

Global overview for probiotics: Trends, markets, and harmonization

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This article discusses current diverging regulations for probiotics as ingredients in foods and dietary supplements and the trends and translational science that have demonstrated probiotic benefits. It emphasizes how aligning a global probiotic harmonized regulatory framework can help navigate the confusion around the regulations to ensure global consumer access to beneficial products of quality.

Keywords – Codex, harmonization, regulations, probiotics, probiotic foods, supplements

Introduction

Background

Probiotics are one of the more intensely researched dietary ingredient categories, and their benefits have been supported in translational science. However, current diverging global regulations present challenges to ensuring consumer access to safe probiotic products of quality, highlighting the need for clear, harmonized regulations and claims to facilitate delivery of foods and dietary supplements with probiotics to consumers worldwide.

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In 2001 and 2002, the UN Food and Agriculture Organization (FAO) and World Health Organization (WHO) published two joint reports with guidelines and recommendations for governments around the globe for the evaluation of the safety and nutritional aspects of probiotics.¹ These recommendations are widely respected and have been extremely helpful to governments, shaping regulations for probiotics internationally. The regulations set a baseline for the probiotic industry but have been interpreted independently, creating gaps as governments developed different requirements at the national levels.

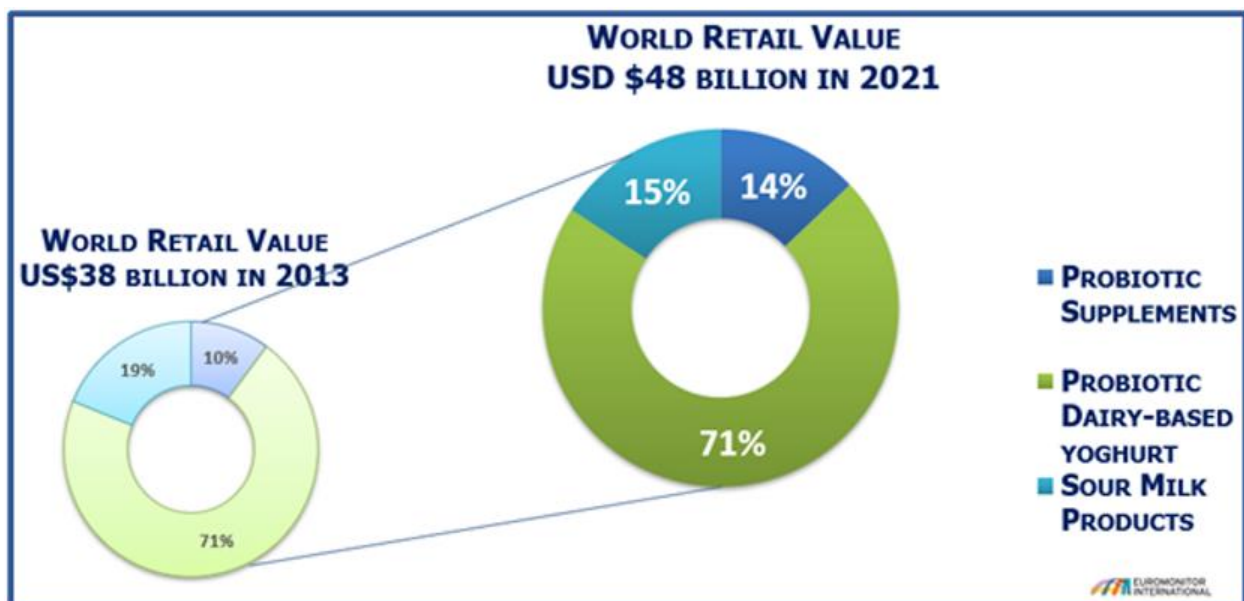
These guidelines and the definition shaped the future trajectory of the industry, and the global probiotics market is now dynamic and diverse. Continued growth, coupled with increasing consumer demand over the years, offers many opportunities for food, beverage, and dietary supplement organizations. The guidelines and FAO-WHO definition have resulted in a complex mosaic of diverse global regulatory frameworks, which presents challenges when commercializing probiotic products but may also be seen as opportunities.

Current landscape

The global probiotics market continues its upward ascent. A 2021 report noted that the total probiotic market was worth more than US\$48 billion (**Figure 1**).² The market grew 8% globally from 2020 to 2021, supported by the research and science tying probiotics to gastrointestinal-related issues and immune support, coupled with an increasing public demand for products for health promotion. Probiotics offer many opportunities both in food, beverage, and dietary supplement applications.

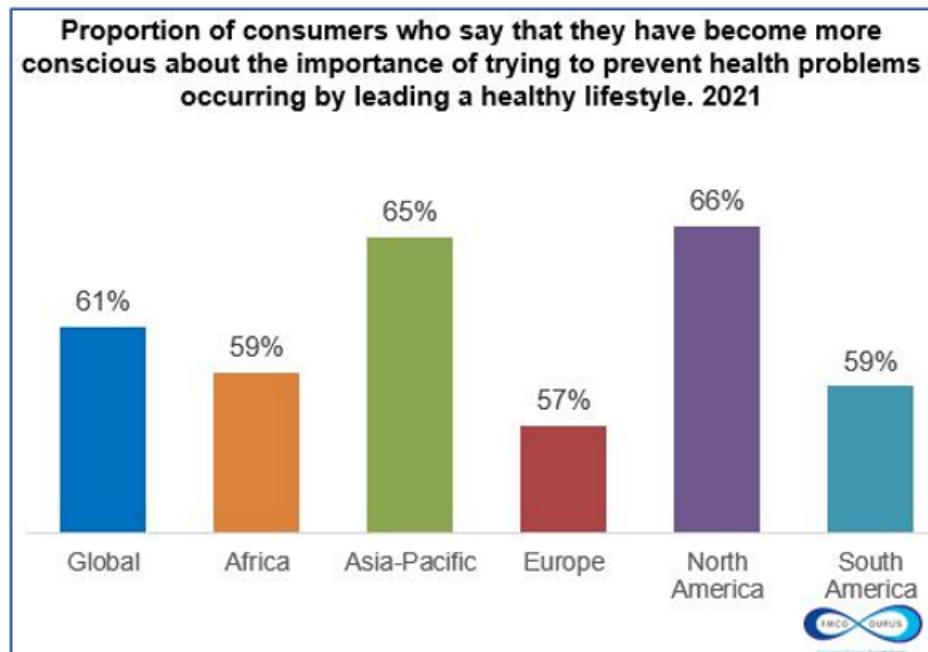
During the past 2 years, while facing the COVID-19 pandemic, consumers were looking to minimize vulnerability to disease and illness, with an increased focus on disease prevention, health, and overall well-being. Optimizing health goals,

Figure 1. Global retail value of probiotic supplements²



Source: Euromonitor International

Figure 2. Consumer perceptions of probiotic supplements³



Source: FMCG Gurus

including supporting immunity and digestive health and helping with allergies and weight management are a few areas consumers have been researching on-line. **Figure 2** shows the proportion of consumers reporting that they have become more conscious about the relationship between a healthy lifestyle and preventing health issues. Another 2021 report, evaluating opportunities for probiotics in a postpandemic society, outlined how consumers seeking probiotics for prevention far outweighed interest in treating illness.³

The ever-increasing e-commerce markets cannot be ignored when discussing market and consumer demand for probiotics. Higher demand, coupled with the more free-flowing virtual commerce space, bring a sense of urgency to the regulatory environment. Probiotic regulations are reasonably aligned within the non-e-commerce space, but when discussing e-commerce, regulatory oversight is evident. The EU is a good example of this. No probiotic claims are allowed on the food supplements on store shelves, but more than US\$120 million of probiotic products still enter the EU via e-commerce platforms, and a majority of these products have claims on the package (**Figure 3**).⁴

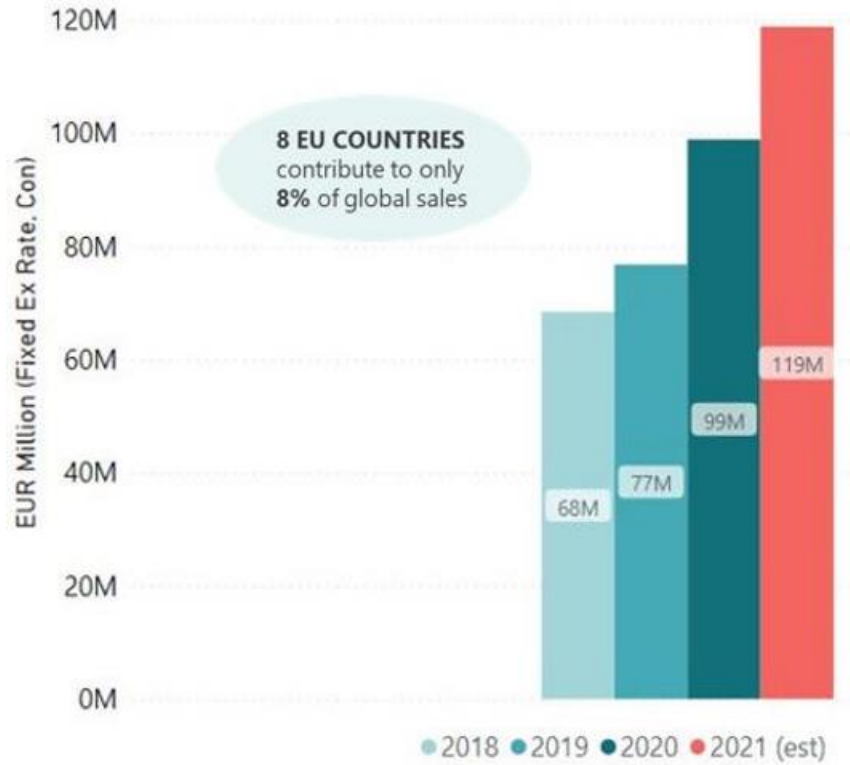
It is important to also outline the largest global dietary supplement markets. The US leads, the way followed by China and Italy (**Figure 4**). At its current 11% year-on-year growth rates, China will be making significant gains as a global player. APAC as a region continues to grow across all probiotic segments and represents more than 55% of the global probiotic category.²

What about the science?

Probiotics have become one of the most researched supplements both by scientists and by online consumers. Probiotics are recognized as having strong

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Figure 3. e-Commerce market size for probiotic supplements⁴



Source: Lumina Intelligence

Figure 4. Global market size of probiotic supplements²

Probiotic Supplements

Market Size ▾

Retail Value RSP, USD million, Current 2020, YOY 2020 Ex. Rates, 2020

\$ £ € ¥ CHF

Global Figure
2021 USD mil
\$6,970



Regional Comparison

2021, USD million



EUROMONITOR INTERNATIONAL

Source: Euromonitor International, for IPA

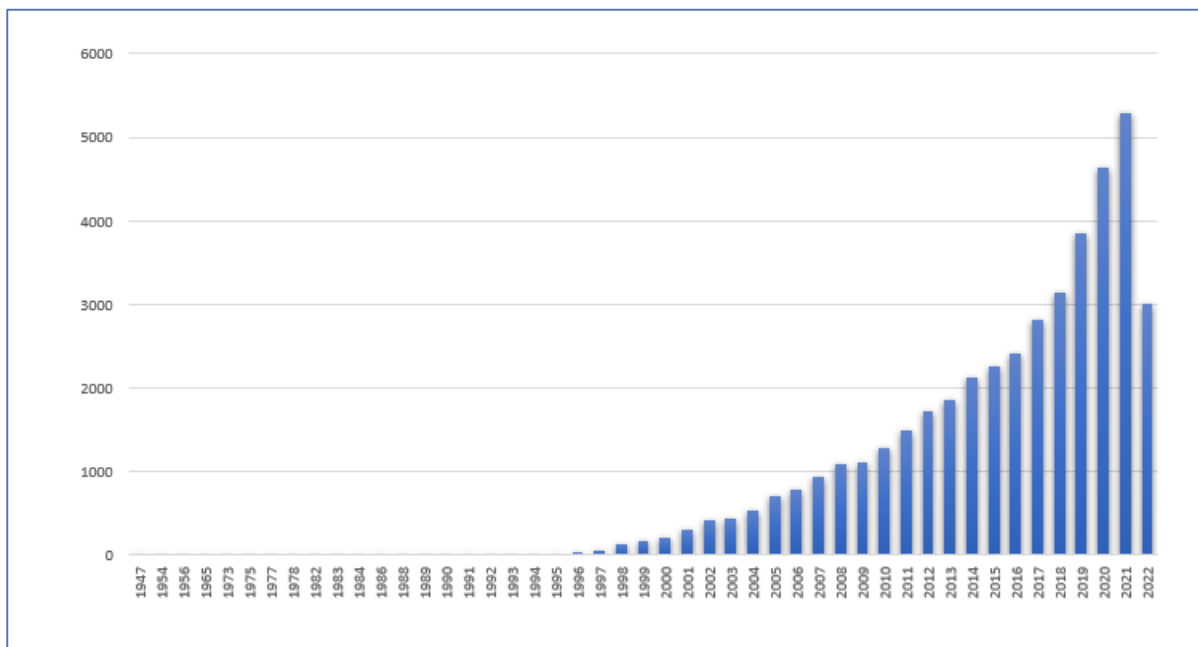
supporting evidence amongst the large amount of ingredient supplements available to consumers.⁵ Furthermore, an online PubMed search reveals over 38,000 publications as of July 2022 (**Figure 5**). There is a significant amount of scientific research into the crucial role of probiotics and their beneficial effects on a variety of indications. In addition to classic indications, such as gastrointestinal and immune health, other areas addressed include the gut-brain axis, metabolic syndrome, rheumatoid arthritis, inflammatory bowel disease, and atopic dermatitis. Dronkers and colleagues have reported more than 1,600 human clinical trials from two databases they reviewed and are now analyzing more than 700 indications noted from those clinical trials.⁶

Systematic reviews combine results looking at all studies performed for a certain indication. These can be useful tools, giving overviews of the amount of research performed in a given area (**Table**).

The amount of research is widespread in many areas of human health. The meta-analyses, reviews, and published articles highlight new targets in emerging areas of health that may be supported with probiotics in addition to the core historical applications. Zommitti et al published a detailed overview of select probiotic clinical studies and their specific effects on human health.¹⁷

The published science for probiotic applications is abundant. Nonetheless, probiotics used in the researched applications have to meet minimum criteria before a micro-organism can be deemed probiotic. IPA¹⁸ and IPA EU¹⁹ have published comprehensive papers on the topic. Moreover, when using probiotics for specific conditions in humans, the products must have sufficient study with

Figure 5. Results of PubMed search for ‘probiotics,’ July 2022



Source: International Probiotics Association

Table. Synopsis of selected reviews of probiotics in specific fields

First author name	Review description
<i>GI-related</i>	
McFarland et al. ⁷	Strain-specific outcomes for IBS
Ford et al. ⁸	Systematic review for IBS
Kaminski et al. ⁹	Systematic review of probiotics and usefulness in chronic constipation
Goodman et al. ¹⁰	Systematic review for the prevention of AAD
<i>Immune support</i>	
Rashidi et al. ¹¹	Systematic review of probiotics on incidence of URTIs
Miller et al. ¹²	Systematic review on immune function in healthy elders
Farahmandi et al. ¹³	20-year review of probiotic meta-analysis on disease prevention
<i>Skin disorders</i>	
Navarro-Lopez et al. ¹⁴	Probiotics in the therapeutic arsenal of dermatologists
<i>Microbiome gut-brain axis</i>	
Zagorska et al. ¹⁵	Systematic review from probiotics to psychobiotics – the gut-brain axis in psychiatric disorders
<i>Metabolic syndrome</i>	
Dong et al. ¹⁶	Systematic review of probiotic foods and supplements interventions for metabolic syndromes

AAD, antibiotic-associated diarrhea; GI, gastrointestinal; IBS, irritable bowel syndrome; URTI, upper respiratory tract infection

the specific strain and are required to be sufficiently researched for their intended use, as outlined by Sanders and colleagues.²⁰

Global policy on probiotics

The FAO-WHO collaboration

In view of the growing popularity of probiotics and the lack of international consensus on the methodology to assess their efficacy and safety, the FAO and WHO began collaborating about 20 years ago to examine the scientific evidence on the functional and safety aspects of probiotics in food. In 2001, the two organizations convened an expert consultation on the health and nutritional properties of powder milk with live lactic acid bacteria in Cordoba, Argentina, and an expert working group was established in 2002 to develop guidelines for the evaluation of probiotics in food.¹

The FAO-WHO expert consultation evaluated available information on the functional and safety aspects of probiotics in powdered milks and examined the products' dietary impact, properties, benefits, safety, nutritional features, adverse effects, and health claims, among other attributes. In addition, it identified priorities for evaluation of safety and nutritional aspects.

The FAO-WHO working group followed up with a proposed methodology to evaluate probiotics and defined criteria for health claims for probiotics. As a

result of their joint work, the FAO-WHO recommended adoption of the current widely used definition for probiotics: “Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host.” However, despite the outstanding work by FAO-WHO with expert recommendations, considerable work is still needed to reach global harmonization of probiotic regulations.

Codex Alimentarius

The Codex Alimentarius standards and guidelines are the international reference point for food regulations and therefore, have the potential to help in the global harmonization of probiotic standards and regulations. There are Codex commodities standards for food categories, including probiotics, in areas such as fermented milk, food supplements, infant formula, and follow-up formula products. In addition, there are horizontal standards and guidelines for food hygiene, food additives, contaminants, labelling, and nutrition and health claims, that apply to food and dietary supplements in general. However, there are no specific provisions for probiotics. It is in this context that a proposal was presented for Codex guidelines for probiotics for use as an ingredient in foods and food supplements. Codex standards are not obligatory but are used by many national authorities as a starting point to build regulations within their own countries. In the spirit of harmonizing the definition for probiotics, the minimum requirements for their use, as well as specific labelling provisions for probiotics, the IPA proposed the Codex Guidelines for Probiotics initiative in 2017.²¹

The proposal was submitted to the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU). A decision on whether to begin developing Codex guidelines for probiotics is expected at the next CCNFSDU meeting in March 2023. Due to a very heavy workload, this committee is required to prioritize its work against specific criteria. These criteria are based on demonstrating impact on public health, food safety, and fair-trade practices, among other considerations. If the committee agrees to prioritize the new work proposal on probiotics, the proposal will be reviewed and the process of exchange and discussion toward harmonization will begin.

Probiotics in foods and dietary supplements

At the national level, we see divergent regulatory approaches for probiotics on aspects such as product classification, definition, permitted probiotic microorganisms, conditions of use and labelling requirements, use of health claims and substantiation requirements, and classification as market access administrative requirements. The same probiotic product can be regulated as a food in one market, a supplement in another, and may require drug type registration in yet another. This makes for an assortment of regulations that oblige industry to navigate regulatory differences to commercialize finished probiotic products globally.

Product classification. In most countries, foods and dietary supplements with probiotics are classified under food law. These may also fall under certain categories that have their own specific regulations. Examples of these include,

“Foods with probiotics” (Argentina), “Food products with additions” (Saudi Arabia, Mexico, Morocco), “Foods with function claims” (Japan), “Health functional food” (South Korea), or “Dietary supplements” (US and/or Canada) to name a few.

However, there are some cases in which products containing probiotics are categorized as drugs. This may be because of the form in which they are presented, the microorganisms used, the health claims used or, in some cases, where dietary supplements are regulated under drug law (South Africa and/or Australia).

Definition. Despite the existing FAO-WHO definition on probiotics, most countries have not yet adopted a legal definition at national or regional levels. Some countries have adopted either broad definitions, referring to probiotics that confer health benefits based on the FAO-WHO definition, or literally, the FAO-WHO definition in their national regulations. Examples of this can be found in China, Indonesia, Malaysia, Philippines, Singapore, Thailand, Saudi Arabia, Argentina, Brazil, and Canada.

Similarly, there are some countries that have adopted a definition of probiotics focused on digestive health. Examples of such countries include Italy, referring to the balance of intestinal flora, or Colombia, with a reference to microbial balance. It is also worth highlighting that in several countries, probiotics are included as an ingredient, and are part of the definition of certain food categories and/or dietary supplements.

Permitted probiotic microorganisms. The regulatory approaches taken to permit probiotic microorganisms in foods and dietary supplement will vary from country to country. Some countries, mainly from Asia, have adopted positive lists of probiotic microorganisms that are allowed to be added to foods and dietary supplements. These countries would include China, India, Philippines, South Korea, Taiwan, and Thailand. Others, such as Malaysia, have adopted positive lists only applicable to foods. In yet other countries, dietary supplement regulations include positive lists of permitted probiotic microorganisms in dietary supplements, such as Brazil and South Africa.

Conversely, other types of lists include probiotic species/strains rather than an exhaustive positive list to be used by regulatory authorities. An example of this is the qualified presumption of safety (QPS) list in the EU.²² This list includes microorganisms that have been assessed by the European Food Safety Authority (EFSA) as not raising any safety concerns. Probiotic microorganisms included therein are therefore regarded as safe by regulatory authorities in the EU.

Although the QPS system was developed within EFSA joint working committees and scientific experts, it is important to discuss the generally recognized as safe (GRAS) guidelines for food additives in the US. These guidelines were developed by the US Food and Drug Administration (FDA) as an amendment in 1958 to the Food, Drug, and Cosmetic Act of 1938 responding to concerns of safety of new

food additives.²³ QPS and GRAS are often considered as being synonymous, but there are distinctions between them, for example:

- GRAS applies to specific applications for food additives that would be granted for specific strains, whereas the QPS list does not define specific uses and is instead applicable to the species level of the organisms.²⁴
- Another example of the distinction between GRAS and QPS is the informative list of probiotic strains that have been included in the Mexican Yogurt Denomination Regulation, now under review.²⁵ The proposal is to transfer this list from the Yogurt Denomination Regulation to Fermented Milks Regulation.

Finally, in some countries, the approach taken is a case-by-case evaluation, independent of QPS or GRAS. Some countries, such as Norway,²⁶ develop comprehensive protocols with established minimum characterization and safety requirements for the evaluation of market entry.

Labelling requirements and conditions of use. National regulations require a minimum number of viable cells present in products, to be able to declare that it contains probiotics or to use a health claim. The minimum requirements vary between 10⁶ and 10⁹ colony forming units (CFU) per g or ml. Different CFU minimum requirements may apply between product categories. This provides consumers with relevant information on the amount of the effective ingredient available in a probiotic food and or supplement.

A CFU is a bacterium that is capable of living and reproducing to form a group of the same bacteria, a colony. Providing the quantity of probiotic ingredients in a food or dietary supplement in terms of the number of CFUs that are in the product throughout the shelf life is an informative measurement for consumers and ensures that the information on the product label is truthful and not misleading. Scientific studies with probiotics are measured in CFUs. Therefore, declaring the quantity of probiotic ingredients in CFUs will enable consumers and health care professionals to select products based on the scientific literature. CFUs are consistent with international standards.

- A number of government agencies have published guidelines on probiotics that specifically recommend how probiotic microorganisms should be reported on labels and quantified; all favor CFUs. For example, in Canada, species identification, strain characterization, and quantification in CFUs is required.²⁷ The Canadian probiotic monograph lists a minimum effective dose level of 10⁷ CFUs of probiotics per day.²⁸ Health Canada's Food directorate clearly indicates that the level of the probiotic strain expressed should be in CFUs in the stated serving size of the food.²⁹
- Italy's Ministry of Health has published a probiotic guideline document. It provides the portion of the product recommended for daily consumption must contain the amount of 10⁹ live cells for at least one strain among those present in the product.³⁰

- In the US, GRAS notifications for live microorganisms used in foods outline the amounts of the ingredients in terms of CFUs, and all accounts of safety are referenced as CFUs within the GRAS dossiers.³¹
- Also in the US, 21 CFR 190.6(b), requires that new dietary ingredient (NDI) notifications include “the level of the new dietary ingredient in the dietary supplement.” There have been several NDI notifications submitted to FDA (and filed without comment) for probiotic ingredients in which the level of the dietary ingredient was expressed only in CFUs.³²

In summary, declaring the quantitative amount of probiotics in CFUs correlates with international standards, scientific data, clinical studies, and viability. Furthermore, listing of CFUs optimizes understanding for health care professionals, and provides transparency and clarity for consumers to make an informed choice.

When looking at the applicable labelling requirements to foods and dietary supplements with probiotics, it is important to observe the applicable: general labelling regulations; specific categories’ labelling provisions; and any additional specific labelling requirements for probiotics, such as the specification of the genus, species, or strain of the probiotic or quantity of viable cells. In this context, it is important to consider that although the term “probiotic” is recognized globally, different approaches are in place regarding the use of the term, particularly in the EU.

The European Commission established restrictive interpretation regarding use of the term probiotics, considering them as health claims not yet approved in the EU.³³ At present there is one claim approved in the EU linking live microorganisms and lactose digestion – “Live cultures of yogurt improve lactose digestion.”³⁴ Many EU member states follow the interpretation of the European Commission. However, Italy and the Czech Republic have permitted use of the term “probiotic.” More recently, other EU member states have formally published a position at national level also permitting the use of this term on products’ labels. These include Spain, by applying the EU principle on mutual recognition; Denmark, by allowing it only in food supplements and requesting the European Commission to clarify its views; The Netherlands, by allowing such use even though there is published statement by the European Commission. Other EU member states allowing use of the term without a formal position are Bulgaria, Greece, Malta, and Poland (see **Additional Reading**, p. 14).

Claims – Permitted use and substantiation requirements. There are some general trends regarding the use of nutrition and health claims for foods and dietary supplements with probiotics. For example, the expansion in use of premarket approval of nutrition and health claims to be used in foods and dietary supplements. Countries are increasingly adopting positive lists of permitted or pre-approved nutrition and health claims in foods and dietary supplements (such as the QPS in Europe), although many still do case-by-case evaluation.

Codex guidelines for use of nutrition and health claims³⁵ recommend governments consider the totality of available, relevant scientific data. However, there are different approaches on the acceptability of the use of health claims, with diverse scientific substantiation requirements and evaluation. Some countries continue to restrict the use of health claims for certain product categories, such as dietary supplements.

Regarding specific trends for probiotics, we can find many foods and dietary supplements with probiotics in the market using generic health claims and/or qualified or specific claims for probiotics. Most of those claims are related to digestive health, balance of intestinal flora, lactose absorption, immune system support, and allergy applications. It is key to look at the actual accepted wording, the conditions of use of the authorized claim, whether different claims are authorized for foods and/or dietary supplements, and other potential conditions or restrictions.

Market access. A variety of administrative procedures are in place globally for probiotics to gain market access. Some countries demand that foods and dietary supplements are authorized before they reach the market. Others require such premarket approval only for dietary supplements. There are those that only require notification of the food and/or dietary supplements at the time of the commercialization of the finished probiotic product, and in others, there are no specific requirements or administrative procedures for probiotics specifically other than applying to the procedures in place for foods and or dietary supplements in general. However, it is worth highlighting that, in some cases, additional information may be required about the probiotic microorganisms contained in the product.

Commercializing probiotics in different countries requires strong knowledge of the local policies and guidelines needed for each of these different markets. The IPA commissioned a global overview report on probiotic regulations that provides a regulatory overview and relevant information currently from 36 regions and countries worldwide.³⁶ As regulatory environments are dynamic and can change, so will this document. IPA's intention is to review and continuously update this manuscript annually. The report does not include a compliance check of specific product formulations or labels.

Conclusion

When it comes to probiotics and their benefits, the science is conclusive. From the thousands of published articles and papers and the human clinical outcomes, applications are abundantly clear that a preventive approach to support health using probiotic foods and dietary supplements are recommended.

The use of probiotics as an ingredient in foods and dietary supplements is well recognized in different regions worldwide. However, regulatory divergences persist. Some countries have adopted a definition of probiotics in their national regulations, with some differences in their approach. Most are based on the FAO-WHO definition. Yet there are important differences regarding the

authorization of probiotic strains in foods and supplements and the conditions of use. Foods and dietary supplements with probiotics must comply with extensive and diverse labelling requirements, conditions on the use of claims, and the applicable administrative procedures.

In the current context, with the growth of the probiotics market through internet sales across borders and the vast proliferation of products with probiotics being commercialized the message is clear: There needs to be international harmonization of regulations for the use of probiotics as an ingredient in foods and dietary supplements. This will ensure access to safe, beneficial, and high-quality probiotic foods and dietary supplements for consumers. Considering the relevance of such an initiative, the development of the Codex guidelines for probiotics would serve such purpose.

Companies still require keeping current with the evolving regulatory environment to develop successful marketing strategies and identify upcoming business opportunities. Hence, the IPA global regulatory manuscript on probiotics, providing members with up-to-date information on the rules and regulations, is an essential tool more than ever as companies seek to commercialize probiotic products and convert the challenges into opportunities.

Acronyms and abbreviations

CFU, colony forming units; **EFSA**, European Food Safety Authority; **EU**, European Union; **FAO**, [UN] Food and Agriculture Organization; **FDA**, [US] Food and Drug Administration; **GRAS**, generally recognized as safe; **IPA**, International Probiotics Association; **ISAAP**, International Scientific Association of Probiotics and Prebiotics; **NDI**, new dietary ingredient; **QPS**, qualified presumption of safety; **WHO**, World Health Organization; **UN**, United Nations; **US**, United States.

About the author

George Paraskevagos, MBA, is executive director of the International Probiotics Association whose mission it is to promote the safe and efficacious use of probiotics globally. He has been involved in the probiotics industry since 2007. During that time, he has grown the association from 40 to more than 100 member companies worldwide; hosted numerous international probiotics conferences; published extensively on probiotics; and collaborated with fellow probiotics associations to advance knowledge on probiotics effectiveness and safety. Paraskevagos represents the IPA in the media and all probiotic stakeholders, including government agencies, at the Codex Alimentarius. He also serves on the advisory council for the Southwest College of Naturopathic Medicine & Health Sciences in Tempe, Arizona. Paraskevagos can be contacted at george@internationalprobiotics.org

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Additional reading

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