not change its safety profile. The IPA Comment stated:

> "…We are willing to consider arguments supported by science demonstrating that particular manufacturing processes do not actually result in a chemical alteration or have an effect on the safety profile…we encourage manufacturers or distributors to arrange a pre-notification meeting with FDA to discuss their basis for this belief"

Jarrow asserts at this point that this argument leads to the conclusion that one's diet should constitute a "chemical alteration" or "shift" of one's own resident bacteria genetics – which is nonsensical. Diet does have a dramatic impact on which flora proliferate and which are suppressed, but there is zero evidence that diet will cause a resident species to shift from beneficial to harmful. There is no science to support such a notion, and no reason to believe that fermenting acidophilus in milk instead of peptones will a pathogen make. Even when bacteria adapt to a media, the adaptation is non-harmful to the host. Speculating on hypothetical risk is bad enough. Speculating for its own sake to the point of absurdity is inexcusable. Then why not argue that a change in the diet would cause an acidophilus to become harmful?

IPA in its Comment takes a similar perspective, but presents it in a different way, and with different examples:

> There are well justified reasons for altering manufacturing processes for microbial food cultures. These can vary from removing allergens to adapt to market demands, improving stability, improving yields, and more importantly to note are the continuous improvements to process optimization as technology advances. However, these improvements do not change the identity of the microbial food culture or alter its safe profile. 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. Changes are not due to media changes, but due to normal heterogeneous populations of cells in any culture. And finally when cultured in different media, glucose, lactose, glucose and lactose, it took 2000 generations, to see a change, and only after extensive screening. From the published scientific articles we recognize that genetic drift potential during fermentation might temporarily change gene expression with a low calculated risk 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 is also inclined to agree with the statements of Amy Smith, the expert consultant at Dupont/Danisco, who maintains that, for example, a change in the fermentation medium does not produce an NDI. Her comments, during a videotaped interview at Supply Side West are as follows:

> However, if you change any aspect of the fermentation media, **[**under FDA current policy in the Revised Guidance**]** it would therefore make it a **new** dietary ingredient. **[**Bold added**.]** And, DuPont has issue with this because we have historical data that shows that the historical way of fermenting and preparing cultures for use in dairy products, and in food in general, provides a strain that is identical to a strain produced using new and novel fermentation ingredients that do not contain things like allergens, so we've removed things like non-fat dry skim milk that were historically used for in fermentation for articles used for food.
>
> And so in changing that fermentation media, the strains that we now produce, we have data to show are 100% identical at a molecular level to the strains that we historically produced using the old methods. And so it's very important for us to provide information, not only as an industry, but as DuPont, to show FDA that a change in fermentation does not equate to a new strain.

Published in "Several Points in the NDI [Revised] Draft Guidance should not Apply to Probiotics," by Stephen Daniells, *NutraIngredients USA* (Oct. 13, 2016). JFI agrees with this reasoning and this approach. Ironically, this analysis above also accords with FDA's own position—in the labeling context—that an "other ingredient" used in the production of a supplement, such as a flow agent, that is <u>not</u> present in the finished product does not need to be declared on the label as an ingredient of that supplement. Similarly, a different fermentation medium does not produce a different (new) Probiotic.

Put in a food context, fermenting peaches with Kimchi strains and then consuming them – even commercially promoting Kimchi peaches – raises zero concerns. Why should there be any concern if the same product uses a structure/function claim and is sold as a supplement?

Recently, on December 9, 2016 there was an article on this issue by Hank Schultz in *NutraIngredients USA*, "FDA open to notion that new fermentation medium doesn't change probiotic identity, expert says." Dr. Greg Leyer, PhD, CSO for UAS laboratories, gave a presentation on behalf of the probiotics industry, at the request of IPA. He presented data showing that the change in fermentation components has no effect in the genetic makeup of the strains. His analogy was "It's still the same organism if I grew it on lactose or glucose or something else. If I eat sushi or I eat spaghetti I'm still Greg." He continued, "As long as you are not adding something that is itself unsafe to the fermentation medium [,] there is no safety concern. That's especially true when you consider the low mutation rate. We are not stressing these organisms."

X. <u>Concurrence with Numerous Points in IPA's December 9, 2016 Comment to FDA</u>

The International Probiotics Association (IPA) filed its Comment on the Revised Draft Guidance on NDIs on December 9, 2016. The IPA is an international organization, deriving its membership from industry and academia. The IPA's goal is to provide a unique forum for the exchange of research and the latest breakthroughs in probiotic technology and new product development. IPA holds NGO status before Codex Alimentarius. As an organization, IPA is the authoritative voice of the probiotics industry in the world, as the majority of the world's

industrial producers are members. We have carefully reviewed the IPA Comment, and find that we are in agreement on the specific positions taken, in addition to the point re fermentation above. Thus, in this section, we present first a quotation from a specific point in the Guidance on which we want to comment, and then our concurrence with the IPA's analysis and conclusions, borrowing from its December 9 Comment, but with modifications of the language to reflect JFI's detailed position and reasoning.

Page 15 Section IV Part A. Article 4.b. '...and the exception to the NDI notification requirement for certain NDIs that have been present in the food supply as <u>conventional</u> foods."

The regulation 21 CFR section 190.6, the one and only FDA regulation on the NDI Notification process, does not use the term 'conventional'. We believe that "foods" should mean all categories of foods—including dietary supplements as a sub-category-- and the exception shall apply whenever long safe history of use as an article used for foods is established. Foods should mean all category of foods lawfully marketed.

<u>JFI Position</u>: The term 'conventional' as a qualifier for "foods" in the guidance should be removed.

Page 17 Section IV Part A. Article 7. '…If a dietary supplement containing a NDI is sold before the manufacturer or distributor submits a required NDI notification.....the sale of the product is not evidence that the dietary ingredient or NDI was lawfully marketed."

We understand FDA position that the sale of a product prior to notification should not constitute evidence that the NDI was lawfully marketed. Filing a NDI notification is a pre-marketing requirement in the United States. However, 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 US should constitute presence in the food supply. Accordingly, when this same ingredient is to be sold in the US in a form that is not chemically altered, it should be eligible to the exemption from a notification. The statute of DSHEA did not link the presence in the food supply to a specific category, place or date.

<u>JFI Position</u>: The addition of 'in the US' in the following sentence '. . . the sale of the product in the US is not evidence that the dietary ingredient or NDI was lawfully marketed."

Page 19 Section IV Part A. Article 11. Pertaining to the development of a grandfathered or *'an authoritative list of pre-DSHEA dietary ingredients based on independent and verifiable data."*

Jarrow does not believe that—under DSHEA—it is the industry's burden to compile or produce a grandfathered list. However, we are willing to provide FDA with a list of Genera and species known to have a long, safe history of use in foods and then establish criteria that would bring a strain belonging to these genera and species to be listed. This would be a good opportunity for government and industry to work together in a more cooperative way.

Page 23 Section IV Part B. Article 1. When is a notification not required for an NDI. ***'...We do not consider prior use in dietary supplements to constitute presence in the food supply."***

We make the same comment as those made earlier about **Section IV Part A. Articles 4b and 7**. Consumption outside the US as a food and/or as a dietary supplement of these ingredients should indeed 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 independently from the mere place of consumption!

Page 23 and 24 Section IV Part B. Article 2. ***Am I required to submit an NDI notification for a dietary ingredient that is an NDI, but has been (a) listed or affirmed by FDA as generally recognized as safe (GRAS) for direct addition to food or (b) approved as a direct food additive in the U.S.***

'Affirmed by FDA as GRAS' 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 FDA's Final Rule, 81 FR 54959, published August 17, 2016; effective October 17, 2016.)

'Similarly, ingredients marketed in conventional foods outside the US are exempt from the NDI notification requirement if they are not chemically altered." We are in agreement with this statement, but suggest the term conventional should be removed as all categories of foods should qualify "provided that safe long history of use is established."

Page 25 Section IV Part B. Article 4. What are examples of processes that chemically alter an article of food present in the food supply?

During the probiotics manufacturing process, there are number of components that comprise the fermentation media to provide essential nutrients for propagation of the live microbes. There are a number of general components that are included and are completely during the growth of the cells--including salts, carbohydrates, protein, and nitrogen sources. In the case of fermentation media, it is important to note that substituting one source of these components with another does *not* chemically alter or change the genetic composition or identification of a strain; it simply provides similar "building blocks" of nutrients required for the cells to grow. For example, if lactose is replaced by dextrose, this simply implicates different metabolic pathways, both providing the sugars necessary for cell growth. *The carbohydrate substitution does not in any way allow the strain to change genetically.* The substitution of one nutrient for another during fermentation could not suddenly provide an avenue for creating a virulent microorganism. This is especially due to the fact that fermentation is completely contained within a closed system, not allowing extraneous entities to become a part of the process in any way. A practical example of the change of components that provides the same nutrient sources could be that of a human diet-- whereby changes in the diet (food consumed) do not produce a change in the genetic composition or identity of that person. Eating Asian food does not change an Italian-American person into an Asian person.

This is especially important to recognize: namely, that modern day changes in fermentation media used pre-1994 could not result in a new strain, or provide any newly demonstrated pathway to virulence. The example of yeast fermentation media containing selenite does *not* apply in any way to probiotics, and should not and does not cause any concerns for safety of the organism. No such similarity or analogy exists for probiotic strains. The example, further, is faulty because the safety concern is the toxicity of excessive selenium. This is not a probiotic issue. It is a selenium issue. The product is primarily a selenium ingredient – selenomethionine produced by fermenting in the yeast. The product contains dead yeast cells and is not sold as a probiotic, but as an enhanced selenium. The example is misleading and conflates two different processes. Many vitamins and amino acids are products extracted and purified from a microorganism fermentation. They are not seen as "probiotics."

JFI Position: Strike the following bullet point: *'Fermentation using a fermentation medium different from the one used to make conventional foods in the food supply. Example: use of a defined commercial growth medium to produce a microorganism previously made by fermenting milk into dairy products like yogurt or cheese'*.

Page 27 Section IV Part B. Article 5. What processes for manufacturing a dietary ingredient from an article of food present in the food supply do not result in chemical alteration?

'…Dehydration, lyophilization…can be said to change the composition of the ingredient, but only by changing the amount of water. FDA regards such a minor change in composition as extremely unlikely to change the safety profile of an ingredient…'

Bacteria culture production has a very rigorous identity, and a preservation process that ensures that each fermentation begins with identical inoculum materials, resulting in the same product-- batch after batch. Pure genetically seed vials are stored cryogenically at -80C to preserve cellular integrity; and only qualified seed vial stock are used for each fermentation process. The entire production process is scaled through consecutive transfers under closed aseptic conditions.

We agree with FDA's statement that lyophilization changes do not alter the safety profile of a probiotic ingredient and consequently do not chemically alter them. Similarly, the change in the fermentation media will not affect the genetic identity or the safety profile of a probiotic strain. Therefore a change in the fermentation of live micro-organisms should be added as an example of process that do not result in a chemical alteration.

JFI Position: Fermentation processes that do not chemically alter or change the genetic identity of a strain should not require an NDIN. The revised List of physical changes that are not chemical or identity changes 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 result in an NDI.

Next, FDA states: ***'...We are willing to consider arguments supported by science demonstrating that particular manufacturing processes do not actually result in a chemical alteration or have an effect on the safety profile...we encourage manufacturers or distributors to arrange a pre-notification meeting with FDA to discuss their basis for this belief."***

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 do not change the identity of the microbial food culture or alter its safety profile. 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.[4] Changes are not due to media changes, but due to normal heterogeneous populations of cells in any culture.[5] 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.[6] From the published scientific articles we recognize that genetic drift potential during fermentation might temporarily change gene expression with a low calculated risk[7] 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 should, since it has prided itself on being a "science-based agency" for over 15 years. (See section below.)

Page 35 Section IV Part C. Article 5. Can FDA provide examples with an explanation to help distinguish situations in which separate notifications are required for dietary supplements containing the same NDI from situations in which the same NDI notification covers multiple dietary supplements?

'...A combination of two NDIs is itself an NDI' Not necessarily. JFI believes that it depends on the nature of the substance and should not be generalized, for example, combining two probiotics that have a reasonable expectation of safety individually, does not produce additional safety concerns. The same principle applies across the DS industry and was clearly

[4] 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.

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

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

[7] 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.

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?

Page 65 and 66 Section VI Part A. Article 17. What additional information should I include if my NDI is a live microbial dietary ingredient?

"FDA will pay particularly close attention to the proper identification of organisms from genera and species that do not have a long history of food use and to those from genera, like *Bacillus and Streptococcus,* ***which contain both species with long histories of use and species known to contain human pathogens."***

This statement in the Guidance suggests that FDA agrees with the role of the species in determining the safety of the strain and its status as new or not. This 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. 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. Examples of species that should not be used in dietary supplements include Escherichia coli, Enterococcus faecalis, and Enterococcus faecium.'

JFI does not agree with this conclusion, and believes there are scientific ways to distinguish pathogenic from non-pathogenic species; and there are scientific ways to establish a comprehensive safety profile for every member in these particular species. Thus, FDA should allow a case by case evaluation. Agreeing with IPA's reasoning, Jarrow's position is that horizontal transfer of any gene cannot be prevented; and once a strain is proven as safe, and has demonstrated safety appropriately according to genomic mining for evidence of virulence factors or toxin production, for the antibiotic resistance profile and transfer potential, and if necessary, demonstrated as safe in animal toxicological studies, then it should be considered for use as a safe dietary ingredient.

The idea of preventing horizontal gene transfer is unrealistic. What is relevant is not whether it 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 Claustridia, for instance, are non-pathogenic and beneficial. Claustridia butyrim 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 NLEA.

Once determined to be safe, this probiotic ingredient must be allowed to be marketed as dietary ingredients/supplements 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. In regards to microbial cultures which lack an established history of safe use, Pariza et al. have published a comprehensive approach to evaluating the safety for cultures and new intended applications.[8]

"FDA considers each strain of a bacterial or yeast species to be a separate ingredient."

"FDA also considers manufacturing process, including the fermentation media, as an intrinsic part of the identity of an ingredient that is viable at time of ingestion."

Jarrow does not necessarily agree with these statements. First, we would like to reiterate that, 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 should be exempted from the notification requirement unless it is genetically modified.

JFI Position: Jarrow supports the IPA position: "IPA and its member companies are working on best practice voluntary guidelines which it intends to share with FDA and will suggest to its members to follow. These guidelines will be about transparency and consistency in our sector to help consumers and regulators understand and compare probiotic products. The labeling recommendations will be for IPA member companies to report products to the strain level with genus and specie amounts, in CFU which are a more meaningful measure of live organisms. There are provisions to address proprietary blends which are allowed by law in the US. The guidelines will also propose stability recommendations as per published standards i.e. ICH or USP. IPA suggests that FDA take into serious consideration these voluntary best practices because IPA professes a proactive, transparent probiotic industry sector, differentiating the companies which produce high quality probiotic products.

Jarrow agrees with the IPA proposal for an expansion of the scope of the welcomed 'grandfathered list' to capture not only pre-DSHEA ingredients but to also consider the established safety of use of bacterial strains that have been marketed in foods and can be generally presumed safe:

> IPA *proposes that 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. Ideally, once the species is confirmed, safety of the strain must be established. Such safety*

[8] http://www.sciencedirect.com/science/article/pii/S02732300 15300143.

criteria can include; history of use, assessment of antibiotic resistance profiles and lack of transferability demonstrated, 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 a form of a Master File within a mechanism that is independent of the NDIN.

Many regulatory and scientific groups around the world have thoroughly investigated probiotics and according to their findings, they compiled similar safety lists considering important elements such as 1) Taxonomy 2) Body of knowledge comprised of history of use, scientific literature, clinical aspects and ecology 3) Pathogenicity to humans 4) End use for the food chain.

As examples of such lists, we can cite the 'QPS' (Qualified Presumption of Safety) of EFSA (European Food Safety Authority, 2007), periodically revised (last revision in 2016), the Probiotics Monograph of Health Canada (NNHPD, 2015), The Therapeutic Goods Administration (Australian Government) listed substances database, and the Italian list compiled by the Minister of Health Italy (Italian Ministry of Health, 2013). Utilizing such a list of Genera and species based on historical use in foods, by the FDA to grandfather or exempt strains would make the procedure for utilizing microorganisms more consistent, and would provide the FDA with a generalized approach based on a history of safe use, in place of a full case-by-case assessment, freeing up resources to focus on those cases that present safety risk or uncertainties and which would require a case-by-case risk assessment. The probiotics industry has demonstrated historically that live microbial organisms listed as meeting regulatory criteria in a number of countries predicts safety, and that as long as safety is demonstrated, each strain within a Genus and species on the list is acceptable for use, and not a new ingredient, provided it meets the strain-specific additional safety parameters.

Another detailed explanation of standards established for confirming safety of microbial strains within a species with a long history of safe use can be found in the decision tree article published by Pariza MW, 2015.[9] *These requirements for safety are ideal, and reasonable for those species with an established history of safe use in foods.*

IPA recommends a list of live microorganisms to be included in a "grandfathered/exempted database" where FDA recognizes the safe history of use in foods based on scientific literature and regulatory agreement of published lists of genera and species along with verified established safety of the particular strains belonging to these species. Please revert to our Appendix 1 to consider the list of IPA proposed 'NDI notification exempt' species and additional criteria to be evaluated for each strain belonging to these species. [Emphasis added.]

[9] http://www.sciencedirect.com/science/article/pii/S02732300 15300143.

The language in italics is borrowed virtually verbatim from the IPA's Comment, as Jarrow is in full agreement. We would add here that the assessments, lists, and compilations above are based on scientific study, and peer-reviewed published scientific papers.

XI. The FDA Describes Itself Repeatedly as a "Science-based Agency, Yet Many of its Guidance Positions on "Live Cultures" are Divorced from Current Science

Science is variously described by the FDA as the heart, the touchstone, the key or the backbone of the agency. Throughout its mission and policy statements, its Committee reports and its press communications, the FDA consistently describes itself as an agency firmly and deeply rooted in science.[10] This concept is especially important for various issues of whether a new probiotic is safe—as shown above. The FDA's Mission Statement[11] is as follows:

> FDA is responsible for assuring the safety of foods, drugs, medical devices, biologics—such as vaccines, blood products, cell and gene therapy products, and tissues—cosmetics, and many other consumer goods, as well as foods and drugs for animals. Since 2009, it has also been responsible for regulating the manufacture, marketing, and distribution of tobacco products. FDA is also responsible for advancing the public health by helping to speed innovations that provide our nation with safe and effective medicines and devices and keep our food supply safe, while helping Americans get the accurate, science-based information they need to use medical products and consume foods to improve and maintain their health.

The FDA was not always a science-based agency. Prior to 1970, the FDA was primarily a law enforcement Agency, relying more on inspectors to handle issues of adulteration and misbranding, and far less on science. However, pre-market review and approval requirements for FDA-regulated products shifted the FDA's work more toward regulatory decision-making. To make those regulatory decisions, the FDA increased its reliance on science (see the 2007 report prepared by the FDA Subcommittee on Science and Technology titled *FDA: Science and Mission at Risk*[12].)

As the regulatory role of the FDA continued to grow and evolve, the FDA began to suffer "from serious scientific deficiencies and was not well-positioned to meet its current or emerging regulatory responsibilities." The 2007 Subcommittee report noted that "the impact of the deficiency is profound precisely because science is at the heart of everything FDA does." [Emphasis added.] We urge the Office of Dietary Supplements to keep that phrase in mind in its rewriting of the NDI Guidance.

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[10] This section was researched and drafted by Maureen Rossi, of Ryley Carlock, and edited by Susan Brienza, Esq.

[11] *http://www.fda.gov/AboutFDA/WhatWeDo/default.htm:*

[12] *http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_fda%20report%20on%20science%20and%20technology.pdf*

Jesse Goodman, Chief Scientist for the FDA, issued a new report in October 2012 titled *FDA Science Looking Forward: Five Years After the Mission at Risk Report*[13]. Goodman states that since the 2007 report, the FDA has: "Broadly advocated for and defined the role and importance of regulatory science" The FDA has accomplished this by creating the Office of the Chief Scientist, the Office of Regulatory Science and Innovation, the Office of Scientific Integrity and the Office of Scientific Professional Development. In addition, the FDA has developed its first Strategic Plan for Regulatory Science.

The Office of Scientific Integrity was established in August 2009. The FDA website section on Scientific Integrity[14] states that:

> Science—both its quality and integrity—is the touchstone of everything we do at FDA. In carrying out our mission to protect and promote the public health, FDA needs the best scientific and technological information available to make decisions on the products we regulate. Critical to our ability to reach sound decisions and to retain the public's trust are high-quality data and a scientific review process that is thorough and unbiased.

Also in 2009, in response to a directive from the President's Office of Science and Technology Policy, the FDA developed policies[15] and procedures to ensure scientific integrity in agency decision-making. FDA also issued key principles of scientific integrity to be followed in all decision-making processes. The first of these key principles is to: "1) Maintain a firm commitment to science-based, data-driven decision-making."

In August 2011 the FDA issued its first Strategic Plan for Regulatory Science.[16] The website for this report offers this opening statement:

> The core responsibility of FDA is to protect consumers by applying the best possible science to its regulatory activities — from pre-market review of efficacy and safety to post-market product surveillance to review of product quality. FDA has developed a strategic plan for regulatory science, the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.

An FDA Transparency Blog post[17] announcing the release of this Strategic Plan opens with the following statement: "Science is the backbone of everything we do at FDA." The post continues with this same theme:

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[13] *http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM322691.pdf*

[14] *http://www.fda.gov/ScienceResearch/AboutScienceResearchatFDA/ucm306446.htm*

[15] *http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm289975.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=smg%209001.1&utm_content=1*

[16] *http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm267719.htm*

> As new discoveries yield increasingly complex products," says FDA Commissioner Margaret A. Hamburg, M.D. "this strategic plan ensures that our experts are equipped to make science-based decisions resulting in sound regulatory policy. It positions us to foster innovation through better science without compromising our high safety standard.

In a March 2012 Blog Post titled *Keeping the Focus on Scientific Integrity*[18], Jesse Goodman opens with:

> Science, both its quality and its integrity, is key to everything we do at FDA. As a physician and researcher, science has always been central to the decisions I make at the bench or at the bedside. And now as the Chief Scientist for FDA, my office works across the agency to support our scientists and their cross-cutting scientific and public health efforts – and to help ensure that our decisions are science-based and protect and promote the health of the American people. [Emphasis added.]

In sum, the FDA has repeatedly described itself as a "science-based agency" since the early 2000s, and prided itself on being grounded in the most advanced and innovative science. And yet many of the terms, specifics, background and underpinnings of this Revised Guidance, and especially the discussion of probiotics or "live cultures" seem divorced from current science of microbiology, gastroenterology, gynecology, immunology, food science, etc. Furthermore, both the language of the statutory definitions for "dietary supplement" and "New Dietary Ingredient," and the precise and detailed phrasing of the FDA's Guidance in statements on species and strains, etc. show that the determinations of whether a new strain is safe or not is primarily a scientific question—not a legal determination.

XII. Re-definition of "Probiotic" Causes a Wrongful Limiting of Sec. 3 of DSHEA

Finally, JFI is concerned that in the Revised Guidance the desire to further define and refine the terms in Section 3 of DSHEA, in which Congress itself created and defined the category of "dietary supplement," in turn seeks to limit what substances can be Probiotics and especially to limit the number and variety of new Probiotics. For example, in Section C. 6 of the Revised Guidance we find:

> A bacterial microorganism is a dietary ingredient if it is a dietary substance (an intentional constituent of food) or otherwise falls within one of the dietary ingredient categories listed in 21 U.S.C. 321(ff)(1). For example, bacteria that are used to produce fermented foods that are eaten without a cooking or pasteurization step (e.g., lactic acid bacteria used to produce cheese or yogurt) could be "dietary substances for use by man to supplement the diet by increasing the total dietary intake," which are defined as dietary ingredients in section 201(ff)(1)(E) of the FD&C Act (21 U.S.C. 321(ff)(1)(E)). FDA does not have a separate regulatory category or definition for dietary ingredients consisting of live or viable microorganisms. [Emphasis added.]

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[17] *http://fdatransparencyblog.fda.gov/2011/08/17/fostering-innovation-through-better-science/*

[18] *http://blogs.fda.gov/fdavoice/index.php/2012/03/keeping-the-focus-on-scientific-integrity/*

The fact that the FDA has not defined Probiotics is not a reason to limit their development. They are indeed part of "an organism's usual food and drink." The Agency's problematic avoidance of the science in attempting to redefine the category of probiotics would eviscerate the Act of its quintessential term "Supplement" and its kaleidoscopic subtleties.

In Section D. 1, the FDA adds the definition of "dietary supplement" and thus "dietary ingredient" found in 21 U.S.C. 321(ff)(1), Section 3 of DSHEA, including "(E) A dietary substance for use by man to supplement the diet by increasing the total dietary intake." Then, for the first time since the passage of DSHEA, Oct. 15, 1994, in this August 2016 Revised Guidance, FDA defines what is meant by "dietary substance," in a passage that was not included in the July 2011 Draft Guidance:

> For purposes of section 201(ff)(1)(E) of the FD&C Act, we interpret "dietary substance" in accordance with its common, usual meaning because the term is not defined in the FD&C Act or by regulation. According to *Webster's II New Riverside University Dictionary* (1994), "dietary" means "of or relating to diet" and "diet" means "an organism's usual food and drink." In conjunction with "for use by man," we interpret "dietary substance," as used in section 201(ff)(1)(E), to mean a substance commonly used as human food or drink. The rest of the definition, which specifies that the substance be for use "to supplement the diet by *increasing* the *total* dietary intake,"31 is further evidence that "dietary substance" is intended to mean foods and food components that humans eat as part of their usual diet. One cannot increase the "total dietary intake" of something that is not part of the human diet in the first place.

We believe that the language of these parts of the Guidance show that FDA is trying improperly to circumscribe the sub-category of Probiotics, and thus to limit new probiotics. It is also a definition impoverished of nutritional biochemistry, the broader workings of gastroenterology – and a clear attempt to make an end run around DSHEA and Congressional intent to include the various workings of the process of human nutrition, not the paltry menu of a picnic definition of "dietary." Free amino acids are dietary supplements. So are probiotics.

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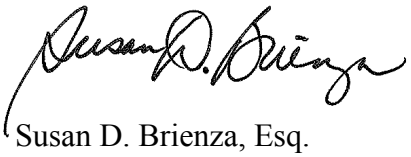
In sum, as shown above, FDA's position on Probiotics in the Guidance contradicts the long history of safe use of various probiotics in foods, Sections 2, 3, and 8 of DSHEA, FDA's prior policy and its officials' statements about Probiotics during the meeting in 2000, FDA's own GRAS letters, and the Agency's desire and claim to be "science-based." As we stated in our December 12, 2016 Comment, this Guidance has the potential to dramatically and negatively impact how supplements (especially Probiotics) are regulated, developed, and manufactured in the future. Indeed, the well-respected Nutrition Business Journal had estimated that under the 2011 Draft Guidance, 70% of the entire supplement industry will be affected; and this 2016 Revised Guidance will cause even more ingredients and products to be considered NDIs.

This document is an attempt to regulate and legislate via a guidance document. As such, it usurps the function of Congress, and violates the APA. For these reasons alone, and based on the legal and scientific analysis in this Comment above, Jarrow maintains that the Revised

Guidance is misconceived, overreaching, and illegal—most particularly as to probiotic supplements. Jarrow respectfully holds the position that the Guidance should and must be withdrawn and further rewritten to comport with existing law, and in the proper form of a Proposed Rule.

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,



Susan D. Brienza, Esq.

P. Scott Polisky, Esq.

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

Members of Congress:

Sen. Orin Hatch, UT
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Janet Poveromo, Editor-in-Chief, *Vitamin Retailer*
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Rick Polito, Editor in Chief, *Nutrition Business Journal*
Julissa Catalan, Editor/Associate Publisher, *Whole Foods Magazine*
Stephen Daniells, Ph.D., Senior Editor, *NutraIngredients-USA*
Carlotta Mast, Executive Director of Content & Insights, *New Hope Natural Media*
Daniel McSweeny, Owner and President of VRM, Inc., Publisher, *Vitamin Retailer*
Anahad O'Connor, Reporter, *The New York Times*
Janet Poveromo, Editor in Chief, *Vitamin Retailer*
Hank Schultz, Senior Correspondent, *NutraIngredients-USA*
Malcolm Spicer, Manager Editor, *The Rose Sheet*, fka *The Tan Sheet*
Heather Wainer, Publisher, *Whole Foods Magazine*

Jarrow Agrees with this List from the IPA Comment of Dec. 9, 2016.

APPENDIX 1

IPA proposed 'NDI notification exempt list'

Bacillus coagulans
Bacillus subtilis
Bacteroides xylanisolvens
Bifidobacterium adolescentis
Bifidobacterium animalis subsp. animalis
Bifidobacterium animalis subsp. lactis
Bifidobacterium bifidum
Bifidobacterium breve
Bifidobacterium lactis
Bifidobacterium longum subsp. infantis
Bifidobacterium longum subsp. longum
Bifidobacterium longum subsp. Suis
Carnobacterium malaromaticum
Lactobacillus acidophilus
Lactobacillus amylolyticus
Lactobacillus amylovorus
Lactobacillus alimentarius
Lactobacillus aviaries
Lactobacillus brevis
Lactobacillus buchneri
Lactobacillus casei
Lactobacillus cellobiosus
Lactobacillus coryniformis
Lactobacillus crispatus
Lactobacillus curvatus
Lactobacillus delbrueckii subsp. bulgaricus
Lactobacillus delbrueckii subsp. delbrueckii
Lactobacillus delbrueckii subsp. lactis
Lactobacillus farciminis
Lactobacillus fermentum
Lactobacillus gallinarum
Lactobacillus gasseri
Lactobacillus helveticus
Lactobacillus hilgardii
Lactobacillus jensenii
Lactobacillus johnsonii
Lactobacillus kefiranofaciens
Lactobacillus kefiri
Lactobacillus lactis
Lactobacillus mucqsae

Lactobacillus panis
Lactobacillus collinoides
Lactobacillus paracasei
Lactobacillus paraplantarum
Lactobacillus pentosus
Lactobacillus plantarum
Lactobacillus pontis
Lactobacillus reuteri
Lactobacillus rhamnosus
Lactobacillus sakei
Lactobacillus salivarius subsp. salivarius
Lactobacillus salivarius subsp. salicinius
Lactobacillus sanfranciscensis
Lactococcus lactis
Leuconostoc citreum
Leuconostoc pseudomesenteroides
Leuconostoc lactis
Leuconostoc mesenteroides
Oenococcus oeni
Pediococcus acidilactici
Pediococcus pentosaceus
Propionibacterium freudenreichii
Propionibacterium acidipropionici
Streptoccocus salivarius
Streptococcus thermophilus
Saccharomyces boulardii
Saccharomyces cerevisiae

IPA would ideally like to see the above list accepted by FDA as the base for 'NDI notification exempt list of strains', where the species have been established as safe and the strains have been verified. IPA recommends this list be used as a 'safe' list, where manufacturers of strains within these species, intended to be used as dietary ingredients, would be responsible for establishing safety based on the bullet list of safety requirements [described in IPA's earlier sections above]. This would be similar to the requirements of global regulatory agencies, which allow strains within each listed species to be anticipated as safe because it is a requirement that additional (abbreviated) safety testing is performed. These additional requirements accompany each regulatory-published grandfathered list.