Key Regulatory Considerations for Next-Gen Probiotics & Postbiotics

Amy Mozingo, MS

Prepared for The Microbiome: Mastering the Market Virtual Conference

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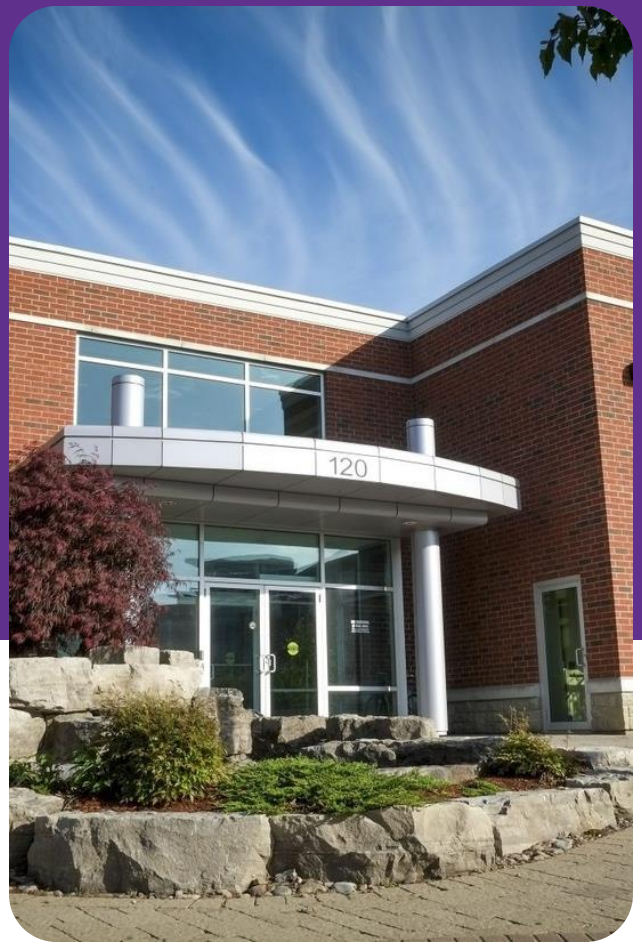
Amy Mozingo, MS

VP, US Nutra Regulatory Sciences

- 20+ years of experience in industry and consulting
- Certificate as a Preventive Control Qualified Individual (PCQI)
- Trained and experienced in ingredient approvals (GRAS, NDIN, FAP, CAP), product labelling, formulation reviews, and current good manufacturing requirements for dietary supplements
- 50+ GRAS and NDIN filings

About SGS Nutrasource



- 23 years in business
- 3,000+ projects successfully completed
- 20k+ supported product launches
- 150+ employees globally
- Over 2,000 clients represented
- Acquired by SGS in 2023

INNOVATIVE STRATEGIES

IN-HOUSE EXPERTISE

"PHARMA-LITE" APPROACH

SUPERIOR QUALITY

INTEGRATED TEAMS

EXTENSIVE CATEGORY EXPERIENCE

US Market Entry Compliance Pathways

What non-drug pathways are available?

- New Dietary Ingredient (NDI) Notification Process
  - Mandatory notification to FDA's Office of Dietary Supplement Programs, Division of Research & Evaluation
- Generally Recognized as Safe (GRAS) Process
  - Voluntary notification to FDA's Office of Pre-Market Additive Safety, Division of Food Ingredients

What is a dietary supplement?

[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 [of the above]

New Dietary Ingredient (NDI)

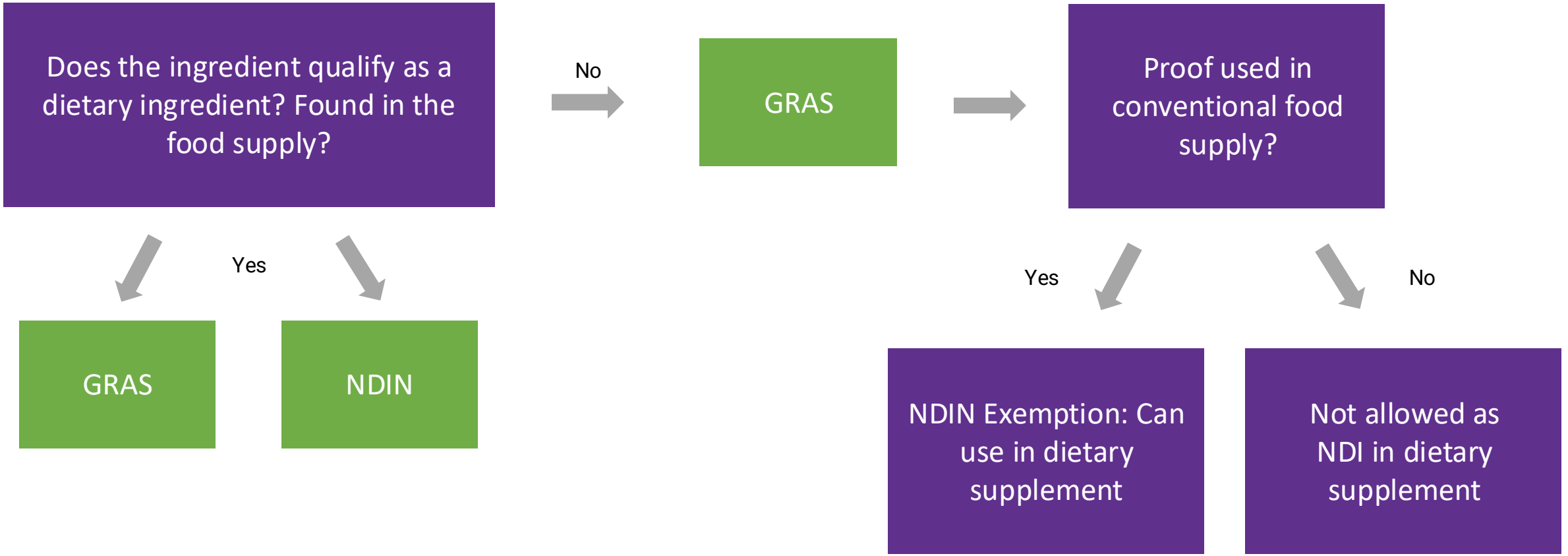
What is a New Dietary Ingredient?

- Was not sold in the US in a dietary supplement before October 18, 1994
- An NDI Notification must be submitted to the FDA 75 days prior to introduction into the US market, unless
- The dietary supplement contains only dietary ingredients present in the food supply as an article used for food in a form that has not been chemically altered
- Safety Standard: reasonable expectation of safety- does not present a significant or unreasonable risk of injury or illness under the labeled conditions of use.

Generally Recognized as Safe (GRAS)

- A U.S. regulatory designation that an ingredient is safe for its intended use in food, based on history of use prior to 1958 OR scientific procedures.
- Requires common knowledge
- Qualified experts agree there is a reasonable certainty of no harm under the conditions of its intended use
- Optional notification to FDA is available

Determine the Pathway



e) A dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

Data Requirements

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Determining the safety of microbial cultures for consumption by humans and animals

Michael W. Pariza [a, *], Kevin O. Gillies [b], Sarah F. Kraak-Ripple [c], Gregory Leyer [d], Amy B. Smith [c]

Considerations for determining safety of probiotics: A USP perspective

Amy L. Roe[a,*], Marie-Eve Boyte[b], Chris A. Elkins[c], Virginia S. Goldman[d], James Heimbach[e], Emily Madden[d], Hellen Oketch-Rabah[d], Mary Ellen Sanders[f], Jay Sirois[g], Amy Smith[h]

Emerging issues in probiotic safety: 2023 perspectives

Daniel Merenstein[a], Bruno Pot[b], Gregory Leyer[c], Arthur C. Ouwehand[d], Geoffrey A. Preidis[e], Christopher A. Elkins[f], Colin Hill[g], Zachery T. Lewis[h], Andi L. Shane[i], Niv Zmora[j], Mariya I. Petrova[k], Maria Carmen Collado[l], Lorenzo Morelli[m], Gina A. Montoya[n], Hania Szajewska[o], Daniel J. Tancredi[p], and Mary Ellen Sanders[q]

GUIDANCE

ej EFSA Journal

ADOPTED: 21 February 2018

doi: 10.2903/j.efsa.2018.5206

Guidance on the characterisation of microorganisms used as feed additives or as production organisms

STATEMENT

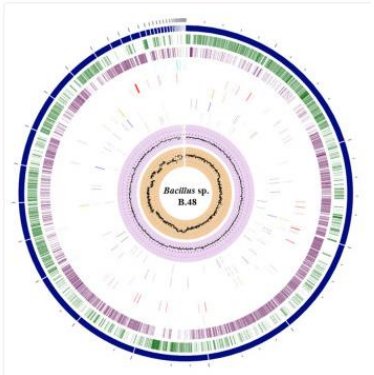
efsa JOURNAL

EFSA statement on the requirements for whole genome sequence analysis of microorganisms intentionally used in the food chain

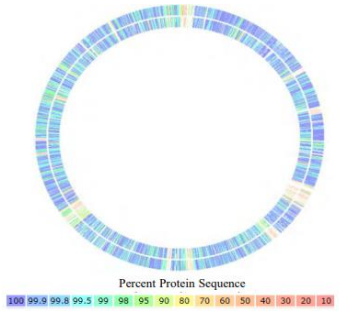
Data Requirements

Identity and Characterization

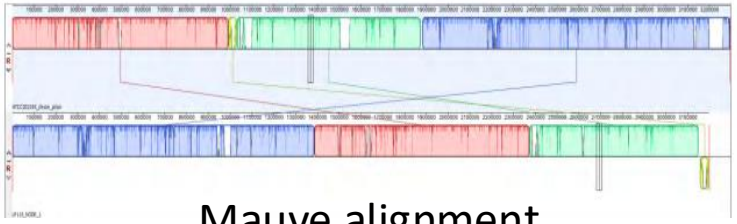
- Whole genome sequencing
- 16S and comparative annotation



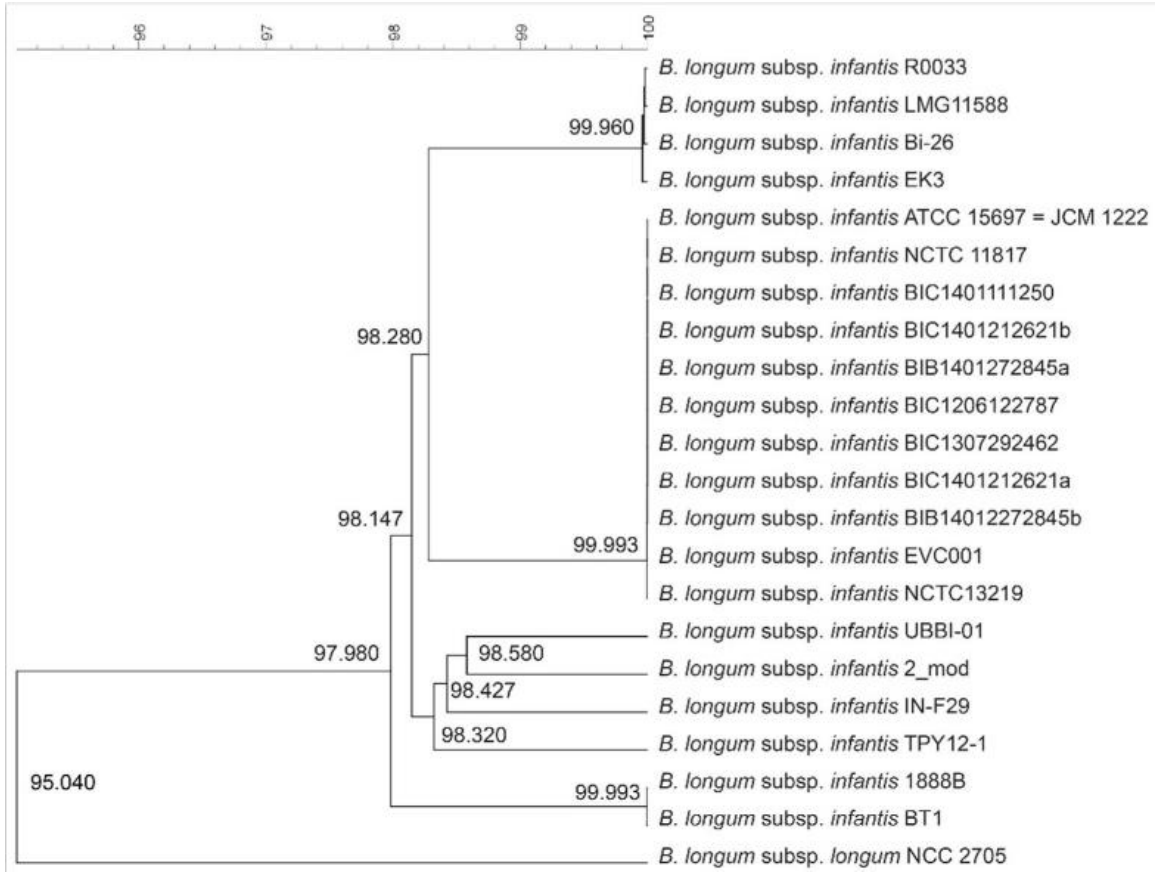
Genomic circular diagram
Ref: Sornchuer et al. 2023



Percent protein sequence



Mauve alignment



Whole genome based phylogenetic tree
Ref: Dubooux et al. 2022

Data Requirements

Safety - Organism as live microbial or as production organism for “post-biotic” must be non-pathogenic and non-toxigenic

Toxigenicity and pathogenicity	Virulence factors: toxin production, invasion and adhesion factors
Antibiotic resistance & Antimicrobial production	Antimicrobial resistance genes (AMR), testing for minimum inhibitory concentration (MIC)

- Secondary metabolites
- Mobile genetic elements

Data Requirements

Safety - Organism as live microbials or as production organism for “post-biotic” must be non-pathogenic and non-toxigenic	
Allergenicity	WGS protein sequence compared to allergen database
Biogenic amines	Histamine, tyramine, cadaverine, putrescine, spermidine, spermine
Mucin degradation	

Data Requirements

Safety: Next-generation probiotics and postbiotics– data requirements beyond those with history of use to the species level

Genotoxicity	Bacterial reverse mutation (OECD 471) Micronucleus test in vitro (OECD 487)
In vivo	14-day range finding oral toxicity 90-day repeat dose oral toxicity (OECD 408) with translocation

Data Requirements

- **Next-generation probiotics and postbiotics– data considerations to avoid mis-steps**
- Chemistry, manufacturing and controls consideration
- Characterizing the ingredient before beginning studies is critical!
- Determine now if you want to go down the drug / live biotherapeutic path later!

Data Requirements

- **Clinical Studies**
- Population
- Safety endpoints and adverse event reporting
- Are your results too good for food?

Dietary Supplement vs Live Biotherapeutic Product

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Psychobiotic *Lactobacillus plantarum* JYLP-326 relieves anxiety, depression, and insomnia symptoms in test anxious college *via* modulating the gut microbiota and its metabolism

Ruizhe Zhu [1], Yilin Fang [1], Hongyu Li [1], Ying Liu [2], Jing Wei [1], Shuwei Zhang [1], Liwei Wang [1], Rui Fan [1], Lingfang Wang [1], Shengjie Li [1], Tingtao Chen [1]

Nutrients. 2024 Sep 2;16(17):2936. doi: 10.3390/nu16172936

Effects of *Lacticaseibacillus rhamnosus* HN001 on Happiness and Mental Well-Being: Findings from a Randomized Controlled Trial

Imad Al Kassaa [1], Maher Fuad [1,*]

Nutrients. 2020 Nov 8;12(11):3422. doi: 10.3390/nu12113422

PROVIT: Supplementary Probiotic Treatment and Vitamin B7 in Depression—A Randomized Controlled Trial

Eva Z Reininghaus [1], Martina Platzer [1], Alexandra Kohlhammer-Dohr [1], Carlo Hamm [1], Sabrina Mörkl [1,*], Susanne A Bengesser [1], Frederike T Fellendorf [1], Theressa Lahousen-Luxenberger [1], Birgitta Leitner-Afschar [1], Helmut Schöggl [1], Daniela Amberger-Otti [1], Walter Wurm [1], Robert Queissner [1], Armin Birner [1], Valerie S Falzberger [1], Annamaria Painold [1], Werner Fitz [1], Martina Brunnmayr [2], Alexandra Rieger [1], Jolana Wagner-Skacel [3], Alexander Maget [1], Renate Unterweger [1], Karin Schwalsberger [1], Bernd Reininghaus [2], Melanie Lenger [1], Thomaz F S Bastiaanssen [4,5], Nina Dalkner [1]

Epub 2022 Nov 11.

Randomised clinical trial: efficacy and safety of the live biotherapeutic product MRx1234 in patients with irritable bowel syndrome

Eamonn M M Quigley [1 2], Louise Markinson [3], Alex Stevenson [3], F Peter Treasure [4], Brian E Lacy [5]

Blautix is a live biotherapeutic product consisting of a lyophilised formulation of a proprietary strain of bacterium. The study dosing regimen was two capsules two times per day for the duration of the treatment period.

Ref: ClinicalTrials.gov

Pathway Take-Aways

- Whole genome sequencing and robust in silico analysis is critical for unambiguous identity and safety
- Determine the appropriate pathway to market and plan accordingly to develop a robust safety dossier in the required format for GRAS or NDIN dossier
- Ensure manufacturing and specifications are set before conducting any safety studies
- Conduct appropriate safety studies under GLP and OECD guidelines and publish results if needed
- Clinical trials should be in a healthy, representative population and AEs clearly reported. Safety endpoints should be considered for inclusion into the design.

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For more information, please contact me at: amozingo@gras-associates.com