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Next steps for probiotics

Innovation, science and evolving strategies drive future growth

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Regrouping for the second wind

Probiotics are at an interesting stage. They rose from relative obscurity to a place of garnering widespread consumer acceptance and visibility in the marketplace. Along the way, sales figures boomed.

A slowdown in probiotic supplement sales emerged in late 2016 that tracked through Q1 2019. On page 29 of this issue, Euromonitor International's Matthew Oster shares more context. Among his observations, he noted the sector experienced "cannibalization from other cultured and fermented products."

While the initial data may seem concerning, industry is merely at a turning point, from which it can expand in numerous exciting (and profitable) directions. In fact, a new report from Market Research Future predicted the global probiotics market will register a compound annual growth rate (CAGR) of 8.48% from 2019 to 2025, reaching an estimated US$3.26 billion—the largest portion ($1.75 billion) coming from functional food and beverages.

Keep an eye on several key factors:

- **Research** – Strong science continues to be published supporting the potential benefits of probiotics on specific populations (such as children) for targeted needs (like immune health). Studies must keep raising the bar; for instance, exploring multi-strain combinations used in actual formulations, or establishing a scientific benefit for decisions such as dosing mega counts of colony-forming units (CFUs).
- **Education** – Consumers may understand the basics, but concepts like strain-specificity and the upcoming changes to the *Lactobacillus* taxonomy can be difficult to grasp. Health care practitioners are at the front line for evangelizing probiotics and should be an intentional focus.
- **Innovation** – Whether in supplements, foods or beverages, a fresh take can often help brands stand out. From delivery format to combination strategies such as synbiotics (probiotics and prebiotics), opportunities abound.

This digital magazine touches on many of these points, as does a recent "Finding probiotic success" audio report, where I spoke with three probiotic pundits. Additionally, if you're joining us in Las Vegas for SupplySide West, October 15 to 19, swing by the International Probiotics Association (IPA) Resource Center on Thursday from 10 a.m. to 5:30 p.m. and Friday from 10 a.m. to 5 p.m. We're also offering the "Extending Your Reach in the Probiotics Space" workshop Saturday morning from 8:30 to 11:30. I'd love to meet you if you're attending.

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Cannabinoids are on everyone's mind—consumers, industry, regulators and marketers. In particular, the ingredient cannabidiol (CBD) has gone from zero to 60 across the dietary supplement, food and beverage markets, with new product releases, marketing campaigns and much more. However, we've also seen major concerns crop up in areas as diverse as testing methods, extraction techniques, regulatory compliance considerations and supply chain transparency.

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The sports nutrition market remains one of the most vibrant, as it shifts from the traditional bodybuilder to the broader active nutrition positioning. First off, explore issues related to ideation and innovation driving the sports nutrition market, including formulation considerations, product formats, and market opportunities and whitespace identified in market research. Next, dive into the emerging ingredients that are fueling innovative product development. From cannabidiol (CBD) to fermented ingredients and unique anti-inflammatories, these ingredients are positioned to fuel new innovative product development.

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Effectively delivering probiotics in food and beverage applications

by Judie Bizzozero

INSIDER's Take

- Probiotic strains are unique, and their properties may influence efficacy and suitability for certain applications.
- Various manufacturing processes can impact probiotics' physiological effects in food and beverages.
- Water activity plays a key role in managing probiotic stability and viability in solid food formats.

The probiotics category continues to evolve as consumer interest in the microbiome and overall gut health fuels demand. As a result, researchers are discovering new health benefits of probiotic strains, while manufacturers improve technologies and techniques to drive solutions. Developments such as spore-forming probiotics and microencapsulation have made probiotics more resistant to processing, inspiring a host of innovative delivery formats, especially in foods and beverages.

Not all strains are created equal

Probiotic strains possess distinct characteristics. Each one is unique, and these properties may influence safety, efficacy and suitability for certain applications.

For beverages, the form of the probiotic strain is dependent on the finished product type and distribution channel. For example, live and active cultures are generally used in refrigerated products such as drinkable yogurt, kefir and kombucha, while the more robust spore form of microorganisms is often used in nonrefrigerated beverages, noted Joe Farinella, vice president of research and development (R&D), Imbibe.

"In terms of specific strains, yogurt drinks are made by adding lactic-acid-producing bacteria, such as *Lactobacillus bulgaricus* and *Streptococcus thermophillus*, into a dairy base and fermenting at elevated thermophillic temperatures," he said. "These strains do not survive the digestive tract, so yogurt drinks can be fortified with additional, hardier organisms like bifidobacterium and other forms of lactobacillus to deliver increased probiotic effect."

Kefir drinks contain similar bacteria strains to yogurt; however, they also contain various yeast strains (e.g., *Candida humilis*, *Saccaromyces unisporous*), Farinella explained. Kombuchas contain a more elaborate cocktail, including bacteria (e.g., *Acetobacteria*, *Aluconacetobacter*) and yeasts (e.g., *Saccaromyces*, *Zygosaccharomyces*).

"Engineered" probiotic drinks, like Kevita probiotic soda, contain the spore form of bacteria, such as *Bacillus coagulans*. "The spore form is much more robust and not only can survive higher temperature exposure from the production process, but also survive in acidic environments and are more likely to reach the intestine," Farinella added.

John Quilter, Wellmune's vice president and general manager, Kerry, said *Bacillus coagulans* are much more resistant to the extremes of pH, heat, cold and pressure than vegetative cells, making them a great fit for the fortification of everyday foods and beverages.

GanedenBC30 (*Bacillus coagulans* GBI-30, 6086) is a patented, GRAS (generally recognized as safe) probiotic ingredient from Kerry found in more than 900 food and beverage products. The shelf-stable probiotic strain has been shown to provide digestive health,[1] immune health[2] and protein utilization benefits.[1] GanedenBC30 is a spore former, which allows it to remain viable throughout most manufacturing processes and the low pH of stomach acid.

"GanedenBC30 can be used in products that are hot, cold, frozen or shelf stable, making them ideal for a wide range of products, including baked goods, frozen and chilled meals, snacks, and hot and cold beverages." Quilter said.

Formulation

Formulating foods and beverages with probiotics requires a fundamental understanding of food and beverage formulation, and how manufacturing impacts probiotics' physiological effects, noted Kantha Shelke, principal, Corvus Blue LLC.

According to the World Health Organization (WHO), "Probiotics are microorganisms that need to be alive when administered and need to be administered in amounts adequate to have a health benefit."

Food and beverage products must fulfill several criteria to ensure probiotics meet their definition. According to the World Health Organization (WHO), "Probiotics are microorganisms that need to be alive when administered and need to be administered in amounts adequate to have a health benefit." Shelke said the definition does not stipulate what an adequate amount is. However, regulators in, for example, Canada and Italy require a minimum dose of 109 colony-forming units (CFUs).[4]

"Meeting these criteria is particularly challenging in food and beverage formats because the associated processes can be harsh, and the ingredients can challenge viability, yield and often even the selection of the culture media ingredients (and therefore, the type of microorganisms) because of allergen issues for optimized dosage and functionality, even at the end of shelf life," Shelke said.

Farinella said ensuring an effective dose of probiotics from production through purchase and consumption is the biggest challenge to formulating probiotic beverages. Live, active cultures used in refrigerated products are sensitive to the high temperatures needed during the manufacturing process, while the spore form of bacteria tends to be stable in high-temperature conditions. In both cases, he said, it is important to overdose the product with probiotics during the batching step in order to ensure delivery of the desired amount post-production.

"The exact overdose levels are product- and process-dependent, so be sure to consult your ingredient suppliers and prepare to perform multiple trials at various levels in order to ensure you achieve the label-stated dosage," Farinella said. "Degradation of probiotic levels also can occur while a product is in distribution and on shelf, so it is important to perform shelf-life studies and measure the actual amount that will reach the consumer."

Quilter noted many strains are fragile and sensitive to processing conditions, limiting their use to products in the refrigerated dairy category. "However, the ability of spore formers to form a protective shell allows them to withstand beverage processes such as powder-blending, HTST [high temperature/short time] and HPP [high-pressure processing] pasteurization, boiling and freezing," he said. "One of the few formulation challenges with spore formers is in shelf-stable liquid beverages, but some of our partners have found solutions through cap dispensers and straw technologies."

Shelke said *Lactobacillus* and *Bifidobacterium* genera have a long tradition as starter cultures in yogurt and fermented dairy production. The right balance between clinical dose, shelf life and cost efficiency is a function of strain type, pH, fermentation temperature (affects probiotic growth), storage temperature, packaging type (oxygen transmissibility), processing steps (heat treatment and homogenization) and interaction with other ingredients (fruits, grains and sweeteners—all of which can be particularly detrimental to probiotic survivability).

"Not all probiotics are suitable for every food and beverage application because they can affect the taste and texture of the products. Traditional *Lactobacillus*, commonly used in yogurts, are not necessarily suitable for kombucha, bars and cereals."

— Fabian Skarvad, sales director, functional food, Probi

Maintaining viability of foods fortified with freeze-dried strains also is a challenge, cautioned Shrilakshmi Desiraju, Ph.D., founder and CEO, Triphase Pharmaceuticals Pvt. Ltd., but one that can be overcome by using temperature-stable probiotic (TSP) strains. "Our TSP strains can be formulated/incorporated at the right point during processing to provide a shelf life of 18 months at room temperature with low water activity," she said.

Fabian Skarvad, sales director, functional food, Probi, said not all probiotics are suitable for every food and beverage application because they can affect the taste and texture of the products. “Traditional *Lactobacillus*, commonly used in yogurts, are not necessarily suitable for kombucha, bars and cereals.” Skarvad also said shelf life is one of the biggest challenges for functional beverages because live and active bacteria are sensitive to ambient distribution and sales considerations.

Trending strains and delivery formats

The prevalence of foods and beverages containing probiotics is rising steadily with growing “pill fatigue” and the perception that consuming probiotics in a food is more natural and effective. According to Shelke, the shelf life of probiotic nondairy foods is distinctly shorter than that of dietary supplements because of harsher matrices and factors such as pH, acids and anthocyanins, and that the probiotic is in a vegetative rather than in a freeze-dried state.[5] A combination of technologies, such as refrigeration and pH balance, help maintain viability while avoiding metabolic activity of the probiotic and spoiling of the juice or the fermented medium, such as kombucha, or the fluid format as nondairy plant-based yogurt analogues.

In traditional probiotic foods such as yogurts and other fermented milk products, the matrix for carrying probiotic health benefits is the product itself, and fermentation provides cost-efficient cell counts.

In shelf-stable beverages, secondary packaging that segregates probiotics in a separate compartment, such as a bottle cap or a straw, help protect and release the proper dosage immediately before consumption, Shelke said.

Water activity plays a key role in managing probiotic stability and viability in solid food formats such as breakfast cereals, chips, chocolate, confectionery, crackers, snacks, peanut butter and crispy granola bars. “In general, the water activity should be less than 0.25 to meet a 12-month shelf life at 25° C,” Shelke noted. “Chocolates and peanut butter products are an exception to this water activity guideline because their fat-based matrixes can support probiotic stability with water activities up to 0.4.”

Ice cream can keep probiotics viable for more than one year. “It is important to keep the ice cream base at neutral or close to neutral pH, with high total solids, and, especially, fat content,” Shelke said, adding overrun is an issue for highly aerated ice creams, which can disturb the probiotic with the increased exposure to oxygen.

Cheese is another emerging format for strains such as *Lactobacillus acidophilus* NCFM (HOWARU Dophilus by DuPont), *Lactobacillus paracasei* Lpc-37 (FloraFit, DuPont), and *Lactobacillus rhamnosus* HN001 (HOWARU, DuPont). Shelke said

these can be included in standard cheeses like gouda and cheddar with cell counts in excess of 108 CFU/g even after 200 days, so that a serving of 10 g of cheese would be sufficient to obtain the desired daily dose.

Probi's *Lactobacillus Plantarum* LP299v strain is being used in a range of products, including fermented fruit and vegetable drinks, sparkling and infused beverages, and traditional dairy and plant-based products. "Fermented plant-based products with a functional benefit is where we foresee the market growth in the coming years," Skarvad said.

Desiraju pointed to increased use of *Lactobacillus acidophilus*, *Lactobacillus rhamnoses* and *Lactobacillus plantarum* strains in gummies, chocolate, muffins, cookies, breads and oral patches.

Fermented products

In traditional probiotic foods such as yogurts and other fermented milk products, the matrix for carrying probiotic health benefits is the product itself, and fermentation provides cost-efficient cell counts, Shelke said, noting utmost care is required to ensure the probiotic culture does not compromise the sensory profile of the product.

"Dedicated and strict hygiene standards is probably the only way sensory aspects and safety can be controlled in these products," she noted. "Suppliers of probiotics have found that frozen pellets rather than lyophilized/milled probiotic powders allow for homogeneity of the product and reduced mixing time without the wettability and dispersion issues with the powdered probiotics."

Desiraju said fermented products can create challenges, including the loss of beneficial bacteria, threat of botulism contamination and spoilage.

The pasteurization process used in the production of some fermented foods will destroy almost all living bacteria, and even raw, nonpasteurized fermented foods may not be backed by sufficient evidence to be considered "probiotic," Quilter said.

According WHO, probiotics are live microorganisms that confer a health benefit. By contrast, fermented dairy products—depending on storage conditions, cultures used and other manufacturing processes—may contain only a small fraction of the active cultures added at the time of manufacture, and probably not enough to confer a health benefit, Quilter advised.

"Manufacturers who want to promote the probiotic benefits of their foods or beverages should fortify them with high-quality, resilient, science-backed probiotic strains," he said. "It is important to work with ingredient suppliers that provide well-researched strains, but also have research and development support."

What's NEXT?

There's no doubt functional food and beverages will continue to trend with health-conscious consumers, and the proof is on the shelf. Brands are rolling out innovative probiotic-rich products, according to proprietary data from Informa Markets' NEXT Trend Database, which tracks all products exhibited at the Expo West and Expo East trade shows. NEXT data found dairy milks with probiotic claims share of growth

increased an impressive 1,019% between 2017 and 2019, followed by snacks, cookies and candy (314%) and dairy and plant-based yogurt (23%).

The breakfast category presents opportunity as well. Packaged Facts' "U.S. Food Market Outlook 2019" report found cereal-makers have joined other food categories incorporating probiotics and other gut-healthy ingredients into new products.

Kellogg's HI! Happy Inside cereal promotes digestive wellness with prebiotics, probiotics and fiber. The cereal contains 1 billion CFUs of live probiotics from active strains, 2.5 g of prebiotics and 8 to 9 g of fiber. Available in three flavors, the cereal is a blend of fruit, yogurt pieces and 100% whole grains. It was developed at WK Kellogg Institute for Food & Nutrition Research. Prior to introducing HI! Happy Inside, Kellogg launched Special K Nourish cereal with probiotics. At launch, Kellogg's said Special K Nourish was the only cereal from a leading brand that contained live and active probiotic cultures. In addition to probiotics, the cereal contains whole grains, peach-flavored flakes, blueberries, raspberries and yogurt pieces.

ThinkThin's line of protein and probiotic hot oatmeal also promotes overall wellness and digestion with 6 g of fiber, 10 g of protein and 1 billion CFUs of live probiotics. The products are non-GMO, gluten-free and have no artificial flavors or sweeteners.

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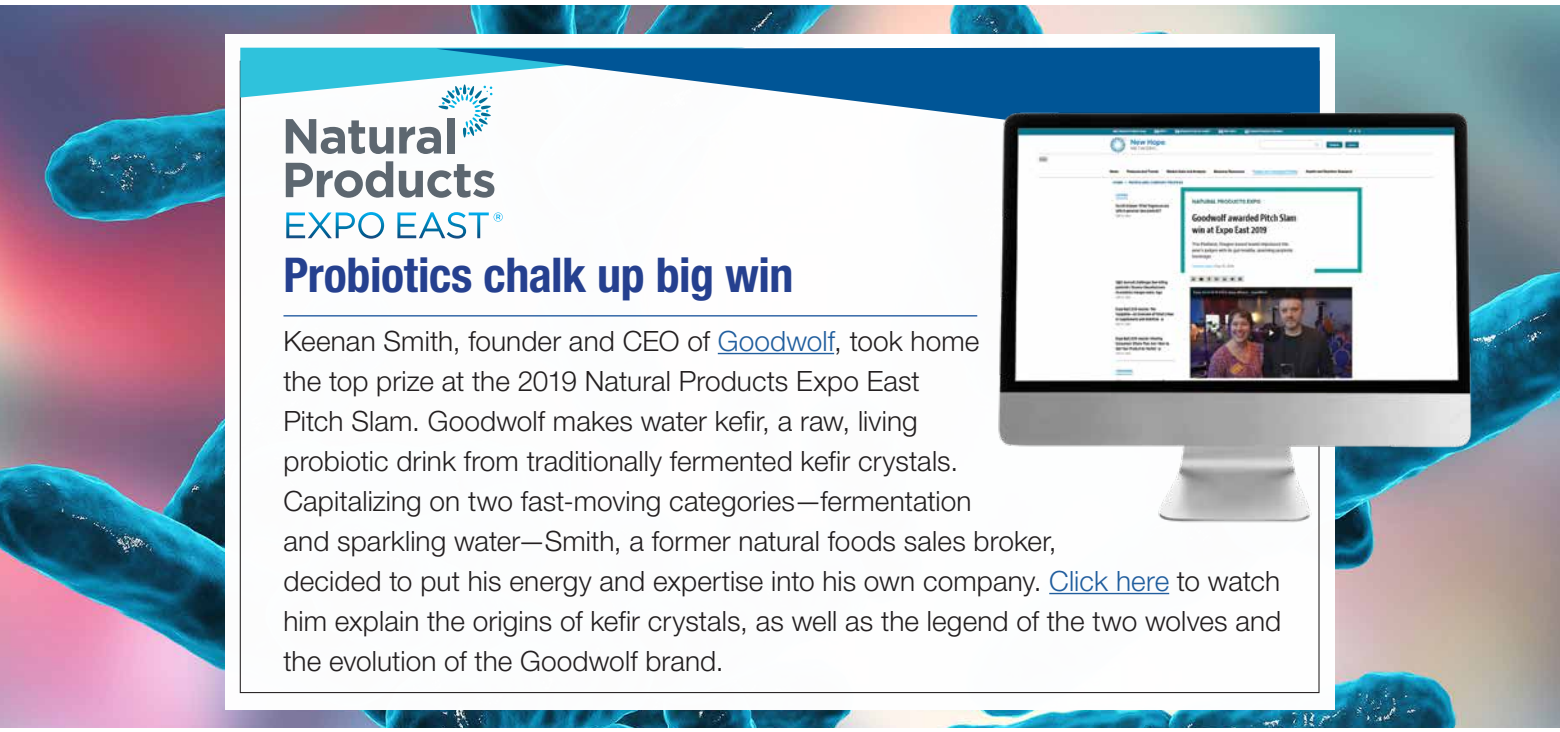

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Looking back to see the future of probiotics

by James LaValle, R.Ph., N.D.

INSIDER's take

- Without solid scientific backing, a probiotic claim on a product dilutes the market, leading to consumer frustration.
- Brands need to affirm the viability, stability and adaptability of their products to ensure bacterial counts meet label claims.
- Formulations boasting multiple probiotic strains should draw from research using those combinations, not solely single strains.

When I first started working as an integrative health clinician 35 years ago, few consumers had ever heard the word "probiotic." In fact, the category was commonly known as the "acidophilus set." Fewer had ever heard the word "microbiome," let alone knew the impact it can have on overall health. Considering this lack of awareness, I was constantly educating my clients on the benefits of supplementing with "good" bacteria. I dedicated myself to learn all I could about probiotics and the science behind the strains, so I could offer the best solutions for my clients.

Over time, popular media contributed to increased consumer awareness of the potential digestive benefits provided by probiotics. More companies began to conduct research on them, paving the way for marketplace applications spanning beyond the initial benefits to gastrointestinal (GI) health associated with probiotics.

Even as the scope of benefits conferred by various strains of probiotics continues to be researched, in recent years, product development has often jumped ahead of scientific findings. This is evidenced in the sheer volume of probiotic-based products on the market today, including everything from pet food, cosmetics, foods and drinks to "shots." While some of these products deliver viable bacteria in beneficial amounts, others may be ineffective due to factors such as incorrect dose or delivery format. As a result, the term "probiotics" seems to have been diluted to a mere marketing buzzword.

Follow the science

While improvements in probiotic strains and manufacturing techniques are welcome developments, clinical research is necessary to validate probiotic supplements' efficacy. Especially needed are studies that encompass a combination of strains or specific dosages of colony-forming units (CFUs), or show benefits for targeted conditions. These studies should be the driving force behind a manufacturer's release of probiotic products, not just the need to meet the latest trends or unique applications.

One trend in the probiotic market is the notion that more CFUs is always better. As a result, some probiotic products are boasting up to 200 billion CFUs in each capsule (and sometimes more). Yet, no research shows that these high CFU counts provide health benefits. Higher-dose probiotics with supporting clinical evidence is a missing piece of the puzzle of maintaining a healthy microbiome, especially in specific conditions where a higher dose may initially be needed.

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What really matters is viability, stability and adaptability. Not all probiotics are made in a manner to guarantee the bacterial counts will meet the label claim through the product expiration. Without this type of assurance, it's hard to tell exactly how many bacteria, if any, are alive when a consumer takes a probiotic supplement. It's also important to ensure the probiotic is resistant to stomach acid. This will ensure that the live bacteria will survive the journey through the stomach and into the small intestine.

The choice of specific probiotic species and strains also matters, since research has shown that different species and strains provide different health benefits. To be effective, the bacteria must be live when ingested and survive to repopulate in the intestines.

The way forward

The microbiome is one of the body's most complex systems—and one of its most important. While promoting healthy digestion and nutrient absorption is an obvious role of the gut microbiome, it isn't the only role. A healthy, balanced microbiome also impacts the body's inflammatory response,[1] immunity,[2] and even functions like mood,[3] blood pressure[4] and cognitive function.[5]

Scientists are still looking to understand how the microbiome might do all of this, but one thing is clear: A healthy microbiome is linked to overall health. A 2018 article in the *British Journal of Medicine* reviewed the powerful effects of the microbiome on nutrition and health in humans.[6] In the June 21 publication of *Pharmacy Times*, a review of the importance of the microbiome in overall health was discussed in detail.

In such a crowded space, it is inevitable that the growth will slow down. Probiotic products will have to stand out in some way to stay viable in the market. They can best do this with studies that show proven benefits. Consumers will continue to look for more evidence showing which products are best for their individual needs. Manufacturers will need to ensure their formulations are backed by research mirroring the multiple-strain combinations they use in their products, not only science on individual strains.

The evolution of probiotics in the marketplace will hopefully follow—where the science leads in the development of products that best meet the needs of today's educated consumers. To relegate probiotics to be included in the next

bag of chips, box of cereal or whatever other marketing trend that arises, can dilute the power and value of probiotic research. Probiotics can offer genuine health benefits and should be a part of everyone's healthy lifestyle.

James LaValle is an internationally recognized clinical pharmacist, author, board-certified clinical nutritionist and naturopathic doctor with more than 30 years of clinical experience. He works with the NFL, NBA, NHL, MLB and the Pro Football Hall of Fame village to offer personalized health, wellness, diet and performance strategies. LaValle is best known for his expertise in metabolic and integrative medicine, with a background in natural products, lifestyle drug/nutrient depletion, and uncovering the underlying metabolic issues that keep people from feeling healthy and vital. He developed health programs for the fitness industry, health care companies and professional sports teams including Corvette Racing team, Orlando Magic, Chicago Blackhawks and Anaheim Ducks. LaValle is author of more than 20 books, including, "Cracking the Metabolic Code," "Nutritional Cost of Drugs" and "Your Blood Never Lies." He has been named one of the "50 Most Influential Pharmacists" by American Druggist magazine. He also serves on the scientific advisory council for Organic & Natural Health Association.

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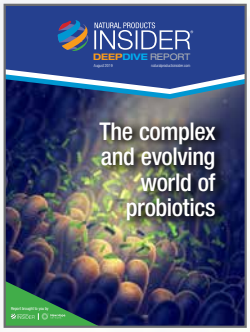

The complex and evolving word of probiotics - deep dive

The global market for probiotics with foods and supplements together hit $43.8 billion in 2018 and is estimated to reach $77 billion over the next seven years. Market potential is high as new strains continue to be identified and researched for their role in the human (and animal) microbiome. For an intricate breakdown of the science, application and market trends behind probiotics read The complex and evolving world of probiotics - deep dive.

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Exploring the probiotics galaxy

by Lisa Schofield

INSIDER's take

- New research on the microbiome is focusing on the gut-brain axis, with science showing digestive health benefits to cognitive function.
- Additional emerging areas of probiotic focus include sports, personal care, and healthy aging as research shows potential inflammation benefits.
- Spore-forming probiotics offer formulators the opportunity to add their microbiome benefits to shelf-stable foods and beverages.

Man is most definitely not alone. Ever. Humans are constantly hosting trillions of entities—bacteria—universes of which exist in various parts of the body, including the skin, mouth and mostly the gastrointestinal (GI) tract, as well as other areas.[1]

It isn't news that probiotics are sizzling hot—many consumers have accepted that these supplemental bacteria may help improve both gut and immune health. In fact, an excitement exists in the dizzying array of probiotic-infused products, from skin creams (for the skin microbiome), to probiotic fizzy shots and kombuchas in exotic flavors, to probiotic dried fruits and cereals.

Linkage Research & Consulting Inc. reported in June 2019 that 87% of Americans understand a connection exists between digestion and health, and 7 out of 10 stated they were proactive about their digestive health.

Sales have been zooming. *Nutrition Business Journal* (*NBJ*) data noted sales of pre-, pro- and synbiotics sprinted from US$1.9 billion in 2016 to an estimated excess of $3 billion for 2020.

This is reminiscent of another statistic that seems to illustrate the major takeoff of pre- and probiotics, from the National Health Interview Survey ("Use of Complementary Health Approaches in the US")—consumption of these products in the five-year stretch from 2007 to 2012 multiplied by four times.

Since then, revelations about the populations of beneficial bacteria residing and working in the human organism have accelerated. The buzz is now all about the microbiome, an intriguing concept as it conjures a wholesome, earth-like entity with bacteria, enzymes and other materials cohabiting, integrating and hopefully, thriving.

Mining the microbiome

Tom Laaman, Ph.D., director of technical sales, Specialty Enzymes & Probiotics, said "an interesting area of recent research has shown the gut microbiome and the brain communicate with each other, affecting the function of each—the gut-brain axis. It increasingly appears that supplemental probiotics may offer help for brain-related conditions, like fogginess and memory. Despite its

Per a June 2019 report, **87% of Americans understand** a connection exists between digestion and health, and **7 out of 10** stated they were proactive about their digestive health.

Reported by Linkage Research & Consulting Inc.

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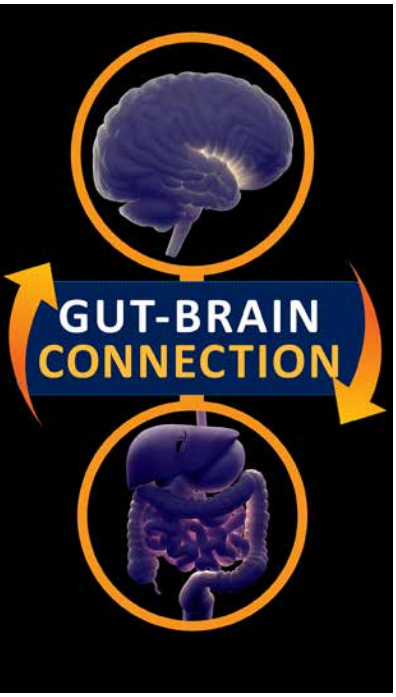
novelty, the microbiome communications system has been researched for at least 10 years, as one study shows."[2]

According to John Deaton, Ph.D., vice president of science & technology, Deerland Probiotics & Enzymes, "Understanding what shapes the various human microbiomes is helping design innovative probiotic products that support maintenance of a healthier body throughout life. Additionally, with the growing awareness that each probiotic, down to strain level, has unique properties and efficacies, utilizing tools such as microbiome analysis in clinical research is key to differentiating the many strains available for targeted applications."

One of the hottest areas for development in the probiotic/ prebiotic market for 2020 will be the gut-brain axis

Cristiana Piangiolino, Ph.D., market manager, nutraceuticals for ROELMI HPC, observed that the microbiome is currently a hot topic not only for the health supplement industry, but also for the beauty and personal care market.

Mariah Saerndahl, global communications, dietary supplements, DuPont Nutrition & Biosciences, commented, "As our understanding of the human microbiome develops, it is only natural for consumer probiotic offerings to evolve with the research."



According to Saerndahl, in 2017, DuPont Nutrition & Biosciences launched the Microbiome Venture—a small and focused entrepreneurial team of strategic partnerships with leading academic groups and startups—to help lead development of microbiome science-based products. Two examples of such products, she added, are DuPont's HOWARU Smile, a probiotic to support gum health, and HOWARU Calm, a probiotic product focused on supporting cognitive health.

Eye on 2020

Next year will be monumental in numerous ways; one of which is the promise of further breakthroughs and developments in microbiome research and pre- and probiotic products.

Deaton said one of the hottest areas for development in the probiotic/ prebiotic market for 2020 will be the gut-brain axis. The advancements in capabilities of microbiome analysis, combined with metabolite and protein research, he stated, "are allowing researchers to understand the microbes and molecules responsible for supporting a healthy mind relating to the gut. We will start to see products developed that help

maintain a calm mind under periods that could cause stress and/or anxiety. This is a particularly relevant area of research and product development in a world that is becoming increasingly fast paced and with heightened levels of pressure both in the home and work."

Two other areas of probiotic targets include sports nutrition and healthy aging. And another newer area that will see increased focus in research and development (R&D) and consumer use is probiotics for brain support and cognitive function, according to Saerndahl. She reported that DuPont invested heavily in research on probiotic supplementation for cognitive health. According to the 2018 "Study of Energy Needs and Solutions" by Multi-sponsor Survey Inc., "It is a fact that 2 out of 3 adults report experiencing some level of stress in their everyday lives," she commented, adding that stress impacts cognitive function.

As the wide world of probiotics is not limited to strains or species in the genera *Lactobacillus* and *Bifidobacterium*, more species will emerge into the R&D development pipeline. For example, according to Piangiolino, a new probiotic research area is focused on next-generation probiotic species like *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*. Although a body of research is growing on how these probiotics act in the body, she said, industrializing the strains of these species is currently challenging. A 2017 meta-analysis showed disparate expression of strains in the genera *Lactobacillus* and *Bifidobacterium*, and in the species *Faecalibacterium prausnitzii* in individuals with irritable bowel syndrome (IBS).[3]

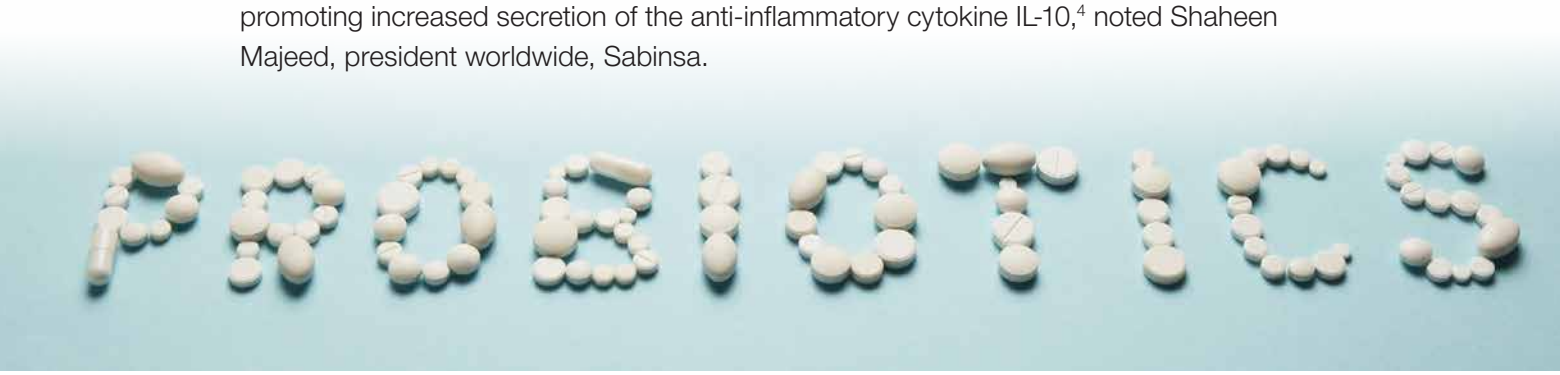
For 2020 and beyond, Laaman said he sees a greater emphasis on probiotic research for healthy individuals rather than targeting specific dysfunctions or conditions. "The goal will be to create heightened levels of vitality and longevity through advanced probiotic products that improve the existing human microbiome," he stated.

In the probiosphere

Indeed, activity is lively in probiotic, prebiotic, synbiotic and microbiome research, with new revelations occurring in swift succession.

Spore-forming bacteria such as *Bacillus subtilis* and *Bacillus coagulans* are hardy, able to withstand challenging environments (such as gastric acidity) and are supported by studies demonstrating a range of uses.

For example, in a recent study, LactoSpore, Sabinsa Corp.'s shelf-stable strain *Bacillus coagulans* MTCC 5856, "exhibited excellent immunomodulatory efficacy" by down-regulating the secretion of the key pro-inflammatory cytokine interleukin (IL)-8 while also promoting increased secretion of the anti-inflammatory cytokine IL-10,[4] noted Shaheen Majeed, president worldwide, Sabinsa.



"The prominent survival during digestion, adhesion capacity and remarkable immunomodulatory potential of LactoSpore—coupled with its known ability to survive the food processing conditions and storage—supports its incorporation into shelf-stable food products targeted at improving and/or treating gut health," said Muhammed Majeed, Ph.D., Sabinsa founder.

Another *B. coagulans* strain, known as SEBiotic (*B. coagulans* LBSC, from Specialty Enzymes & Probiotics) was originally perceived by researchers to be a part of the *Lactobacillus* genus because it also produces lactic acid, until more sophisticated genomics revealed it belonged to the *Bacillus* genus, Laaman pointed out. As with other *Bacillus* species, SEBiotic forms protective endospores, enabling it to withstand high temperatures and acidic pH, increasing shelf stability.[5]

"But the most important issue beyond stability is whether it offers healthful benefits," he commented. "In a randomized, double-blind, placebo-controlled study on participants with severe diarrhea with abdominal pain, SEBiotic effectively treated both the diarrhea and resulting pain.[6] A second, [unpublished,] randomized, double-blind, placebo-controlled study concluded that SEBiotic is effective in alleviating overall pathophysiological symptoms of IBS evaluated through stage-II clinical trial."

Life stages, such as pregnancy, provide key opportunities for probiotic products.

Specialty Enzymes & Probiotics provides two bacillus species—SEBtilis (*Bacillus subtilis* PLSSC) and SEBclausii (*Bacillus clausii* PLOSC), Laaman added.

Deerland has several clinical trials underway that investigate the performance benefits of its *Bacillus subtilis* DE111 supplementation for athletes and physical fitness professionals and devotees, according to Deaton. "Based on extensive protein and metabolite [unpublished] research already conducted on our novel *Bacillus subtilis* strain of probiotic, improved recovery and increased body fat reduction are being addressed," he commented.

Two studies using 1 billion colony-forming units (CFUs) of DE111 had statistically significant results in both male and female athletes. In a study involving female collegiate athletes during offseason training, researchers found that compared to the placebo, DE111 produced statistically significantly improvements in the reduction of body fat percentage, and a strong trend indicating improved performance of the deadlift exercise.[7] In another study of male collegiate athletes during offseason training, DE111 promoted tissue recovery and reduced likelihood of injury.[8] The results of the study showed that compared to the placebo, the probiotic DE111 produced a statistically significant reduction of tumor necrosis factor alpha (TNF-a).

A clinical study evaluating the effect of 5 billion CFU of DE111 on digestive health resulted in a significant influence on gut microflora measured prior to and after consumption, Deaton reported.[9] Fecal samples showed presence of more *B. subtilis* and *Bifidobacterium* (good bacteria), and less *E. coli*.

Another clinical study showed a reduction of constipation and diarrhea in those taking 1 billion CFU of DE111 compared to placebo.[10]

Life stages, such as pregnancy, provide key opportunities for probiotic products. For example, DuPont's HOWARU Protect Prenatal+ supports the health of mother and child during pregnancy and beyond, according to Saerndahl. "This clinically studied product not only promotes vaginal health,[11] but also happiness and calmness in new mothers,"[12] she said. In addition, this combination of strains has also been shown to support healthy immune function in both mothers and their infants,[13] and healthy blood glucose levels in pregnant women.[14]

Further innovation in strain R&D includes ROELMI HPC's development of different approaches to interact with localized microbiomes via biofermentation, according to Piangiolino. The SynBalance line of proprietary strains in the genera lactobacillus and bifidobacterium address numerous targeted health areas, according to internal company data, such as skin inflammation, cognitive function, urogenital support, pregnancy, cardiometabolic health, and for sports and energy.

Recently, she reported, ROELMI HPC introduced a new technology that protects probiotics, enabling their use for food application by encapsulation. "Stability, compatibility and feasibility trials have been carried out to develop innovative probiotic concepts," she said.

Additionally, ROELMI HPC "moved to a different market, from nutraceutical to cosmetics, designing specific ingredients for the skin, such as deactivated probiotics with prebiotic and immune-mimetic effect and postbiotics," she described. "Both new product lines have been studied in vitro during the screening phase and then on humans by looking at the metagenomics of microbiomes and skin improvement by measuring specific parameters." These studies are unpublished. The product lines are ProbiOFF (deactivated probiotics) and ÆCTive (skin microbiota balancer).

Search "*Lactobacillus*," on pubmed.com, and 37,434 results pop up; 3,731 show for "*Bifidobacteria*," and 101,659 for "*Bacillus*." The realm of research, development, usage and demand for all things probiotic will only continue to expand as the future unfolds. It appears this category is, indeed, alive.

Lisa Schofield is a veteran writer and editor who got her start interviewing rock stars for national music magazines. She now writes and edits content for B2B media and suppliers in the natural health product industry. In the industry, she has served as editor for Vitamin Retailer and Nutrition Industry Executive, and prior to that as associate editor for Whole Foods. For fun, Schofield writes Stephen King-inspired short stories.

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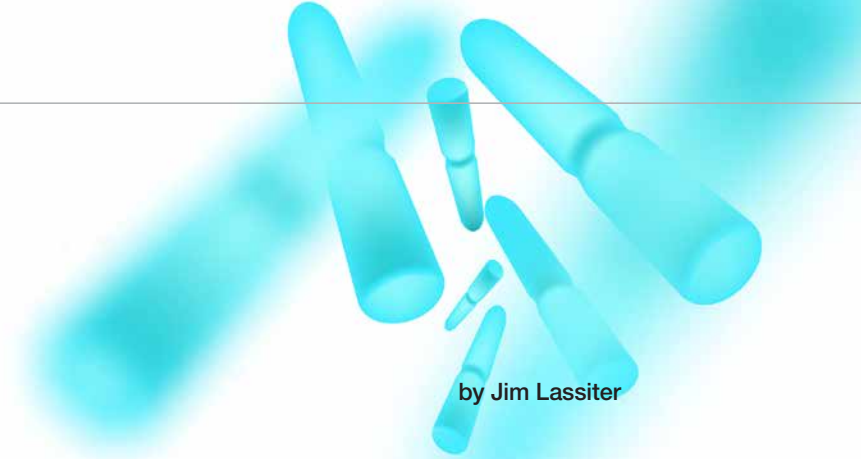

Gut reaction

by Jim Lassiter

INSIDER's take

- As more probiotic products enter the market, brands look for ways to differentiate their offerings.
- Probiotics in shelf-stable foods must be tested to ensure microorganism viability until the end of shelf life.
- Brands that market new strains need to ensure they are safe, and they may require NDI notification.

"You need the right balance between data and gut feeling."

— Torger Christian "Toto" Wolff, Austrian investor and former race car driver

The industry expanded the category of digestive health. Increased awareness has driven the discussions and scientific evidence emerging about healthy microbiota. The consumption of these microorganisms is as old as cultivated food; however, consumer education, interest and understanding are expanding. Probiotic brands are challenged to differentiate their products while also accounting for various regulatory requirements.

The range of products offered in the probiotic category is no longer limited to a liquid suspension that requires refrigeration. A beautiful meld of science and customer demand led the industry from capsules and sachets to probiotics added to beverages and other shelf-stable forms. However, regulatory issues arise with shelf-stable probiotic claims.

In September 2018, FDA issued "Draft Guidance for Industry: Policy Regarding Quantitative Labeling of Dietary Supplements Containing Live Microbials." The guidance noted FDA enforcement discretion applies only toward "live microbials." To quote FDA: "Our exercise of enforcement discretion does not apply to other foods that contain live or viable microbial ingredients, to dietary supplements that do not contain live microbial dietary ingredients, or to any other FDA-regulated commodities."

FDA's current thinking is that these products' presentation depends on whether the microorganisms are alive throughout the shelf life. The demonstration of this viability with scientifically valid methods is essential to determine FDA's acceptance of the probiotic ingredient. Industry and FDA need to move toward an understood definition of "viable organisms" to include the shelf-stable products that dominate the marketplace. As with most new topics, FDA is not current on the matter, and it behooves industry to educate the regulatory agency.

Once a brand accurately labels its probiotic product until the end of shelf life, it can focus on how to differentiate the product in the market. Brands can do this by combining different strains of microorganisms, each that are independently acceptable

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for use. This approach doesn't require notification to FDA for a new dietary ingredient (NDI), but potency claims can be a challenge. Or, brands can introduce different strains of existing microorganisms that have not been notified as NDIs or GRAS (generally recognized as safe) ingredients. These different strains qualify as new ingredients as either food additives or NDIs. Reliance on the data already in place for a related strain is possible, but brands should not bank on it. Knowing the similarities and demonstrating the similarities of the new related strain is mandatory to merit a positive review from FDA. Identification of the differences in the strains must also be addressed. Brands must show not only on the immediate finding (gut reaction) that the two strains are interchangeable, but should also provide the data necessary to support the contention that the differences are inconsequential.

The successful introduction and use of probiotic components in foods and dietary supplements is not necessarily a regulatory minefield.

A close review of the dossier, either internally or with the assistance of an outside expert, is a good idea before committing to using a new strain of any tried-and-true microorganism. The person or company working on the dossier should not be the expert who will sign off on the material's GRAS status. FDA will surely object to this conflict of interest during inspection of the documents, warranting a potential recall of the ingredient and any finished products containing that ingredient. While FDA doesn't demand a review of GRAS self-declarations, the market mandates it.

The successful introduction and use of probiotic components in foods and dietary supplements is not necessarily a regulatory minefield. Brands have ample opportunity to address all of FDA's concerns when new strains are introduced.

As chief operating officer, Jim Lassiter oversees all consulting operations at REJIMUS. He has more than four decades of experience in quality control (QC), and government and regulatory affairs throughout the pharmaceutical, dietary supplement and natural product industries with organizations such as Nutrilite, Robinson Pharma, Irwin Naturals, Chromadex, the American Herbal Products Association (AHPA) and the Council for Responsible Nutrition (CRN). A respected author and speaker, Lassiter has served on numerous industry and trade boards.

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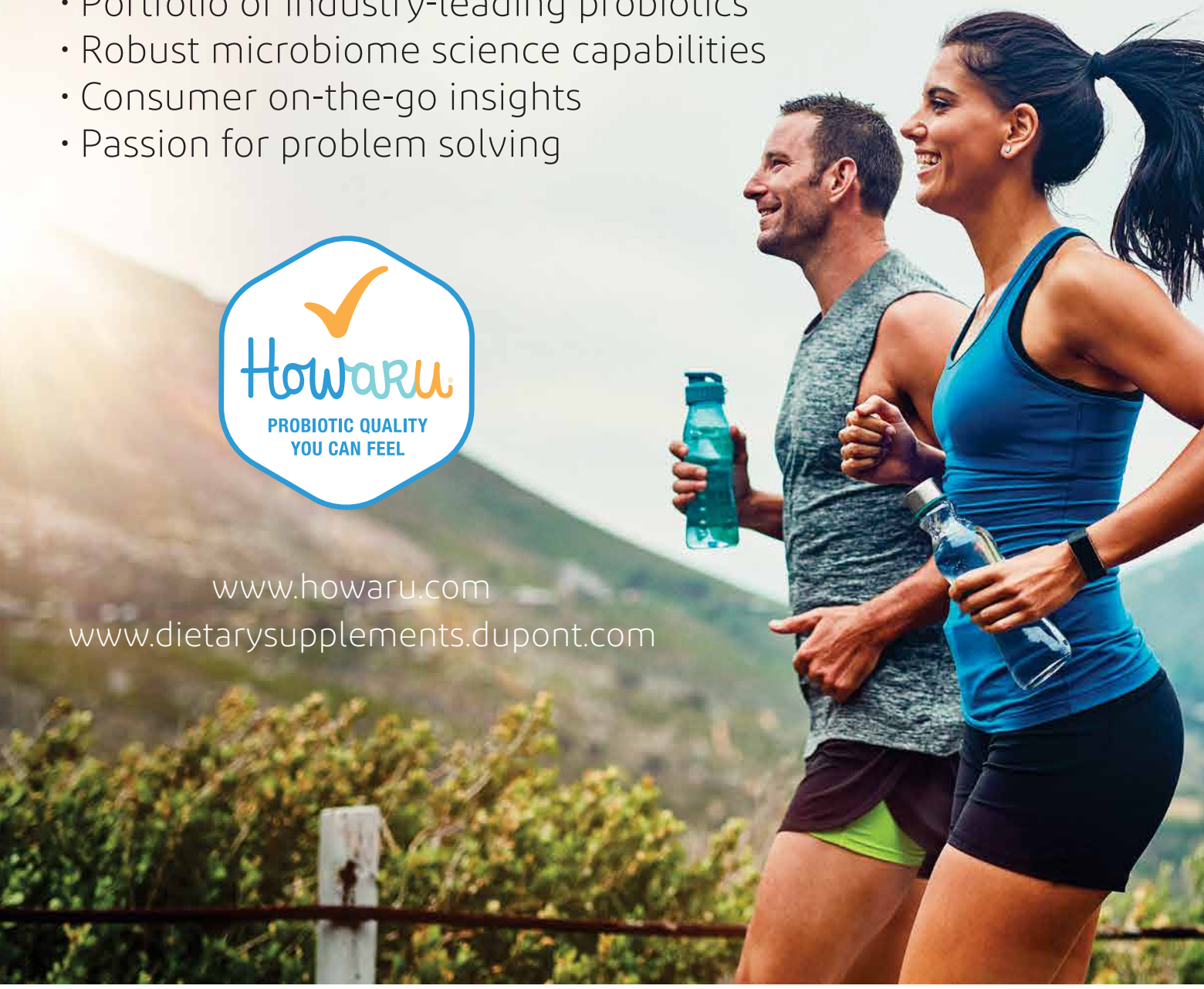

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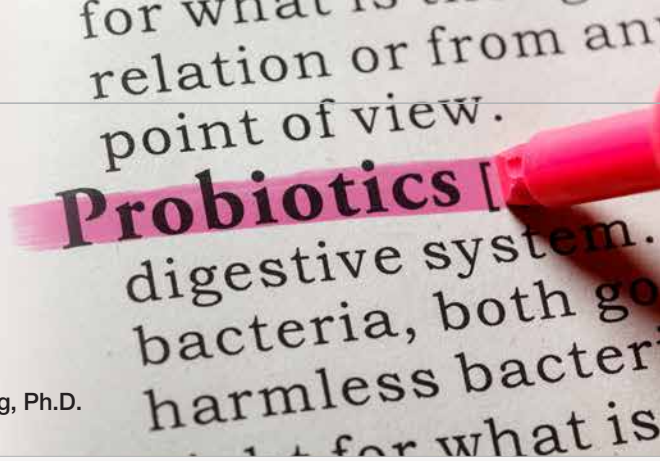

Advancing probiotic innovation with science and advocacy

by Andrea Wong, Ph.D.

INSIDER's take

- Manufacturers are tasked with creating products that meet standards—but those standards should bring clarity, not confusion, to consumers.
- FDA should allow probiotic supplement brands to label quantities in CFUs rather than requiring them to list the ingredients by weight.
- In 2019, the California State Assembly presented legislation that was inconsistent with FDA's current probiotic policy and regulation.

The supplement aisles of local retailers and the expo halls of industry trade shows offer an excess of product innovation in the probiotics space. These live organisms are being incorporated into a wide array of supplement and food products, providing consumers with more purchasing options than ever before. Consumers can find probiotics in traditional dietary supplement delivery forms like powders, capsules and gummies, as well as in food products, like chips or cheese puffs.

As probiotics continue to trend in the dietary supplement industry, and consumers continue to seek alternative delivery forms, the industry has a heightened responsibility for creating products with high-quality and reliable standards to ensure trust and dependability for consumers.

Labeling updates

In September 2018, FDA issued a draft guidance titled, "Policy Regarding Quantitative Labeling of Dietary Supplements Containing Live Microbials: Guidance for Industry," that announced its intent to exercise enforcement discretion to allow supplement companies to use colony-forming units (CFUs) when declaring the quantity of live microbials on a Supplement Facts label. While encouraging, the draft guidance also stated that the label must also list the quantitative amount by weight, as is required by current regulation for dietary ingredients. The Council for Responsible Nutrition (CRN) submitted comments in response to the draft guidance, commending FDA for recognizing the appropriateness of CFUs for describing probiotic quantity, but expressing concern with the agency's position that supplement labels should also list the quantity of probiotic ingredients by weight. It is not possible to accurately correlate probiotic quantity in both weight and CFUs on a consistent basis. Therefore, the recommendations in the draft guidance cannot be implemented in a manner that is not potentially misleading to consumers.

Noting a lack of action since the draft guidance was issued last year, CRN sent a letter to FDA in August, reiterating its request for FDA to eliminate the condition that

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live microbial quantity must be listed in terms of weight, in addition to quantity in CFUs, and to formally exercise enforcement discretion when marketers declare quantity of probiotic ingredients in CFUs only so that manufacturers and marketers of probiotic products could provide consumers with accurate and meaningful label information. CRN is still waiting for a response from FDA.

State legislation concerns

Earlier this year, the California State Assembly presented legislation concerning the labeling of dietary supplement products containing live microorganisms, including probiotics. The introduced Assembly Bill AB 1178 required probiotic dietary supplements to label ingredients by genus, species and strain, and to identify quantity at end of shelf life by CFU. The bill's requirements are inconsistent with FDA's current policy and regulation, putting industry in a difficult position and potentially causing confusion among consumers.

To foster innovation in this sector and to maintain a responsible market, it's important that industry continues working to ensure proper labeling, regulation and research of this category.

CRN worked to have the CFU requirements removed from the Senate version of the bill, leaving only the genus, species and strain requirement. While the requirement created a state-imposed labeling obligation in addition to federal requirements, it was not conflicting with current federal regulation.

The bill did not progress out of committee before the legislative session ended in mid-September, giving the responsible industry the opportunity to continue working with the bill's author—California Assemblyman Bill Quirk (D-Hayward)—to find compromise language should the bill be reintroduced in next year's legislative session, since he had not agreed to the Senate revision.

Many Americans rely on probiotics as part of their health and wellness regimens. To foster innovation in this sector and to maintain a responsible market, it's important that industry continues working to ensure proper labeling, regulation and research of this category.

Andrea Wong, Ph.D., is the senior vice president, scientific and regulatory affairs, of the Council for Responsible Nutrition (CRN), a trade association for the dietary supplement and functional food industry.

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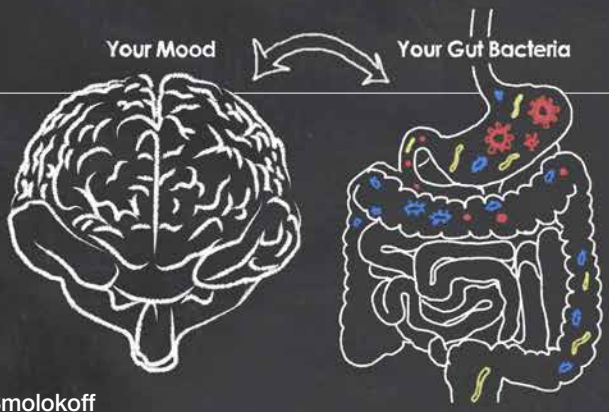

Probiotics show promising benefits against anxiety

by Alex Smolokoff

INSIDER's take

- Probiotics are being touted for benefits far beyond digestion as more is learned about the gut-brain axis.
- Meta-analyses and recent research indicate pre- and probiotics show promising benefits for sleep and mood.
- Research shows probiotics could be beneficial for consumer groups like pregnant women and new mothers.

Not all that long ago, gut health was a taboo topic. But as the myriad benefits of a healthy microbiome continue to be better understood by consumers and researchers alike, products to help maintain a healthy digestive system are on the rise.

As consumers have begun to understand that probiotics can aid not only digestive health,[1] but also the brain,[2] heart,[3] immune system[2] and more, sales of probiotics have continued to inspire. As Claire Morton, senior industry analyst at *Nutrition Business Journal*, said in **Natural Products INSIDER**'s February 2019 Formulator's Resource, "The probiotics category is huge—US$2 billion—and we are still seeing a tremendous growth rate."

And now, consumers may have even more reason to turn to probiotics and other microbiome-supporting interventions.

A study review published in May in the journal *General Psychiatry* concluded, "People who experience anxiety symptoms might be helped by taking steps to regulate the microorganisms in their gut using probiotic and non-probiotic food and supplements."[4]

The review included 21 studies covering more than 1,500 participants. Of those 21 studies, 14 included probiotic intervention; the other seven included non-probiotic measures to regulate and improve intestinal microbiota, such as dietary adjustments.

The authors concluded, "Overall, 11 of the 21 studies showed a positive effect on anxiety symptoms by regulating intestinal microbiota, meaning that more than half (52%) of the studies showed this approach to be effective."

While the review did note that non-probiotic treatments—which included low-FODMAP (fermentable oligo-, di-, monosaccharides and polyols) diet and short-chain fructooligosaccharides (FOS)—had a higher rate of effectiveness in reducing anxiety (86% of the non-probiotic treatments were effective, compared to 36% of the probiotics), other studies show support for probiotics in addressing anxiety and other mood states.

A March 2019 double-blind, placebo-controlled study of 38 healthy volunteers concluded after six weeks, "Overall, probiotics intake was noted to exert a positive effect on depressive mood state and sleep quality.[5] This effect was specific for the experimental group, thus ruling out confounding factors like learning, expectations or maturation."

Noting caution, the researchers added, "These findings provide new support to the notion that probiotics may exert a beneficial psychological influence."

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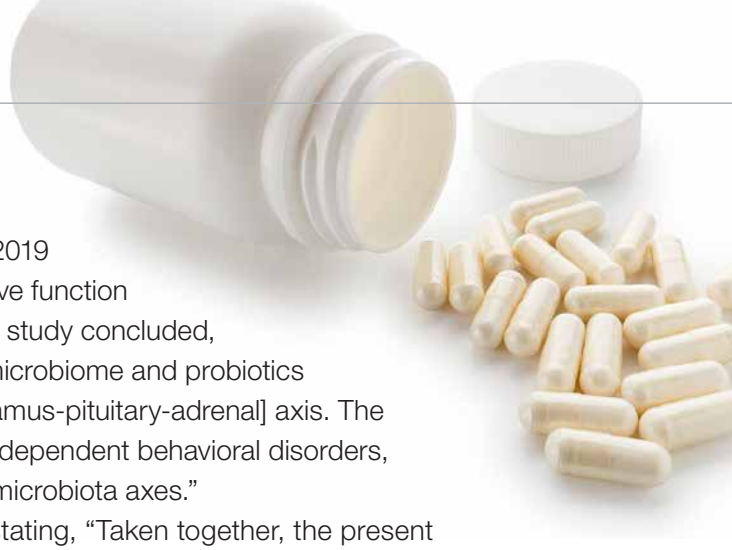
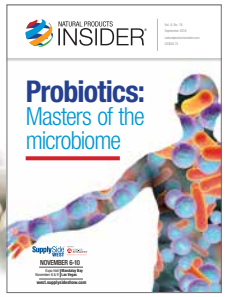


An even more recent study published in May 2019 sought to test the effects of probiotics on cognitive function and anxiety-like behaviors in pregnant rats.[6] That study concluded, "Our findings confirmed a link between the gut microbiome and probiotics with the behavioral functions and HPA [hypothalamus-pituitary-adrenal] axis. The probiotic treatment favorably affected the stress-dependent behavioral disorders, and the interaction between HPA and gut-brain-microbiota axes."

The authors further elaborated their results, stating, "Taken together, the present results indicate that exposing to stress during the fetal life disturb[s] the brain-related behaviors. The probiotic supplementation, either during fetal life or postnatal period, convincingly improves the impaired behavioral functions. Also, the probiotic treatment before and after birth normalize the serum concentration of corticosterone in the stressed rats." Corticosterone is involved in stress responses in many animal species.



While this is good news for just about the entire population—who doesn't suffer from stress and anxiety, at least occasionally?—it could be especially good news for certain consumer groups. As noted in **Natural Products INSIDER**'s September 2018 digital magazine, "Probiotics: Masters of the microbiome," new mothers could benefit from probiotic treatment of stress and anxiety.

"A double-blind, placebo-controlled study of healthy, breastfeeding mothers explored probiotic supplementation from early pregnancy through six months after delivery," wrote Karen Butler, senior editor.[7] "Women in the [probiotic] group [taking *Lactobacillus rhamnosus* HN001] reported lower depression and anxiety scores than those in the placebo group."

Whether a new mother or just someone trying to conquer the day, all kinds of consumers are looking to relieve the stress and anxiety of everyday life. With this and other promising research, just like the way to one's heart, the way to a healthier mental state might just be through the stomach.

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Entering a new era for probiotic supplements

by Matthew Oster

INSIDER's take

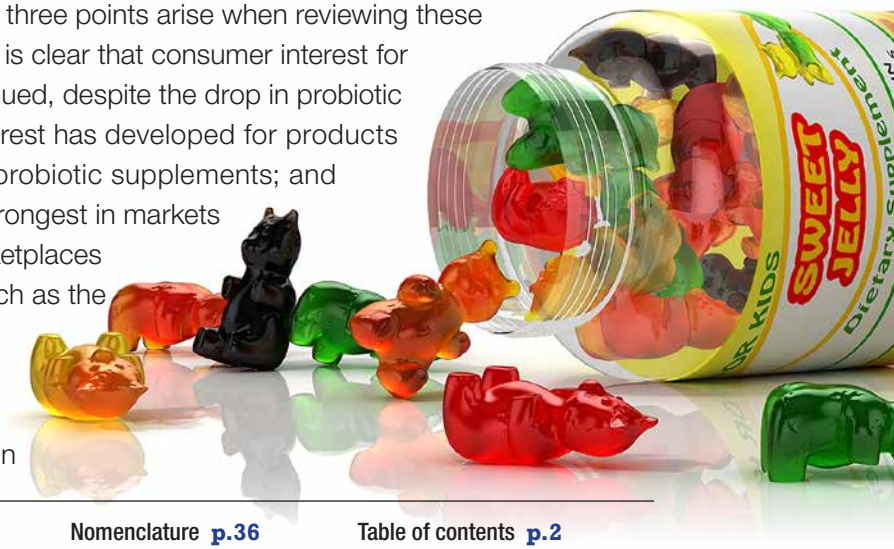
- The global market for probiotic supplements has declined since 2016, but innovation can rebound sales.
- Consumer interest in the microbiome is still high, as seen with growth of kombucha, prebiotics and synbiotics.
- Brands can revitalize the market by targeting specific niches, such as immunity, children and athletes.

After years of heady growth, the global market for probiotic supplements showed a deceleration starting at the end of 2016, bottoming out at negative growth in the first quarter of 2019. This slower growth cycle came at the same time as broader interest in the gut microbiome and its effects on a wide array of health functions, leading to speculation about what caused the slowdown and what it portends for future growth in this space.

After a handful of years since the initial slowing, it is clear that cannibalization from other cultured and fermented products played a leading role, signifying entry into a new phase for probiotic supplements, where growth requires the industry to lead with science and innovation to win back wayward consumers.

The competitive area in which probiotic supplements play is getting more crowded each year, with consumers engaged with several similar cultured and fermented products claiming comparable benefits to probiotic supplements. An example of a fast-rising category adjacent to probiotic supplements is kombucha. The fermented ready-to-drink (RTD) tea has seen much interest due to the product's purported health benefits, principally digestive health and immunity, that overlap with those of probiotics.

It is arresting to see the stark overlap in probiotic supplements' decline with kombucha's emergence in the U.S. That is not to say kombucha was necessary and sufficient to the probiotic supplements' decline, but three points arise when reviewing these categories against each other: 1 It is clear that consumer interest for cultured health products has continued, despite the drop in probiotic supplement sales; 2 particular interest has developed for products that have similar health claims to probiotic supplements; and 3 kombucha's appeal has been strongest in markets with big probiotic supplement marketplaces seeing recent sales slowdowns, such as the U.S. and Australia.



Recent interest in prebiotics and synbiotics adds to the crowded cultured health product, especially in

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the U.S. Prebiotics differ from probiotics in that they contain food-based compounds stimulating the growth of beneficial flora (bacteria and fungi) in the gut that purport to have health benefits principally in the form of digestive health,[1] but also in immunity[2] and weight management,[3] among others. (Probiotics contain live bacteria that provide health benefits through colonization of the large intestine). Synbiotics refer to the combination of live bacteria (probiotics) and prebiotics that help induce growth of beneficial microorganisms in the gut.[4]

Interest in prebiotic/synbiotic supplements jumped in recent years, with several new entries in the U.S. marketplace either through direct-to-consumer (D2C) websites or Amazon, with Google searches for these products consistently increasing over time. Given this expanding interest, more companies are experimenting with formulations that include prebiotics as a mechanism to support or stimulate gut bacterial growth.

While the marketplace for prebiotic/synbiotic supplements has heated up, formulators and manufacturers have also experimented with several ways of infusing live probiotics into food-based nutritional products or topical solutions for skin health. The broader probiotics marketplace is innovating to a great degree, with live probiotic cultures being found in new products from energy bars, functional soft drinks and pancake mixes to peanut butter and potato chips.

Re-energizing probiotic supplements

Probiotic supplement sales growth may be down, but continued interest in the microbiome supports the contention that it is not out. In fact, scientific progress demonstrating broader benefits of probiotics points to a scenario whereby the 2016 to 2019 declines represent the end of the first wave of probiotic supplement growth, while future gains will be achieved through innovation and extensions of product offerings. The category will rebound as it evolves over time.

Undergirding this prediction is the fact that the positioning and formulation of probiotic supplements stands to change markedly in the coming years. The probiotic supplement aisle is still dominated by products positioned around digestive/gut health, marketed toward consumers suffering from digestive issues like irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD). Probiotic supplements positioned around other prevention and treatment issues like immunity, oral health,

weight management, feminine/vaginal health and skin health are also in market but have never been significant sales drivers compared to digestive-positioned products.

Health applications for probiotics have increased significantly in recent years, with recent developments perfecting non-pill delivery systems (gummies, chews and sachets/powders), segmentation around consumer groups (pediatric especially, but also neonatal/pregnancy, teen, women/men, athletes and the elderly) and expanding positioning to a seemingly endless array of concerns (heart health, childhood development, etc.). However, one innovation that will cause significant enough interest to result in a category rebound will be scientific developments around the gut-brain axis. Studies have shown that the gut is heavily involved in regulating emotion,[5] stress/anxiety[6] and depression,[7] with the activation of certain gut sensory neurons significant in improving emotional states. This space will explode as the science becomes more established.

Younger consumers (under the age of 40) were the first to retreat from the category, as many of them were influenced to try the product when it was considered new and in vogue.

Consumer interest also will influence a market rebound for probiotic supplements. Younger consumers (under the age of 40) were the first to retreat from the category, as many of them were influenced to try the product when it was considered new and in vogue. As many of these consumers' cases for using probiotic supplements are broad or vague, their adherence and persistence were lower than older consumers using the product to treat acute conditions. Understanding the consumers who have left the market is crucial for a category rebound in the near-term.

Surveys conducted by Euromonitor International demonstrate that younger consumers still have a high support for probiotic supplements, with consumers ages 15 to 29 and 30 to 44 showing similar usage of these products, both at the U.S. and global level. However, they are not using these products in a similar way to older consumers; while consumers 60 and older overwhelmingly use probiotic supplements for digestive health (68% of global respondents), younger consumers have more diverse demands. Of course, many still look to probiotic supplements for digestion, but increasingly, they are using these products to support memory (24% of 15- to 29-year-

old respondents), beauty/skin health (24% of that cohort), energy (22% of that cohort) and mood/relaxation (21% of that cohort). As probiotic supplements supported by strong scientific evidence enter these need spaces, they will be met by eager younger consumers ready to engage again with the category.

How long this period of softer growth continues is well within the industry to shape. Most signs point to a re-emergence of probiotic supplements in the near-term, led by younger cohorts and diversified positionings and formulations. But this rebound is not preordained; as with other supplements, commercial interest follows the science. Attracting consumers again might just well be the byproduct of understanding the gut microbiome better in the coming years.

Matthew Oster is the head of consumer health at Euromonitor International, overseeing the industry's research and analysis and leading a team of experts in 100 markets worldwide. Oster provides insight into the consumer trends, key markets, competitive landscape and growth opportunities in the global consumer health space to help organizations make strategic business decisions. His expertise is presented at industry conferences, including WSMI General Assembly, AESGP Annual Meeting and SupplySide West, among others, and featured in business and trade publications. Prior to this role, Oster was the head of institutional channels, where he analyzed the changing global health care landscape.

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A historical perspective on taxonomy changes

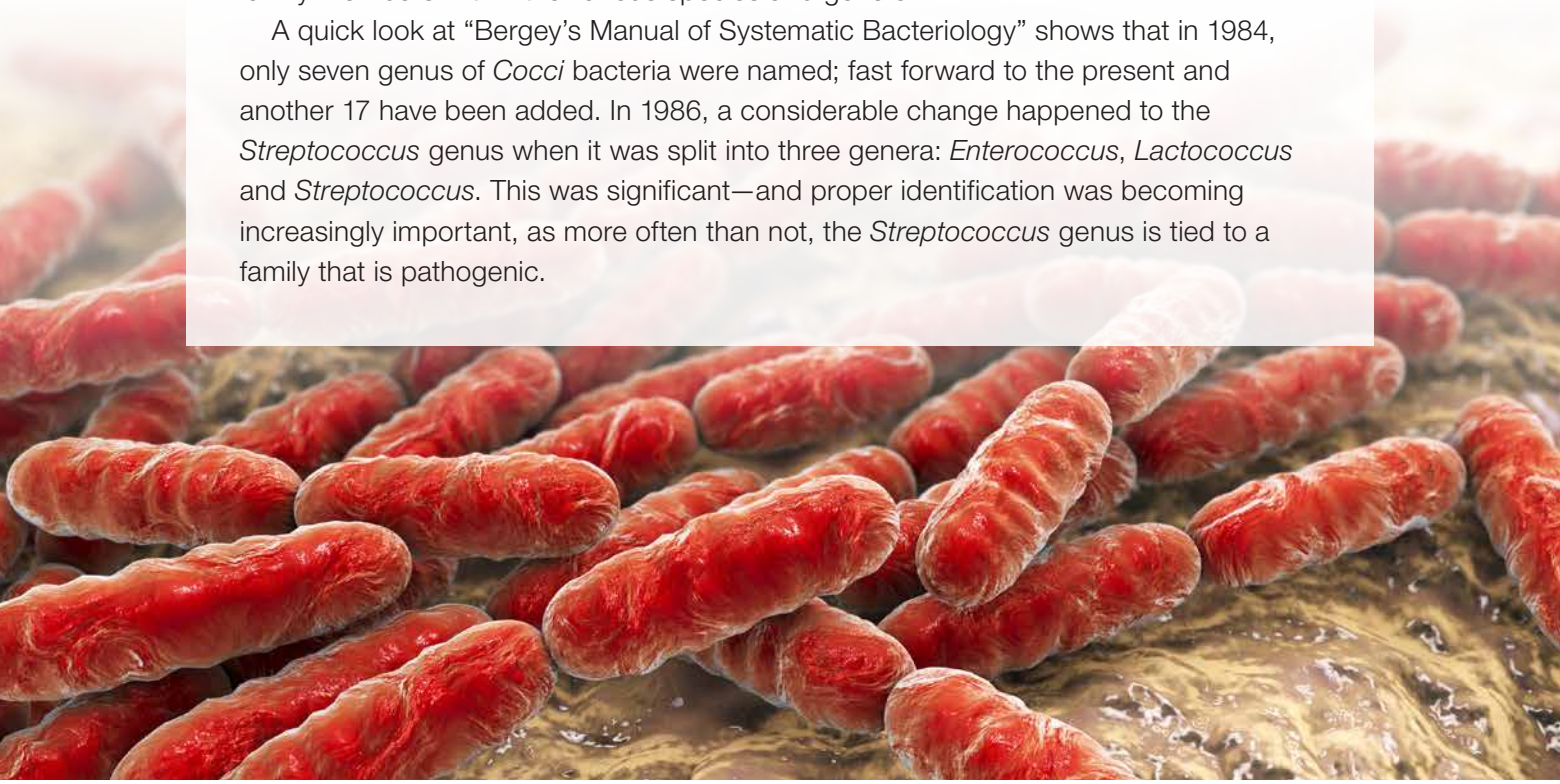
by George Paraskevakos and Solange Henoud

INSIDER's take

- All probiotics used to be commercially referred to as "*Bifidus*," "*Acidophilus*," "*Dophilus*" and other similar terms.
- In 1984, seven genus of *Cocci* bacteria were named in a key reference manual; by 2019, 17 had been added.
- Taxonomy does not happen by coincidence; it is an art of science that follows proper rules and procedures.

Since 1673, when Antonie van Leeuwenhoek first observed microorganisms in his single-lensed microscope and called them "animalcules," bacteria have gone through a long journey of classification and reclassification with scientists continuously searching for the most appropriate place in taxonomy. For example, *Lactobacillus rhamnosus* was once classified as acidophilus, casei, etc.; numerous species were classified under the genera *Bacillus* or *Thermobacterium*; *L. brevis* was called *Bacillus*, and so on. Historically, all probiotics used to be commercially referred to as "*Bifidus*,'' "*Acidophilus*,'' "*Dophilus*'' and other similar terms, resulting in what today is a large catalogue of individual strains, each unique, although sharing common traits with their family members within the various species and genera.

A quick look at "Bergey's Manual of Systematic Bacteriology" shows that in 1984, only seven genus of *Cocci* bacteria were named; fast forward to the present and another 17 have been added. In 1986, a considerable change happened to the *Streptococcus* genus when it was split into three genera: *Enterococcus*, *Lactococcus* and *Streptococcus*. This was significant—and proper identification was becoming increasingly important, as more often than not, the *Streptococcus* genus is tied to a family that is pathogenic.



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Another example can be found in this table, where we see *Lactobacillus* species transferred to other genera:

Old name	Synonymous with	Renamed to	Synonymous with (Final name)	Reference
'Lactobacillus' carnis	*'Lactobacillus piscicola'*	*'Carnobacterium piscicola'*	*Carnobacterium maltaromaticum*	Mora et al. 2003
'Lactobacillus' catenaformis			*Eggerthia catenaformis*	Salvetti et al. 2011
'Lactobacillus' confusus			*Weissella confusa*	Collins et al. 1993
Pediococcus dextrinicus			*Lactobacillus dextrinicus*	Back 1978; Haakensen et al., 2011
'Lactobacillus' divergens			*Carnobacterium divergens*	Collins et al. 1987
'Lactobacillus' fructosus		*'Leuconostoc' fructosum*	*Fructobacillus fructosus*	Endo and Okada 2008
'Lactobacillus' halotolerans			*Weissella halotolerans*	Collins et al. 1993
'Lactobacillus' kandleri			*Weissella kandleri*	Collins et al. 1993
'Lactobacillus' maltaromicus			*Carnobacterium maltaromaticum*	Mora et al. 2003
'Lactobacillus' minor			*Weissella minor*	Collins et al. 1994
'Lactobacillus' minutus			*Atopobium minutum*	Collins and Wallbanks 1993
'Lactobacillus' piscicola		*'Carnobacterium piscicola'*	*Carnobacterium maltaromaticum*	Mora et al. 2003
'Lactobacillus' rimae			*Atopobium rimae*	Collins and Wallbanks 1993
'Lactobacillus' uli			*Olsenella uli*	Dewhirst et al. 2001
'Lactobacillus' viridescens			*Weissella viridescens*	Collins et al. 1994
'Lactobacillus' vitulinus			*Kandleria vitulina*	Salvetti et al. 2011
'Lactobacillus' xylosus			*Lactococcus lactis subsp. lactis*	Schleifer et al. 1985

Source: Bruno Pot et al. – Labip expert panel meeting

As the science advanced, *Lactobacillus* seemed to be the appropriate genus for new finds; in 2017, it expanded to over 260 (and increasing) different species. In the age of next-generation genetic and proteomic sequencing, a new taxonomic system has been proposed for the *Lactobacillus* genus to more properly classify this consortium of bacteria, splitting the grouping into 20-odd new genera. Hopefully this classification will last for some time, but it certainly will not be the last change.

Taxonomy does not happen by coincidence; it is an art of science that follows proper rules and procedures. Technology will continuously evolve and understanding of the genome will improve, but the genome itself remains the same; hence, properly naming microorganisms allows for better characterization, identification and communication.

A search for *Lactobacillus* on PubMed (an online database of scientific references) produces more than 37,000 results—and on Google, over 15 million hits. Thanks to smartphones, a constant barrage of information invades human existence from the moment a person awakens. A name change for a major genus such as *Lactobacillus* can have a major impact on all stakeholder groups of the probiotic industry, including but not limited to consumers, scientists, health care providers, regulators and probiotic producers.

In the face of this challenge, the probiotic industry has united and is not only collectively communicating among each other, but with an outward-facing message as well. It will be key in underlining the importance of this evolution to parties which might be affected with the taxonomy change in an easy-to-understand, "What are the next steps to get prepared?" approach. An initiative of this significance requires preparation and proper messaging in order to help with the transition and, moreover, hopefully serve as an example for the future.

George Paraskevakos is executive director of the International Probiotics Association (IPA).

Solange Henoud is global regulatory affairs director at Lallemand Health Solutions and chairs IPA's regulatory committee.

Forthcoming changes in *Lactobacillus* taxonomy

by Anthony Thomas and Jessica ter Haar

INSIDER's take

- Taxonomic names are a result of extensive research by academic groups to classify genera into stable groups according to genotype and phenotype.
- Although the genus name *Lactobacillus* will change, the organisms and species names will not, and new genera names will start with an "L."
- Knowledge of the taxonomic relatedness of lactobacilli will serve as a new framework for the further identification of probiotic microbes.

An accurate and stable taxonomic system is necessary for proper microbial identification and community analyses. Thus, reclassification of organisms is an integral and continuous process as the science is updated with new genetic and phenotypic data, and the discovery of new species. The current genus *Lactobacillus* is too heterogeneous, with over 230 *Lactobacillus* species that exhibit substantial diversity[1] and novel species added annually, making it among the largest genera and no longer a stable taxonomic group.[2] According to Principle 1 of the International Code of Nomenclature of Prokaryotes (2008 revision, "the Code"), taxonomic names should be stable; in other words, not have to constantly change.

This problem has been recognized for some time, but the methodologies needed to reliably group species into new genera were not previously available. *Lactobacillus* taxonomy has historically been based on phenotypic and morphologic characteristics (e.g., carbohydrate fermentation patterns, cell wall composition, etc.).[2,1] Genomic data provides more reliable insight into the evolutionary relationships of microbial species, and coupled with phenotypic data, has proven to be a powerful tool for achieving stable classification of new genera in the past.[3,4] However, many current *Lactobacillus* species share 16S rRNA gene sequence identity higher than conventional cutoffs (i.e., threshold ambiguity).[2,1]

Many *Lactobacillus* species have a long history of safe and legal use in foods, whereas other species within the genus do not benefit from this status. Consequently, accurate taxonomic nomenclature is a prerequisite for appropriate safety assessment. Many regulatory agencies have safe lists of strains (e.g., qualified presumption of safety [QPS], GRAS [generally recognized as safe] lists), which are usually species-based. Furthermore, the taxonomic analysis of probiotic strains is necessary for both basic and applied research since reliable identification at the species and strain level are the basis for safety assessment, quality assurance (QA) and nonfraudulent labeling. This implies keeping groups reasonably compact and distinctive, comparable to analogous genera, is essential. Thus, this particular genus must be divided and reclassified.

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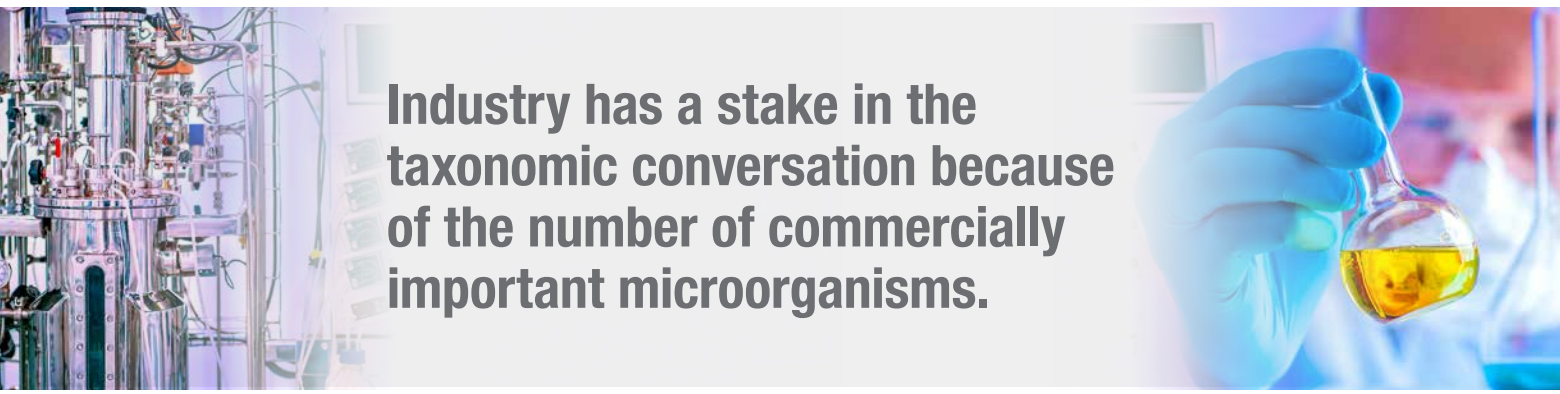
Using a combination of phylogenetic analysis (i.e., multilocus sequence analysis of ribosomal proteins and a set of housekeeping genes) and the assessment of the average amino acid identity and the percentage of conserved proteins, Salvetti et al. analyzed 269 *Lactobacillus* and related species (e.g., *Pediococcus*, *Leuconostoc*, *Fructobacillus*, *Oenococcus*) to show the current genus lactobacillus can be divided into at least 10 robust phylogenetic groups.[1] Each of these phylogroups would represent at least one new genus.

The 10 phylogroups

1. *Lactobacillus delbrueckii* (which contains *L. acidophilus*)
2. *Lactobacillus alimentarius* (which contains *L. farciminis*)
3. *Lactobacillus perolens*
4. *Lactobacillus casei* (which contains *L. rhamnosus* and *L. paracasei*)
5. *Lactobacillus sakei*
6. *Lactobacillus coryniformis*
7. *Lactobacillus salivarius*
8. *Lactobacillus reuteri* or *Lactobacillus fermentum*
9. *Lactobacillus buchneri* (which contains *L. brevis*)
10. *Lactobacillus plantarum*

Source: Salvetti et al. (2018)

These findings support results of another group that showed the average nucleotide identity—a pairwise comparison of homologous sequences—for *Lactobacillus* species was as low as values typically seen at the taxonomic level of an order.[5] Commercially important probiotic *Lactobacillus* species can be found in at least seven of these phylogroups. The Salvetti research group has undertaken further study to perform the complete taxonomic reclassification for the *Lactobacillus* genus and will ultimately be submitting its findings for publication in the *International Journal of Systematic and Evolutionary Microbiology* (*IJSEM*), thereby making the changes in *Lactobacillus* taxonomy official.



The formal process of how these changes will occur

The International Committee on Systematics of Prokaryotes (ICSP) is responsible for the naming of bacteria; the subcommittee of the ICSP responsible for naming lactobacilli is the Taxonomic Subcommittee for Lactobacilli, Bifidobacteria and Related Organisms. The ICSP's further task is to curate and communicate regarding new taxonomic nomenclature in its official journal, the *IJSEM*. Taxonomic names are a result of extensive research by academic groups to classify genera into stable groups according to genotype and phenotype. Once a new name and description is published, then it becomes scientifically valid and official, and names are permanently associated to the type strain of a species (Rule 15 of the Code).

Industry has a stake in the taxonomic conversation because of the number of commercially important microorganisms. This led to the establishment of the Lactic Acid Bacteria Industrial Platform (LABIP) in 1995, with the purpose of securing a link between academic research and industry; a workshop was convened in October 2018 to discuss stakeholder interests of the impending changes to *Lactobacillus* taxonomy. The academic research group involved was receptive to the concerns of industry and consensus was reached that reclassification should aim to achieve taxonomic stability. While this likely translates to a higher number of new genera derived from the current *Lactobacillus* genus, it would give more flexibility to accommodate future novel species. Conclusions from this workshop included:

- The genus name will change
- The organisms will not change
- The species names will not change
- The new genera names will start with an "L" to minimize disruption

Timeline of key and expected events related to the taxonomy changes

Pre-2012	Sept. 2018	Oct. 2018	July 2019	? 2019/2020?	? 2019/2020?	? 2019/2020?
Scientific group of Italians, Belgians, Germans working on this taxonomic group	Decision to split genus, Berlin • Comparative genetics publication by Salvetti et al.	LABIP expert workshop, Verona	Impact of reclassification publication by Pot et al.	Manuscript submission for peer review in the *International Journal of Systematic and Evolutionary Microbiology* (*IJSEM*)	Publication in the *IJSEM* • Name changes are official • Old/new names can be found on LSPN website	Grace period for label/commercial literature changes • GRAS/QPS list updated • Etc.

Substantial advantages are associated with reclassifying the *Lactobacillus* genus. By creating more accurate nomenclature and reducing diversity of the current genus, misidentification of species and communication will be improved. Compact, clear and

stable taxa will better reflect genetic relatedness of species. This will be an essential step in attributing and supporting mechanisms of specific probiotic groups to allow for precise description of genus-specific markers and development of novel identification tools.[6] Furthermore, structured knowledge of the taxonomic relatedness of health-promoting and technologically important lactobacilli will serve as a new framework for the further identification and selection of innovative probiotic microbes.

Anthony Thomas, Ph.D., is director of scientific affairs at Jarrow Formulas.

Jessica ter Haar, Ph.D., is scientific director of the International Probiotics Association (IPA).

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The probiotic formerly known as Lactobacillus

by Ivan Wasserman and Nina Vinot

INSIDER's take

- With more than 200 species (and counting), *Lactobacillus* has grown into one of the biggest genera in the bacterial taxonomy.
- As *Lactobacillus* is split into many new genera with new names, the impact on various stakeholders is expected to be disruptive.
- Some of the affected parties include researchers, consumers, regulators, product manufacturers and border control officials.

New genetic sequencing technologies have led to a huge rise in the number of probiotic species classified under the *Lactobacillus* genus. With well over 200 species, it has grown into one of the biggest genera in the bacterial taxonomy. It is extremely diverse and expanding every year. As the genus has exceeded the acceptable "normal diversity," it will be split into many new genera—all with new names. This means that many probiotic species with substantiated clinical importance may soon no longer be called "*Lactobacillus*." Hence, a substantial communication challenge looms ahead to reduce the inevitable confusion regarding the old and new nomenclature.

The International Committee on Systematics of Prokaryotes (ICSP)—which itself was formerly known as the International Committee on Systematic Bacteriology—is the body that oversees the nomenclature of prokaryotes (bacteria and other single-celled organisms). Once ICSP publishes new nomenclature in its official journal, the *International Journal of Systematic and Evolutionary Microbiology*, the changes will be valid and official, and many "formerly known as *Lactobacillus*" probiotics will be on the market.

A subdivision of these probiotics into different genera will represent an opportunity to improve discrimination of similar groups, as well as the understanding of the bacteria metabolism, ecology and properties. It will also be an occasion for deepening communication and education about the new groups' characteristics and specificities.

At the same time, the new classification will represent a challenge for stakeholders—in particular, probiotics producers and brands. Importantly, what may help to minimize confusion is that even though the genus name will change, the probiotic's species and strain names will not change. Further, ICSP will also try to propose new genera names that begin with the letter "L." So if a company identifies the probiotic species currently known as *Lactobacillus acidophilus* as *L. acidophilus*, which is common, and the name of its genus is changed to, say, *Larrymoecurlyus*, it can still be identified as *L. acidophilus*. The strain name will also remain the same.

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Even so, this change is likey to cause confusion in the short term as different stakeholders adopt the new nomeclature at different times. The confusion could also be long lasting, as clinical studies, patents, trademarks, commercial agreements, ingredient and product approvals, official lists and more may use the old names, while product labels and more may use the new names.

A substantial communication challenge looms ahead to reduce the inevitible confusion regarding the old and new nomenclature.

While nobody wants to create a panic, it is important for stakeholders to be aware of and plan for these changes. The impact will be manageable with time and resources, but with a non-negligible cost for the industry, as individual companies will be responsible for communicating changes on their product labels and services, and explaining the facts to their prescribers, customers and consumers.

Potential areas that this change will affect include:

- Companies, around their research and publications, manufacturing and quality documentation, master regulatory dossiers, product authorizations and certificates, marketing materials including websites and products lists, safety dossiers, ingredients lists and labeling, patent monitoring and more;
- Consumers, who may have doubts on a change of contents when they see different names, and should be reassured of the fact that probiotics themselves do not change—in particular, when clinical studies exist on a specific *Lactobacillus* and the new name doesn't allow to trace back to that publication;
- The scientific, medical and veterinary communities, who will need to take into account both the former names and the new names in literature searches and new publications;

- Transportation and border control, who will need to be well informed to avoid delays because officers may not be aware of the official new names for organisms that used to be approved under different designations for import/export;
- Regulators and governments, who will need to compare laboratory reports with biosafety and biosecurity lists, and update the existing positive lists of safe species with the new names (qualified presumption of safety [QPS], GRAS [generally recognized as safe] approvals, etc.); and
- Lawyers and intellectual property (IP) professionals and litigants when checking prior art on patents and trademarks for 10,000 patents including *Lactobacillus* in the title and abstract.

Ivan Wasserman is the managing partner of law firm Amin Talati Wasserman LLP.

Nina Vinot is area sales manager for Probiotical.

Takeaways: Probiotic market highlights diversification

by Connor Lovejoy

The probiotic supplement market might not be leading the natural products pack, but the category is still seeing a fair amount of activity. According to Statista, the estimated value of the probiotics market will hit $US56.6 billion in 2020 and $69.3 billion in 2023. With continued advancements in strain-specific research and delivery innovation, the probiotic market is still ripe (so to speak) for the picking.

Taxonomy and you

Probiotics, and how the scientific community has come to understand them, can experience changes as the pool of research broadens. A big driver for that change surrounds taxonomy or the classification of organisms. For instance, new genetic sequencing has resulted in a notable uptick in the number of probiotic species classified under the *Lactobacillus* genus, leading experts to undergo a reclassificaton process. This change may result in some market confusion—both for those in the industry, as well as consumers—surrounding the classification and characteristics of numerous probiotics.

Times they are a changing

Long gone are the days when consumers relied on probiotics solely for digestive support. The gut-brain axis isn't just a buzzword in the industry anymore. In fact, probiotic products are being researched for many different areas of consumer need, including mental and heart health. As 2019 unfolds into 2020, it's feasible that probiotics will start to cross more barriers and gain greater applicability in the wider health and nutrition market.

Variety is the spice of life

Yogurt is still a popular delivery form for probiotics, but innovation is the rule, not the exception, for natural products. Probiotic delivery is continuing to trend along with the greater natural products space, i.e., functional foods and beverages. Probiotic applications in products like kefir, kimchi, chips and chocolates are starting to line mainstream retail shelves with greater regularity.

Innovation and growth in the probiotic space are here to stay, particularly as consumers are open to and looking for claims about potential health benefits. Brands just need to ensure the specific strains they use are backed by science, and a formulation allows for viability through the end of shelf life.

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Inside INSIDER

How have probiotics impacted the natural products industry?

A. As gut health becomes a higher priority for consumers, they are looking to get their daily dose of probiotics from delivery formats other than supplements. This puts the pressure on many food and beverage companies in the natural products industry to deliver a variety of items that offer probiotics.

Marisa Finnegan
Show Director, Health & Nutrition

A. Probiotics have become increasingly popular as consumers understand the importance of preventive care. Not only does this increase demand for products containing probiotics, but also has consumers researching other natural ingredients that impact overall health.

Leez May
Program Marketing Coordinator

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