

**Comment on Docket No. FDA-2011-D-0376**

Submitted electronically to <http://www.regulations.gov>

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville MD 20852

Dear Sir or Madam:

The following comments are submitted by the [International Scientific Association for Probiotics and Prebiotics](#) (ISAPP) in response to the draft guidance, “Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues.”

[ISAPP](#) is an association of independent academic and industrial scientists involved in research on fundamental and applied aspects of probiotics and prebiotics. The scientists participating in ISAPP have a common interest in generating high quality scientific information for the [probiotic](#) and [prebiotic](#) fields and providing guidance for collaborative and multidisciplinary research. ISAPP is the only scientific organization dedicated specifically to probiotics and prebiotics, bringing together scientists from all pertinent disciplines, including food science, microbiology, immunology, biochemistry, nutrition, and medicine.

We recognize that the term “probiotic” was not used in this draft guidance. However, the scientific definition of probiotic (live microorganisms which when administered in adequate amounts confer a health benefit on the host) would encompass live microbial dietary ingredients, as defined in the guidance (a single-celled prokaryotic or eukaryotic microorganism that is intended to be viable at the point of ingestion).

As scientists representing a broad variety of disciplines with an interest in probiotics and prebiotics for a range of applications—drugs, foods, and dietary supplements—we applaud FDA’s efforts to clarify when a substance is a dietary ingredient, when it is a new dietary ingredient, and when an NDIN is needed. Furthermore, your efforts to clarify the appropriate information that should be submitted with a NDIN are also appreciated. The decision tree (Appendix A) and the NDI Notification Form (Appendix B) providing a template for submissions will be greatly helpful to industry. However, ISAPP’s scientists are concerned about several aspects of the draft guidance as it relates to the science behind the probiotic and prebiotic fields. The aspects of this guidance of particular concern are:

1. Identity of a live microbial ingredient
2. Chemical alteration
3. Assessment of antibiotic resistance gene transfer
4. History of safe use
5. Strain- vs. species-specific information
6. Requirements for filing a NDIN for the product, rather than the ingredient

***Our comments are grounded in the overall principle that NDIN requirements should have a reasonable potential to add to the overall understanding of safety (or to the existing data base with respect to a risk) and, if that potential is very low, we recommend that FDA endorse the use of discretion to conclude that additional testing is unnecessary.***

### 1. Identity of a live microbial ingredient.

ISAPP agrees with the FDA guidance regarding information necessary to identify a microbial ingredient to the strain level. This requirement includes a description of “methods used to establish the identity of the strain, such as identification by internationally recognized third-party repositories (e.g., the American Type Culture Collection), and the relationship of the strain to the strain(s) of the same species used to establish the history of use or other evidence of safety for the dietary ingredient.”

We suggest in addition to those requirements, genomic sequencing of the proposed live microbe be required. When combined with functional annotation of the gene sequences, this information can provide a measure of confidence in the lack of transferrable antibiotic resistance genes, toxins or relevant virulence factors.

ISAPP does suggest, however, that the guidance be clarified by including a specific exemption to all of these requirements. Under question #16, the guidance states that “Poorly defined microbiological mixtures are acceptable if there is a long history of use in production of food (e.g., mixtures used to make dairy products like kefir or cheese) and the fermentation substrate is consistent with that history of use.” This statement should be included under question #17 as a specific exemption to the requirements for identity.

Furthermore, ISAPP would like to make the point that antibiotic resistance genes are not toxins, and considering the scope of the response includes antibiotic resistance, we suggest rewording of the question “How should the identity section of my NDI notification **deal with toxins** in related plants or microorganisms?” to “How should the identity section of my NDI notification **deal with toxins or other deleterious constituents or properties** in related plants or microorganisms?”

### 2. Chemical alteration.

The concept of “chemical alteration” is a cornerstone to knowing if a NDIN is needed. Since the guidance specifically includes changes in fermentation conditions as an example of chemical alteration, this requires manufacturers to either file a NDIN or consult the FDA for a change in fermentation conditions that significantly changes chemical composition. This is difficult to assess for live microbes, as they are complex organisms, not simple chemicals. Clearly, it is not reasonable to assume that any small processing change (changes in sources of ingredients, final product flavors, addition of cryoprotectants and other stabilizing ingredients to improve cell viability during storage, or process changes to improve the environmental impact of manufacturing, etc) would result in the transition of a microbe safe for its intended use to one that is not safe for that same use. Although numerous process changes could result in changes in cellular composition as well as gene expression, there is no reason to believe that such shifts in metabolism or physiology in microorganisms that have a long history of safe use would lead to an unsafe use.

**ISAPP recommends that the FDA clearly stipulate in the guidance document that in the case of live microbes, only substantive changes in processing or fermentation conditions that have a reasonable potential to impact safety require re-filing. We request improved clarity for when a NDIN is required and when one is *not* required.**

### 3. Assessment of antibiotic resistance gene transfer.

Regarding live NDIs, the guidance stipulates that “You should document resistance to any clinically relevant antibiotics, and if applicable, the genetic nature of the resistance. If the microbial NDI is resistant to any clinically relevant antibiotics, it is also recommended that you perform an assessment of the ability of the antibiotic resistance genes to mobilize and transfer to human pathogens under the conditions of use of the dietary supplement.” Although ISAPP agrees that the presence of transferable, clinically relevant antibiotics is an

important factor to consider in the safety of a probiotic, methodologies do not exist for conclusive demonstration of *lack* of transferability.

**ISAPP recommends that the FDA accept a genetic assessment approach whereby the presence of antibiotic resistance genes in proximity to genes that promote rapid transfer (such as insertion sequences, etc) be acceptable as an approach to establish the absence of a significant likelihood of transferable antibiotic resistance genes.** To supplement this approach, established methods for assessment of phenotypic antibiotic resistance patterns can be used. Strains exhibiting phenotypic resistance outside the norm for the species would warrant further investigation.<sup>1</sup>

#### **4. History of safe use.**

The draft guidance defines history of safe use as 25 years of widespread use. This seems arbitrary and unfounded. First, the definition of widespread is not clear. Second, some substances might be widely consumed and safety could be reasonably established within months, whereas other substances that might be rarely consumed (albeit over a large geographic region) may not be sufficiently understood from a safety perspective for decades. **Instead of a blanket 25 years, ISAPP suggests that the FDA follow the lead established by Congress in the 1958 Food Additives Amendment**, when they established the "history of use" basis for GRAS as "substances that are recognized, among qualified experts, as having been adequately shown ... through experience based on common use in food to be safe under the conditions of their intended use."

This standard is based on what qualified experts reason is adequate. That should be the standard for dietary ingredients also.

ISAPP would also like to comment on the stated requirements for studies if your product does not have a history of safe use. It is reasonable for the FDA to suggest one possible approach for safety tests. However, the FDA should make clear that this is one suggested path and should acknowledge that experts in the fields relevant to the particular dietary ingredient may determine relevant and irrelevant tests for safety for that particular dietary ingredient.

#### **5. Strain- vs. species-specific information.**

ISAPP's position on the level of strain-specific information that should be required to establish safety of a probiotic is consistent with the approach taken by the [European Qualified Presumption of Safety of Microorganisms for Use in Food and Feed](#) (QPS) list. The QPS list is a list of microorganisms for which there is a sufficient body of knowledge that indicates that all strains within a species can be presumed to be safe absent evidence to the contrary. The QPS list covers only selected groups of microorganisms that have been evaluated by the EFSA. In essence, strain-specific information on safety is required to establish the absence of transferrable antibiotic resistance genes, and in the case that a strain is a member of a species or genus containing some members known to produce toxins, infections or opportunistic infections, or specific virulence factors. This list is reviewed and updated yearly.

ISAPP would like to make clear, however, that while we do not believe that safety must be demonstrated at the strain level for QPS species, it should be done at the strain-level for non-QPS species. Also, identification (including genomic sequencing) and characterization (including relevant phenotypic and genotypic tests descriptive of the probiotic) must be conducted at the strain-level for all probiotics.

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<sup>1</sup> Vankerckhoven V, Huys G, Vancanneyt M, et al. Biosafety assessment of probiotics used for human consumption: recommendations from the EU-PROSAFE project. Trends in food science & technology 2008; 19:102-14.

## 6. Requirements for filing a NDIN for the product, rather than the ingredient.

Although not unique to the probiotic and prebiotic fields, we are compelled to comment on the focus of the guidance on NDINs being tied to the final product, rather than the ingredient.

**ISAPP recommends that the FDA use the same approach for safety of NDIN as is used for the food-additive and GRAS processes,** which focus on the safety of the *ingredient* for an intended use. It does not require a separate safety assessment for every product and every manufacturer. The likelihood of such requirements providing any meaningful additional, new or helpful information capable of influencing an ultimate safety decision is very low.

### Conclusions

ISAPP believes that the NDIN draft guidance document, specifically as it pertains to probiotics and prebiotics, would be improved through use of approaches to safety already well established in existing regulatory frameworks. Appropriate elements of both the GRAS process for food ingredient safety and the QPS process for listing live microorganisms that are considered safe for use in the generally healthy population should be adopted.

Clearly, ongoing research will offer insights into how modifications in process or delivery might impact safety and efficacy of live microbial dietary supplement ingredients. Approaches such as that used in the recent study by McNulty et al.<sup>2</sup> may provide animal models that can screen system-wide impacts of physiological changes in a live microbe. But these methods are still under development and it will take time for both the methods and a system to quantify the relevance of observed changes to be established. However, such approaches may be more relevant to efficacy evaluations than safety, especially when considering microorganisms generally considered safe, such as those on the QPS list.

Respectfully submitted by:

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<sup>2</sup> McNulty NP, Yatsunencko T, Hsiao A, Faith JJ, Muegge BD, Goodman AL, Henrissat B, Oozeer R, Cools-Portier S, Gobert G, Chervaux C, Knights D, Lozupone CA, Knight R, Duncan AE, Bain JR, Muehlbauer MJ, Newgard CB, Heath AC, Gordon JI. [The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins.](#) Sci Transl Med. 2011 Oct 26;3(106):106ra106.