IFAC Guide: Probiotics, New Dietary Ingredient Notifications (NDIN), and Relevant Information

Introduction and IFAC Position

In July 2011, the U.S. Food and Drug Administration (FDA) issued "Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues"[1] for comment purposes only. After the comment period ended, FDA expressed its intention to revise the draft guidance. A revision was completed and published in August of 2016,[2] also for comment purposes only.

The International Food Additives Council (IFAC) has developed this Guide to outline current industry thinking and best practices, based on the latest scientific evidence, on how the new dietary ingredient notification (NDIN) and related regulatory requirements apply to the special nature of probiotics. IFAC is a global association representing manufacturers of food ingredients, including live microbial dietary ingredients used in the production of dietary supplements. It is the position of IFAC that:

1. Each strain or isolate of microbial cultures which is intended for use in dietary supplements must be evaluated individually for safety and for whether a NDIN is needed.

2. Strains that have been determined to be safe and belong to a microbial species that was marketed in a dietary supplement in the United States prior to October 15, 1994 are not New Dietary Ingredients (NDIs).

3. Strains that have been determined to be safe[3] or have Generally Recognized As Safe[4] status and belong to microbial species with a history of safe use as starter culture used for food fermentation or as a probiotic in food (together termed MFC, "Microbial Food Cultures") can be NDIs but are exempted from notification. For those with a GRAS affirmation, the intended intake level should be equal to or less than that declared in the GRAS determination.

4. Strains belonging to microbial species that have established history of safe use in food or supplements outside the United States, can be NDIs in the U.S., but exempted from the NDI notification requirement.

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[1] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition. Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues. July 2011. Retrieved from: https://www.federalregister.gov/documents/2011/07/05/2011-16711/draft-guidance-for-industry-dietary-supplements-new-dietary-ingredient-notifications-and-related.

[2] U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition. Draft Guidance for industry: Dietary Supplement: New Dietary Ingredient Notifications and Related Issues. August 2016. Retrieved from: https://www.fda.gov/media/99538/download.

[3] Stevens, Haley Curtis; and Lyn O'Brien Nabors. Microbial Food Cultures: A Regulatory Update. *Food Technology*. 2009. Retrieved from: https://www.foodingredientfacts.org/regulatory-update-food-microbial-food-cultures/.

[4] U.S. Food and Drug Administration. Substances Generally Recognized as Safe; Final Rule. *Federal Register.* 21 CFR Parts 20, 25, 170 et al. August 17, 2016. Retrieved from: https://www.govinfo.gov/content/pkg/FR-2016-08-17/pdf/2016-19164.pdf.

5. Microbial strains without such safe history of use either in a dietary supplement before October 15, 1994 or in a food, or individual strains that have been chemically altered from the strain that was used in a dietary supplement prior to October 15, 1994 or in a food, must be evaluated for safety for use in dietary supplements and a NDIN is required.

6. IFAC defines chemical alteration as changing the genetic identity (i.e., genome) of a given microbial culture. This does not include changes to fermentation media or changes in fermentation method as long as such changes do not change the genetic identification of the culture.

7. FDA is exploring development of a pre-DSHEA list of dietary ingredients, as well as use of a master file system for reference. Industry wishes to be consulted as FDA proceeds with these activities.

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I. Background

The Dietary Supplement Health and Education Act of 1994[5] (DSHEA) places dietary supplements in a special category under the general umbrella of "foods." Consequently, under DSHEA, the probiotic manufacturer or distributor is responsible for:[6]

1. Ensuring the product is safe and that any representation made about it is truthful and not misleading.

2. Determining if an ingredient is a "dietary substance," a "new dietary ingredient," and if a NDIN is required, or exempt from notification.

3. Maintaining documentation to support pre-DSHEA sales in the U.S. to prove the ingredient is not a new dietary ingredient. This information does not need to be submitted to the FDA, but must be available to the FDA if requested.

4. Submitting a NDIN to the FDA 75 days prior to marketing the dietary supplement containing the NDI in the United States, if required.

Thus, the manufacturer or distributor of the dietary supplement or dietary ingredient is responsible for the determination that the product is **safe** before it reaches the market and the FDA is responsible for taking action against any product demonstrated to be **unsafe** once marketed.

II. Definitions

"Dietary supplement" is defined as "a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), (E)."[3,7]

"Dietary substance" is defined generally (there is no formal FDA definition) as a substance already used as an ingredient of food.[8] By law, food includes conventional foods, infant formula, medical foods, and dietary supplements.

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[5] 103rd Congress. Dietary Supplement Health and Education Act of 1994. Retrieved from: https://ods.od.nih.gov/About/DSHEA_Wording.aspx.

[6] Additionally, the probiotic manufacturer or distributor is responsible for ensuring compliance with other applicable laws and regulations, such as: the Federal Food, Drug & Cosmetic Act; Current Good Manufacturing Practices (21 CFR Part 111); Adverse Event Reporting Requirements; The Bioterrorism Act; The FDA Food Safety Modernization Act; and the Food Allergen Labeling and Consumer Protection Act.

[7] Federal Food, Drug & Cosmetic Act, Subchapter II - Definitions. Retrieved from: https://www.govinfo.gov/content/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapII-sec321.pdf.

[8] Pfeiler, Erika; and Dan Levy. Regulatory Review of Live Microbial Ingredients for Dietary Supplements. Poster at New York Academy of Sciences Conference. 2010. Retrieved from: https://www.nyas.org/media/13734/100611_probiotics_poster_abstract_booklet.pdf.

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"Dietary ingredient" is defined as "(A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), (E)."[3,5]

"New dietary ingredient" (NDI) is defined as "a dietary ingredient that was not marketed in the United States in a dietary supplement before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994."[3,9]

The Probiotics Industry defines "probiotics" as safe, live microorganisms that when represented as a dietary ingredients or supplements, are intended for a healthy population.[10,11]

"Strain" is defined as a population of organisms that descends from a single organism or pure culture isolate.[12] Each strain must have measurable phenotypic and genotypic identity by which it can be differentiated from other populations.

III. General Information

Regardless of whether a NDIN is needed, it is the manufacturer's and/or distributor's responsibility to ensure a strain is safe before it is used in a dietary supplement. Accurately identifying a strain is the first task to achieve. Independently from its origin, the safety determination of a strain depends on its taxonomy, the genera and species to which it belongs along with meeting a certain number of criteria prior to its selection for human consumption. These criteria are outlined in the safety decision tree determining the safety of microbial cultures for consumption by humans and animals.[13]

Thus, taking into consideration its taxonomy, genera, and species to which it belongs, any probiotic strain that has been shown to be safe must be evaluated to determine if it is a dietary substance. If it is considered a dietary substance, then it must be determined if it is a New Dietary Ingredient (NDI). If it is considered to be a NDI, then it must be determined whether a NDI Notification (NDIN) is required to be filed with the FDA.

[9] FDA recognizes that there is "no authoritative list" or "grandfathered list" of those ingredients.
[10] Huber, Machteld; Knottnerus, J André; Green, Lawrence; van der Horst, Henriëtte; Jadad, Alejandro R; Kromhout, Daan; et al. How should we define health? *BMJ.* 2011; 343: d4163. Retrieved from: http://www.bmj.com/content/343/bmj.d4163.
[11] Food and Agricultural Organization of the United Nations and World Health Organization. Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food. 2002. Retrieved from: https://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf?ua=1.
[12] Willery, Joanne; Sherwood, Linda; and Woolverton, Christopher. (2008). *Prescott, Harley, and Klein's Microbiology: Seventh Edition.* New York, NY: McGraw-Hill. Retrieved from: https://www.academia.edu/12037960/Prescott_Harley_Kleins_Microbiology_7th_Edition.
[13] Pariza, Michael W.; Gillies, Kevin O.; Kraak-Ripple, Sarah F.; Leyer, Gregory; and Smith, Amy B. Determining the safety of microbial cultures for consumption by humans and animals. *Regulatory Toxicology and Pharmacology*. 2015; 73: 164-171. Retrieved from: https://www.foodingredientfacts.org/wp-content/uploads/2019/08/Pariza-et-al_Determining-the-safet-y-o-f-microbial-cultures-for-consumption-by-humans-and-animals.pdf.

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Chemically Altered

FDA's guidance discusses chemical alteration as a key condition for demonstrating safety and determining whether a dietary ingredient is new or if it is able to rely on its history of safe use. The current NDIN guidance is broad and written to capture the entire dietary supplement industry. In section B.4, FDA provides the following example:

- "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."

This example has created confusion and concern in the dietary supplement industry and displays a lack of understanding of the production process and varied uses of microbial food cultures, including probiotics, since the 1950s. Further, this logic is not based on a sound scientific application of microbial physiological principles.

The definition of chemical alteration should only encompass changes that lead to an alteration of the chromosomal genetic make-up of the microorganism (e.g., genetic engineering).[14]

Substituting a defined medium for a complex and variable raw material like milk, for example, does not impact the genetic composition of a food culture, when conducted in accordance with microbial food culture cGMPs (such as proper cell banking and taxonomic identification),[15,16] and therefore is not *prima facie* evidence of chemical alteration. The following rationale, outlined by Sanders et al,[14] details instances when a change in fermentation media does not alter the genome of the microorganism and should not constitute a chemical alteration:

1. Substitution of one safe and suitable carbon source for another, e.g. providing a cell with glucose instead of lactose in milk. Such changes take advantage of the cells inherent biochemical capabilities and do not elicit a change in the cells capacity to use substrates. In fact, if one analyzes a culture preparation grown on milk, one will find glucose in the cell preparation as a result of beta-galactosidase hydrolysis of lactose to its glucose and galactose components.

2. Substitution of one safe and suitable source of amino acids, such as milk, for another such as yeast extract. If one uses milk or yeast extract or any other protein source in

[14] Sanders, ME; Klaenhammer, TR; Ouwehand, AC; Pot, B; Johansen, E; Heimbach, JT; Marco, ML; Tennilä, J; Ross, RP; Franz, C; Pagé, N; Pridmore, RD; Leyer, G; Salminen, S; Charbonneau, D; Call, E; and Lenoir-Wijnkoop, I. Effects of genetic, processing, or product formulation changes on efficacy and safety of probiotics. *Ann. N.Y. Acad. Sci.* 2014; 1309: 1-18. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24571253.

[15] Limiting genetic drift and retaining the genetic identity (i.e., maintaining the original genome sequence) of microbial cultures is one of the main tasks for culture manufacturers. Bacteria should be manufactured from a single, well-identified, frozen cell bank, and then scaled up using subsequent fermentation batches. Current good manufacturing practices (cGMPs) must be followed for the manufacture of starter cultures and probiotics.

[16] Gasch, AP; Spellman, PT; Kao, CM; Carmel-Harel, O; Eisen, MB; Storz, G; Botstein, D; and Brown, PO. Genomic expression programs in the response of yeast cells to environmental changes. *Mol. Biol. Cell.* 2000; 11(12): 4341-4257. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/11102521.

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a fermentation, analysis will only find the same 21 amino acids in the cellular amino acid pool after uptake of the substrate by the cells.

3. Removal of fermentation raw materials. Regardless of the substrate used, centrifugation removes fermentation raw materials from the final culture preparation.

4. Use of ammonia or other safe and suitable GRAS or approved food additives to buffer the pH of a fermentation to enhance the fermentation yield.

5. Use of safe and suitable GRAS or approved food additives to stabilize culture preparations during lyophilization.

None of the examples listed above are intended to carry over functional substances that are not common constituents of the culture preparation. None alter the chromosomal genetic make-up of the culture strains. All utilize substrates that are reasonably assured to be safe in the production of food in general, including dietary ingredients. Most importantly, all of these conditions have been used to produce microbial food cultures, including probiotics, as articles of food since the advent of the industrial starter culture industry and thus have been in the food supply for at least 60 years. This satisfies the dual criteria for exemption from filing an NDIN based upon presence in the food supply as an article of food and not being a chemically altered form of such products.

IV. Determining Whether a Probiotic Strain is a Dietary Substance

Independently from its origin, the probiotic must be a dietary substance in order to be a dietary ingredient. When a probiotic is identified as belonging to a species that has been used in a food or dietary supplement (anywhere in the world, at any time), the strain is considered a dietary substance, provided safety of the strain has been determined. Several examples of publicly available literature, data and information which document the history of safe use of probiotics include the IDF,[17] QPS,[18] IJFM[19] and other positive lists or monographs.

[17] International Dairy Federation (IDF). Safety Demonstration of Microbial Food Cultures (MFC) in Fermented Food Products. *Bulletin of the International Dairy Federation.* 2012. Retrieved from: http://www.google.dk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0ahUKEwj9qqTJ4LvYAhUDbVAKHfiVBioQFqgyMAE&url=http%3A%2F%2Fstore.fil-idf.org%2Fproduct%2Fsafety-demonstration-of-microbial-food-cultures-mfc-in-fermented-food-products-2%2F%3Ffree_file_download%3D2069&usg=AOvVaw1ttgYxm-8WOIbloOOYXGUQ.

[18] EFSA Panel on Biological Hazards (BIOHAZ); Ricci, Antonia; Allende, Ana; Bolton, Declan; Chemaly, Marianne; Davies, Robert; Girones, Rosina; Herman, Lieve; Koutsoumanis, Konstantinos; Lindqvist, Roland; Nørrung, Birgit; Robertson, Lucy; Ru, Giuseppe; Sanaa, Moez; Simmons, Marion; Skandamis, Panagiotis; Snary, Emma; Speybroeck, Niko; Ter Kuile, Benno; Threlfall, John; Wahlström, Helene; Cocconcelli, Pier Sandro; Klein, Günter; Maradona, Miguel Prieto; Querol, Amparo; Peixe, Luisa; Suarez, Juan Evaristo; Sundh, Ingvar; Vlak, Just M.; Aguilera-Gómez, Margarita; Barizzone, Fulvio; Brozzi, Rosella; Correia, Sandra; Heng, Leng; Istace, Frédérique; Lythgo, Christopher; and Fernández Escámez, Pablo Salvador. Scientific Opinion on the update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA. *EFSA Journal.* 2017; 15(3): 4664. Retrieved from: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4664.

[19] Bourdichon, F; Casaregola, S; Farrokh, C; Frisvad, JC; Gerds, ML; Hammes, WP; Harnett, J; Huys, G; Laulund, S; Ouwehand, A; Powell, IB; Prajapati, JB; Seto, Y; Ter Schure, E; Van Boven, A; Vankerckhoven, V; Zgoda, A; Tuijtelaars, S; and Hansen, EB. Food fermentations: microorganisms with technological beneficial use. *International Journal of Food Microbiology.* 2012; 154(3): 87–97. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22257932.

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V. Determining Whether a Probiotic Strain is a New Dietary Ingredient

A strain that was not sold in the U.S. prior to October 15, 1994 as a dietary ingredient in a dietary supplement is considered a NDI, regardless of whether it was sold as a food ingredient.

VI. Determining Whether There is a Need for a Notification

If it has been determined that a strain is a NDI, a NDIN may be required to show why the consumption of the strain is reasonably expected to be safe under the labelled conditions. A strain that has been present in the food supply as an article used for food (anywhere in the world, at any time), and is in a form that has not been "chemically altered," or has applicable GRAS status, is exempt from a NDIN.

VII. Information Needed for a NDIN for Probiotics

The below information follows 21 CFR 190.6, Requirement for premarket notification.

A. General Requirements of the Notification

Where it has been deemed necessary and appropriate to submit a notification, the manufacturer or distributor of the dietary supplement that contains the NDI, or the manufacturer or distributor of the NDI, must notify the FDA at least 75 days before the dietary supplement containing the NDI is marketed in the United States.

Cooperation between the manufacturer and distributor of a dietary supplement that contains a NDI may be necessary to provide the FDA with required information. Some information may need to be confidentially shared with FDA by the manufacturer or distributor.

FDA regulations require the submission of an original and two (2) copies of the notification and attachments.[20]

B. Body of the Notification

Currently, the requirements for a NDIN include identification of the notifier and various administrative, identification, manufacturing, specification, conditions of use, stability, safety, and toxicological information.[2]

[20] U.S. Food and Drug Administration. New Dietary Ingredients in Dietary Supplements – Background for Industry. 2018. Retrieved from: https://www.fda.gov/food/new-dietary-ingredients-ndi-notification-process/new-dietary-ingredients-dietary-supplements-background-industry.

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C. Filing Process

The FDA will acknowledge receipt of a notification and will notify the submitter of the date of receipt. The date of receipt is considered the filing date for the notification. The manufacturer or distributor of the product may not introduce or deliver the product for introduction into interstate commerce until 75 days after the filing date.

If additional information is requested by the FDA and provided by the submitter, the FDA will review that information and if they deem it a substantive amendment to the submission, may reset the 75 day wait period by assigning a new filing date. The submitter will be notified as to the new filing date. Again, the product may not be introduced or delivered for introduction into interstate commerce until 75 days after the new filing date.

If the FDA fails to respond to a notification, this does not constitute a positive or negative finding by the agency as to the safety of the new dietary ingredient. Nor does it confirm if the product is adulterated or not under Section 402 of the Federal Food Drug and Cosmetic Act.

After 90 days from the filing date, the information in the notification will be placed on public display, except for any information that is deemed a trade secret or considered confidential commercial information by the submitter of the notification.

D. Industry Notes and Recommendations

- It is not necessary to provide efficacy data unless it is included in references that also provide identity information and is unavoidable.

- Both published and unpublished studies are considered by FDA.

- It is not necessary to provide safety data when the intake level of the NDI is proposed as equal to or less than that consumed historically, with a demonstrated safe history of use as a food or dietary supplement. However, the toxicology requirements from the draft Guidance are listed for a variety of proposed usages, which the industry recognizes as extreme, especially when a safe history of use has been demonstrated. As listed in the guidance document, proposed uses where toxicology data is required for an NDI are for (1) daily use at lower than historical levels when the historical data is for intermittent use; (2) daily use at greater levels that the historical data is for daily use; (3) daily use at greater than historical levels when the historical data is for intermittent use; (4) intermittent use at greater levels than the historical data for intermittent use; and (5) no history of use. The toxicology testing listed for all seem extreme and are not commonplace for probiotic strains within a Genus and species with a safe history of use where similarity within the Genus and species has been demonstrated. IFAC believe it to be of the utmost importance to meet with the

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agency about the safety data required for probiotic NDIs to move forward with a clear understanding of what is realistically expected of the probiotics industry.

- It is advisable to prepare a master file for each strain prior to notification to facilitate internal company processes and the FDA review process.

- If the strain was genetically modified using either random mutagenesis or bioengineering, the NDIN should describe the process used and how the properties of the new strain were characterized.

- FDA requires the use of scientific names for botanical ingredients (21 CFR 190.6(b)(2)) and it is recommended for probiotics as well.[2] Per industry practice, scientific names for probiotics must be used to identify the strain. The FDA recommends using the Bacteriological Code (1990 Revision),[21] the German Collection of Microorganisms and Cell Cultures,[22] or the List of Prokaryotic Names with Standing in Nomenclature.[23]

- It is important to note taxonomy is a science that continues to evolve. Due to this evolving science, the nomenclature of many microbial strains may currently have different classifications than what was used for the same strain in the past. These changes, when documented, do not affect the ability of the industry to rely on the history of use of these substances.

- The FDA has also stated that they regard all members of a species that contain human pathogens, such as *Escherichia coli*, *Enterococcus faecalis*, and *Enterococcus faecium,* as potentially harmful to human health, and therefore inappropriate for use as dietary ingredients. The industry believes these species should not be entirely excluded, as non-pathogenic versions of these bacteria exist. Therefore, more stringent screening is needed and specific documentation of safety must be provided.

- **Section 912 (301(ll)) and NDINs –** It is important to note at this point, that before filing a NDIN, section 912 (301(ll)) must be taken into consideration. In this guidance, the FDA does not take into consideration section 301(ll), so the responsibility falls on the manufacturer/distributor. Section 301(ll) states the introduction or delivery for introduction into interstate commerce of any food to which has been added a drug approved under section 505, a biological product licensed under section 351 of the Public Health Service Act [42 U.S.C. § 262], or

[21] Lapage, S.P.; Sneath, P.H.A.; Lessel, E.F.; Skerman, V.B.D.; Deeliger, H.P.R; and Clark, W.A., editors. International Code of Nomenclature of Bacteria: Bacteriological Code, 1990 Revision. Washington (DC): American Society for Microbiology Press; 1992. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21089234.
[22] Leibniz Institute. DSMZ-German Collection of Microorganisms and Cell Cultures GmbH. Catalogue of microorganisms. Braunschweig, Germany. 2019. Retrieved from: https://www.dsmz.de/collection/catalogue/microorganisms/catalogue. [Note that content on this website is updated frequently. Use the search function in the link to retrieve the current validated name of a bacterial organism.]
[23] Euzéby, J.P. List of Bacterial Names with Standing in Nomenclature: a Folder Available on the Internet (now the List of Prokaryotic Names with Standing in Nomenclature (LPSN) Database). *Int J Syst Bacteriol.* 1997; 47(2): 590-592. Retrieved from: https://www.microbiologyresearch.org/content/journal/ijsem/10.1099/00207713-47-2-590. [Note that content on this website is updated frequently. Use the search function in the link to retrieve the current validated name of a bacterial organism.]

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a drug or a biological product for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, with some exceptions.[24] The one exception that is of importance in this paper is if the drug or biological product was marketed in food before any drug or biologic approval and before any substantial clinical investigations involving the drug or biological product have been instituted (Section 301(ll)(1)).

The intention of this regulation was to protect the drug and biological products, however, regardless of the intentions, when this regulation is combined with the NDIN requirements in DSHEA, and without careful consideration, filing a NDIN could be detrimental to the dietary supplement and food industry.

When filing a NDIN to the Agency, per the definition of a NDI, a notification is in fact, telling the Agency that the NDI subject to the notification has not been marketed in the U.S. as a dietary ingredient in a dietary supplement or in food before 1994. Many probiotics in use today are believed to be old dietary ingredients. In the years since DSHEA was enacted and until a guidance document was published, many substantial clinical studies have been completed and published on these probiotics. Because of this, filing a NDIN should indicate to FDA that despite previous evaluation in substantial clinical studies, that the NDI is intended for use as a dietary ingredient in a dietary supplement or food.

Previous evaluation of the NDI should not render categorization of this ingredient as a biological drug product. Because of this, a manufacturer or distributor should carefully consider the type of notification for their strain.

VIII. Conclusion

It is the responsibility of a dietary supplement manufacturer and/or distributor to determine whether a dietary ingredient is new and therefore requires the filling of a new dietary ingredient notification (NDIN) per the Dietary Supplement Health and Education Act (DSHEA) of 1994. IFAC believes this Guide will be a valuable tool for manufacturers and users of live microbial dietary ingredients used in dietary supplements to determine whether they are in compliance with DSHEA and relevant regulations and guidance documents, and how to develop a NDIN.

This Guide includes notes and recommendations which indicate opportunities for process changes and improvements, and IFAC acknowledges the evolving nature of science and industry advances to meet consumer demand. IFAC looks forward to continuing to work with FDA and the dietary supplement industry to ensure clarity, transparency, consumer safety and innovation opportunity for the manufacture and use of live microbial dietary ingredients.

[24] U.S. Food, Drug & Cosmetic Act, Section 301(ll). Retrieved from: https://legcounsel.house.gov/Comps/Federal%20Food,%20Drug,%20And%20Cosmetic%20Act.pdf.

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