The Unregulated Probiotic Market

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BACKGROUND & AIMS: **This narrative review provides an overview of the current regulation of probiotics, with a focus on those used for the dietary management of medical conditions (Medical Foods).**

FINDINGS: **The probiotic market has grown rapidly, both for foods and supplements intended to enhance wellness in healthy individuals, and for preparations for the dietary management of disease. Regulation of probiotics varies between regions. Unless they make specific disease-related health claims, probiotics are regulated as food supplements and regulation is focused on the legitimacy of any claims, rather than efficacy, safety and quality. Many properties of probiotics are strain-specific, and safety and efficacy findings associated to specific formulations should not be generalized to other probiotic products. Manufacturing processes, conditions and ingredients are important determinants of product characteristics and changes to manufacturing are likely to give rise to a product not identical to the "original" in efficacy and safety if proper measures and controls are not taken. Current trademark law and the lack of stringent regulation of probiotic manufacturing mean that the trademark owner can commercialize any formulation under the same brand, even if significantly different from the original. These regulatory deficits may have serious consequences for patients where probiotics are used as part of clinical guideline-recommended management of serious conditions such as inflammatory bowel diseases, and may make doctors liable for prescribing a formulation not previously tested for safety and efficacy.**

CONCLUSIONS: **Current regulation of probiotics is inadequate to protect consumers and doctors, especially when probiotics are aimed at the dietary management of serious conditions.**

Keywords: Probiotics; Regulation; Manufacturing; Inflammatory Bowel Disease.

The definition of probiotics as live microorganisms that when administered in adequate amounts confer a health benefit on the host was established by the Food and Agriculture Organization of the United Nations and the World Health Organization in 2001.[1] However, the label "probiotic" is often misused by being applied to products that do not meet the criteria.[2] Furthermore, even though significant progress has been achieved in understanding the possible applications and health benefits of specific probiotic strains, many doctors, scientists, and consumers are still confused by the "probiotic umbrella" concept that is commonly promoted by the probiotic industry. The umbrella concept seeks to take advantage of results obtained with a specific probiotic by extending them to others, blurring the specificity of the product, dose, duration of intake, combination of strains, and methods used to manufacture the formulation with which the benefits were obtained. Because of the relatively unregulated nature of the probiotic market, such transferal of claims from the tested product to one that has material differences in its formulation or manufacture opens the door to many problems and questions. In addition, in cases where probiotic formulations are used to help manage major conditions such as inflammatory bowel diseases or disorders characterized by immunosuppression such as human immunodeficiency virus (HIV), this lax regulation may have serious consequences for patients, as explored in the later sections of this review.

Historically, the concept of probiotics was developed in around 1900 by the Nobel laureate, Elie Metchnikoff, who discovered that the consumption of live bacteria (*Lactobacillus bulgaricus*) in yogurt or fermented milk improved some biological features of the gastrointestinal tract.[3] In 2013, the worldwide market for probiotics was worth $36 billion.[4] In addition to their use in the management of a range of health conditions,[4] probiotics are

Abbreviations used in this paper: CFU, colony-forming units; EFSA, European Food Safety Authority; FDA, Food and Drug Administration; HIV, human immunodeficiency virus.

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being aggressively promoted to consumers as a mean to increase or maintain health, fueled by media coverage. Bacteria with claimed probiotic properties are now widely available in the form of foods such as dairy products and juices, and also as capsules, drops, and powders. Contained (or claimed to be contained) within these food supplements, there can be many different strains of bacteria. The most common commercially available strains belong to the *Lactobacillus* and *Bifidobacterium* species. Well-studied probiotic species include *Bifidobacterium* (*adolescentis*, *animalis*, *bifidum*, *breve*, and *longum*) and *Lactobacillus* (*acidophilus, casei, fermentum*, *gasseri*, *johnsonii*, *reuteri*, *paracasei*, *plantarum*, *rhamnosus*, and *salivarius*). An international consensus statement in 2014 accepted that these are likely to provide general health benefits such as normalization of disturbed gut microbiota, regulation of intestinal transit, competitive exclusion of pathogens, and production of short chain fatty acids.[2]

However, the consensus panel also noted that many of the other effects that have been shown for various probiotics are species-specific and, in some medical conditions, strain-specific. Mechanisms that are likely to be species-specific include vitamin synthesis and gut barrier reinforcement, while neurological, immunologic and biochemical effects are likely to be dose- and strain-specific.[2] The consensus panel stressed that claims for a number of such "medical" benefits can only be made for the strains in which they have been demonstrated. Further, they noted that although a single strain may display multiple mechanisms of beneficial action, no single strain would be expected to have all the effects known to derive from probiotics.[2]

There is a large body of preclinical and clinical research on the gastrointestinal benefits of probiotics in healthy individuals and in a wide range of both minor and serious health conditions. These include treatment and prevention of acute diarrhea, prevention of antibiotic-associated diarrhea, treatment of hepatic encephalopathy, symptomatic relief in irritable bowel syndrome, and prevention of necrotizing enterocolitis in preterm infants.[4] Specific probiotics have gained a place in the treatment of ulcerative colitis and pouchitis and are recommended as options in several major clinical guidelines (Figure 1).[4–6]

Safety of Probiotics

Commercially available probiotic products can be divided into monostrain (defined as containing 1 strain of a well-defined microbial species) and multistrain (containing more than 1 strain of the same species or genus). The term multispecies is also used for products that contain strains from more than 1 genus.[7] Treatment with probiotics may involve the consumption of large quantities of bacteria, so safety is a primary concern. There are 2 aspects to safety: establishing the adverse effect profile of specific monostrain and multistrain preparations (ie, the safety of the products per se), and ensuring that marketed preparations meet stringent quality standards to make certain that the correct strains are present and that the product is free of contamination.[8]

The principal theoretical risks from probiotics are infection, ill effects from toxins produced either by the

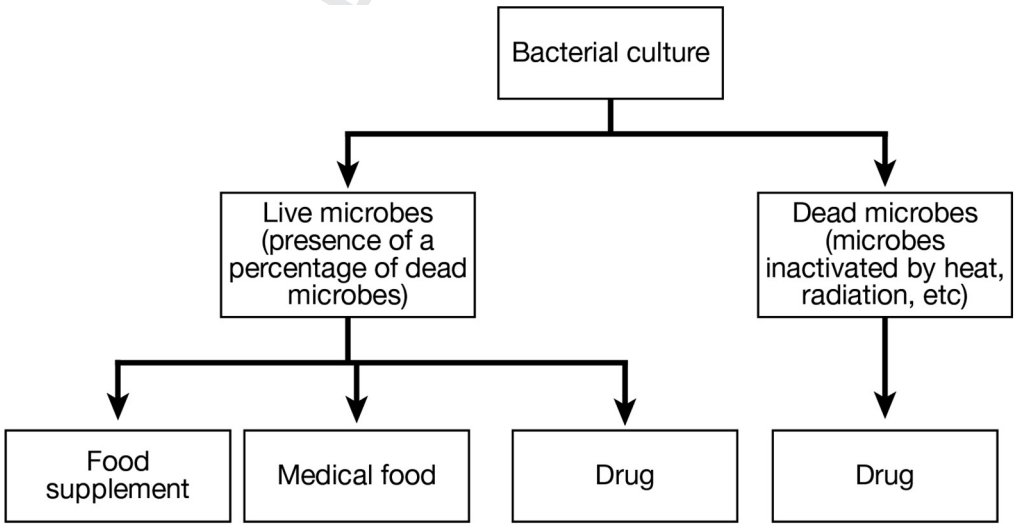

Figure 1. Bacterial culture can be inactivated by different means (ie, by heat or radiation) to produce formulations containing bacterial lysates, which cannot be defined as probiotic and are regulated as drugs. Bacterial cultures containing live bacteria, but also a certain percentage of dead bacteria (live bacteria cannot be separated from the dead bacteria, the amount of dead bacteria in the preparation being inversely proportional to the quality of the product) can be utilized as: (1) food supplement: species or combinations of species, supported by evidence of general beneficial effects; (2) medical food: strains or combination of strains supported for the dietary management of a disease that has distinctive nutritional needs that cannot be met by normal diet alone (needs to be supported by high quality clinical trials and positive meta-analysis); or (3) drug: strains or combination of strains with specific indications regulated as drugs.

probiotic strains or contaminants, and immunological effects.[9] Safety assessments should take into account the nature of the probiotic microbe, method of administration, level of exposure, health status of the recipients, and the physiological functions the microbes are intended to perform.[9] However, most probiotics in commercial use are derived from fermented foods with a long history of safe consumption, or from microbes that may colonize healthy humans.[4] All common probiotic species are considered safe for the general population by the European Food Safety Authority (EFSA),[10] although this definition does not provide guidance on the increasing use of probiotics in people with medical conditions, and the term *probiotic* is not easily accepted by EFSA even though tolerated by health authorities in some countries such as Italy. The U.S. Food and Drug Administration (FDA) classifies probiotics individually but has classified many as safe for food use.[11]

The great majority of clinical trials of probiotics reported in the literature have not given rise to major safety concerns[9]; however, a few examples of serious adverse effects from probiotics have been documented independently of the formulation, dosage, and daily intake. Those that have been reported include cases of bacterial sepsis linked to probiotic supplements containing lactobacilli, and the death from gastrointestinal mucormycosis of a preterm infant associated with mold contamination of a probiotic supplement.[8,12] In patients with predicted severe acute pancreatitis, treatment with a multispecies probiotic preparation was associated with an increased risk of mortality.[13] Therefore, careful safety evaluation is required before use of probiotics in vulnerable groups,[8,9] including patients with damaged intestinal mucosa or immune dysregulation such as can occur in patients with inflammatory bowel diseases, liver diseases, HIV, and other conditions. Safety becomes a more sensitive issue with the small number of products that contain high concentrations of up to 450 - 900 billion bacteria per dose. (Note: this review does not include a discussion of adverse effects associated with the yeast *Saccharomyces boulardii*, a natural yeast originally extracted from the lychee fruit and present in some probiotic formulations. *S. boulardii* has been reported to be associated with fungemia in critically ill patients as well as in immunocompromised individuals.[14,15] An analysis of the side effects versus the benefits of this biotherapy is beyond the scope of this article mainly focused on lactobacilli and bifidobacteria).

A systematic literature review of probiotic safety published in 2014 found that "the overwhelming existing evidence suggests that probiotics are safe" for the general population, and that critically ill patients, postoperative and hospitalized patients and immunocompromised patients were the most at-risk groups where adverse effects did occur. The authors recommended consideration of the risk-benefit ratio before prescribing probiotics.[16] A recent pilot study in persons with HIV infection and treated with combined antiretroviral therapy found that the probiotic employed was safe and was associated with a number of immune-related benefits and improved integrity of the gut epithelial barrier. However, the authors stressed that the safety and efficacy findings associated with that specific probiotic formulation should not be generalized to other probiotic products.[17]

Quality Control of Probiotics Intended to Have a Medical Impact

The definition of probiotics is acceptable when the probiotic products are intended to improve an otherwise normal diet in the healthy population, but is inadequate when the probiotics are recommended as part of the dietary management of specific clinical situations such as pouchitis, ulcerative colitis, hepatic encephalopathy, etc. To ensure that a commercial product will deliver the claimed beneficial health effects to patients with serious disorders, among the prerequisite elements, there should be proper labeling information about the presence of live bacteria at a specific concentration, but also about the number of dead bacteria. Gut-derived bacterial translocation is not an infrequent occurrence, and bacterial DNA constitutes a disrupting factor that imbalances individuals' inflammatory responses by triggering a Th1-biased proinflammatory response through Toll-like receptor-9 and nuclear factor kappa-B activation. As a matter of fact, it has been reported that bacterial DNA translocation into blood of patients with Crohn's disease in remission increases the risk for relapse at 6 months and is an independent risk for hospitalization and initiation of steroid treatment.[18] Most probiotic products are generally used in healthy individuals and contain only a few billion bacteria. In this typical scenario, the number of dead bacteria in a given probiotic product is of negligible value when evaluating product safety. However, with probiotic products containing hundreds of billions of bacteria, the issue of the number of dead bacteria is a totally different, and of particular concern when the products are administered to diseased individuals. During the manufacturing process, dead bacteria and their fragments cannot be separated and removed from the live bacteria; consequently, the final product will contain not only live but also dead bacteria as well as a number of microbe-associated molecules and fragments. Only the number of live bacteria able to form colonies when cultivated to be counted on agar plates, expressed as colony-forming units (CFU) is reported on the label of the products. Therefore, doctors are not informed about this "hidden content" and the "real potency" of the product they are administering to the patients. In subjects with dysreactive immune disorders, even live or dead, entire or fragmented, "good" bacteria can be harmful if present at numbers high enough to impact on the balance between anti- and proinflammatory cytokines as well as other cell functions.[19–21]

The precise identity of the bacteria at the strain level is also a fundamental requirement. Initially the taxonomy of lactobacilli and bifidobacteria was defined according to their morphological and biochemical characteristics, but it has been under extensive revision thanks to modern genomic techniques. However, the genetic reclassification of the strains, usually reported as a footnote on the product's label, generates confusion among doctors and patients, who are uncertain if the new reclassified product offers the same benefits of the old one. Taking advantage of such a taxonomical confusion, some manufacturers state that their strains are genetically equivalent or that they are nearly identical, but such claims do not make any sense since bacteria are either genetically identical or different. As a general rule, the strains should be deposited at a biodepository such as the ATCC (American Type Culture Collection) or DSMZ (Deutsche Sammlung von Mikroorganismen und Zellkulturen) so that microbiologists and industry can secure a backup of their own cell cultures with their inherent physiological characteristics, independently from any "modernized" reclassification. Certain strains may have in common some "isofunctional enzymes" for some biosynthetic pathways, but this does not imply that those strains are isofunctional or equivalent or that they perform the same when used in patients. Quality controls for the probiotics intended for medical use therefore should be not limited to viability, adhesive properties, acid, and bile stability, but should also include an assessment of the biochemical and immunological profile of the product, and if differences are detected, the products should undergo new testing in animals and then in humans.[21] Quality control standards of the food industry are therefore not sufficient or acceptable for probiotic products aimed at the prevention or treatment of serious gastrointestinal disorders.

Current Regulation of Probiotics

The regulatory aspects that need to be considered for probiotics are efficacy, safety, quality control of manufacturing, and regulation of the health claims that can be made for individual products. If probiotic preparations make a health claim that implies treatment, therapy, prevention, relief or diagnosis of a disease, they are classified as medical or pharmaceutical products and regulated as such. In this case, as they are live complex organisms, probiotic products will fall under the existing regulations for biologics. However, the great majority do not make disease-specific claims and are therefore classified as food supplements or dietary supplements. In some cases, when the clinical data are convincing for a certain probiotic formulation, the product can be classified as a medical food intended for the dietary management of a specific disease (ie, pouchitis). Both of these categories are regulated much less stringently than pharmaceutical products.

The regulation of probiotics differs between countries: there is no universally agreed framework. In the European Union, probiotics and food supplements are regulated under the Food Products Directive and Regulation (regulation 178/2002/EC; directive 2000/13/EU). All health claims for probiotics have to be authorized by the EFSA. The EFSA has issued a list of microbial cultures that have a Qualified Presumption of Safety,[22] meaning that they do not require safety assessments. The EFSA is also responsible for assessing health claims made for probiotic products. So far, EFSA has rejected all submitted health claims for probiotics. Thus, on the one hand there is rigorous scrutiny of product claims, but on the other hand there is little regulation of the manufacturing process and almost no postmarketing regulatory follow-up.[23]

In the United States, most probiotic products are classified as foods or dietary supplements. Dietary supplements are required to comply with Good Manufacturing Practice guidelines, but these do not extend to testing quality or efficacy.[23] As in Europe, dietary supplements cannot make disease-specific claims, but in the United States they are allowed to make structural or functional claims such as "supports healthy digestion," accompanied by an FDA-mandated disclaimer. Claims must be truthful, not misleading, and substantiated by scientific evidence.[24] There is also a category of probiotics which are formulated to be consumed or administered enterally under the supervision of a physician and which are intended for the dietary management of a specific disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. These formulations fall in the category of medical foods in the United States.[25] Medical foods are not drugs and, therefore, are not subject to any regulatory requirements that specifically apply to drugs. However, a medical food that bears a false or misleading claim would be considered misbranded under section 403(a)(1) of the Federal Food, Drug, and Cosmetic Act.[25]

For research purposes probiotics are generally viewed by U.S. regulators as drugs, meaning that human studies must be conducted within the FDA's Investigational New Drug framework—even for probiotic foods and dietary supplements that are not intended to be marketed as drugs.[26] This includes a requirement for safety studies to be performed before efficacy studies can take place, even for widely used probiotics that have a Generally Recognized as Safe designation.[26] In terms of marketing, the U.S. approach is complex and depends largely on the claims being made for the product.[24]

In both regions the current situation leaves a regulatory void which does not take into account the complex nature of probiotic products—the fact that they are living organisms and therefore dynamic and not static; the fact that their characteristics vary significantly among both species and strains; and the additional complexities that arise in multispecies or multistrain

products where the individual components may interact with one another.[27] It is increasingly recognized that the current approach to regulation is inadequate and can lead to problems of quality, safety, and claim validity in commercial probiotic products that are used in a medical context, including those used in vulnerable populations.[23]

The quality of probiotic products depends heavily on the manufacturing process. From a safety perspective, it is crucial that manufacturing and packaging are adequately controlled to prevent contamination. However, manufacturing also affects efficacy. A position paper by The European Society for Paediatric Gastroenterology Hepatology and Nutrition recently published a call for improved quality control of probiotics, noting that *"procedures such as fermentation, matrix composition, cell harvesting, spray-drying, freeze-drying and storage conditions like temperature, humidity and pH, are just several out of a wider array of manufacturing determinants that can affect microbial survival, growth, viability and ultimately the study results and/or clinical outcomes."*[23]

One example of the way that variations in manufacturing may lead to efficacy or safety changes is the issue of the number of dead bacteria present in the product at the time of consumption. Dead bacteria are inevitably present in probiotic products and originate from the manufacturing, harvesting, lyophilization, and degradation processes; these dead bacterial bodies "accompany" the live bacteria from the very initial steps of manufacturing and cannot be eliminated from the product. To maintain the advertised number of live bacteria, it is common practice to "overfill" each sachet or capsule with excess bacteria to allow for the fact that a proportion will inevitably die during storage.[22] If the bacteria produced under particular manufacturing conditions have reduced viability, a larger overfill will be needed and the user will consume a larger number of bacteria (live bacteria + dead bacteria) compared with what is reported on the label for each dose. The current regulations for labeling of probiotic products require that the consumer is informed about the number of live bacteria expressed as CFU per dose. This does not take into account the number of dead bacteria, so the information provided in terms of CFU does not properly inform the consumer about the "total number" of bacteria he or she is ingesting.

Manufacturing processes play a major role not only in the live-dead bacteria ratio of the final product at the origin and at different time periods, but also on its biochemical and immunological profile. Probiotic products manufactured at different facilities, even if containing the same number of live and dead bacteria per dose, may still be not equivalent in terms of safety and efficacy. Biagioli et al[23] recently confirmed that the metabolic variability of a multispecies probiotic preparation impacts its anti-inflammatory activities. Two samples of a probiotic mixture prescribed for the dietary treatment of inflammatory bowel disease, available in the United Kingdom, one manufactured in the United States and the second in Italy, showed divergent results when tested in mice models of colitis. The Italian product was not able to attenuate the "clinical" signs of colitis in the dextrane sulfate sodium and trinitrobenzenesulfonic acid models, while the U.S. product was protective. A metabolomic analysis of the 2 formulations allowed the identification of 2 specific patterns, with at least 3-fold enrichment in the concentrations of 4 metabolites, including 1,3-dihydroxyacetone, an intermediate in the fructose metabolism, in the Italy-made supernatant, which is able to increase the gut permeability.

Brand Name Legacy and Probiotics: Good for the Producer but not Always for the Consumer

Contrary to the situation with biosimilar biopharmaceuticals, which must undergo pharmacodynamic, pharmacokinetic, safety, and efficacy testing to verify equivalence to the original product, tests of equivalence to the original product are not strictly regulated in the event of any changes made to a probiotic product, including changes to the manufacturing process. From a scientific point of view, there is no doubt that changes to a probiotic product, for example in the manufacturing process of the strains used, require new data to verify its efficacy and safety. This is particularly important when the product is used to manage chronic illnesses or other vulnerable groups.

The matter is further complicated by the fact that, unlike drugs, probiotics generally do not have single generic names for their active ingredients, especially in the case of multistrain formulations. A probiotic mixture shown in the scientific literature to be effective in the treatment of specific diseases or conditions will be referred to by doctors, experts, and patients solely by its trademarked name, because it is not eligible for a standard generic name as given to pharmaceuticals, and referring to the full list of ingredients is not practical. This can create a unique scenario in which the lack of a generic nomenclature, and the inherent difficulty in mentioning each strain in the formulation, makes the commercial name the only way to recognize a specific formulation for its origin, efficacy and safety. From a scientific and ethical point of view, the safety and efficacy data should only apply to that trademark as long as the composition and manufacturing of the product commercialized under such trademark remains unaltered from the version used in the studies.

However, the lack of regulation in the probiotic market means that there is no control over the composition or manufacturing of products marketed under a trademarked brand name, while there is a strong protection by the law of the rights associated to a trademark

ownership. The trademark terms approved by the U.S. Patent and Trademark Office do not require the trademark to be associated with a probiotic (even baby food could be labeled under the same trademark), and in theory 2, 3, or more probiotic formulations with different characteristics could be commercialized under the same brand at the same time. This offers the possibility that any probiotic, even untested, can be sold under a trademark that was used in the past to refer to a formulation well known for origin, efficacy, and safety. This state of affairs is surprising, and is in marked contrast to the regulations that exist even for foods and drinks, such as cheese, wine, or spring water. Consumers would be less likely to buy a wine if they learned that it claimed to be from a specific region such as Champagne or Napa Valley, but in actuality was not, as they think that a wine, cheese, or water's region of origin is fundamental in determining its quality. In the case of probiotics, as well as being fundamentally misleading, this situation could have serious consequences for vulnerable patients in cases where the probiotic is being used for the management of a serious disease. It is important that medical professionals and patients are fully informed about any changes to a product, so that they can make informed decisions when choosing treatments, but this unfortunately does not always occur.

Real World Consequences

It is therefore of fundamental importance that the probiotic product sold under a certain brand name maintains its uniformity during the entire marketing period, especially if it is used or recommended for populations with compromised medical history, based on previously published data and studies. This is even more true for multistrain preparations where not only the physiological properties of the single strain but also the biochemical and immunological characteristics of the final blended formulation should be maintained. This means that whoever markets a probiotic product with a certain trademark should be able to control the full know-how required to ensure the product's uniformity during the shelf-life to assure that it continues to provide the effects reported in scientific literature and related claims, independently from the evolution in the industry's processes over time.

The focus of the industry on the strain genetics is not enough to certify the consistency of the product over time, as also carrier matrices, such as proteins, carbohydrates, and lipids have an impact on the probiotic efficacy and viability. Insufficient attention to the probiotic-matrix relationship will lead to the production of lots which are not consistent with what previously manufactured and clinically tested (Figure 2*A* and *B*). But what are the consequences if the owner of the brand no longer has access to the "original" probiotic formulation and does not possess or have access to the know-how? And what will happen if the possessor of the know-how does not have access to the trademark that was previously associated to the "original formulation" and is also prevented from referring to the scientific studies by the owner of the trademark?

In the first case, a number of checks mandatory for biosimilar drugs should be taken into due account. According to the FDA, *"Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer. This is because a manufacturer who modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established controls and acceptance parameters. In contrast, the manufacturer of a proposed product will likely have a different manufacturing process (e.g., different cell line, raw materials, equipment, processes, process controls, and acceptance criteria) from that of the reference product and no direct knowledge of the manufacturing process for the reference product. ... Therefore, in general, more data and information will be needed to establish biosimilarity than would be needed to establish that a manufacturer's post-manufacturing change product is comparable to the pre-manufacturing change product."*[27]

These considerations should apply to the manufacturing of a probiotic, for example when its production is moved to a different and unrelated manufacturing site. If in vitro and animal studies show differences between the new and original formulations, then clinical studies should be mandatory, but this requires time and money. For the players in the probiotic arena there could be the temptation to exploit the goodwill of the trademark, ignoring all the previously mentioned aspects, which are important for ascertaining safety and efficacy of the product. Trademarks have an enormous impact on the consumer's choice, and once familiarized with a product, consumers will skip reading the list of ingredients usually reported in small print on the packaging, focusing on the large-printed trademark. The matter is further complicated if the formulation is mentioned in clinical guidelines under the previous trademark, since doctors relying on the trademark will end up prescribing a product untested for efficacy and safety. In the case of adverse effects or lack of efficacy, the liability could be on the doctor who did not pay attention to the list of ingredients and source of manufacturing of the product they prescribed.

Conversely, the holder of the "source" or owner of the know-how who does not have access to the trademark previously associated to the original formulation, has to struggle with how to properly define that specific formulation without interfering with the previously utilized trademark, and in the absence of a generic descriptor. The holder of the source could also be limited

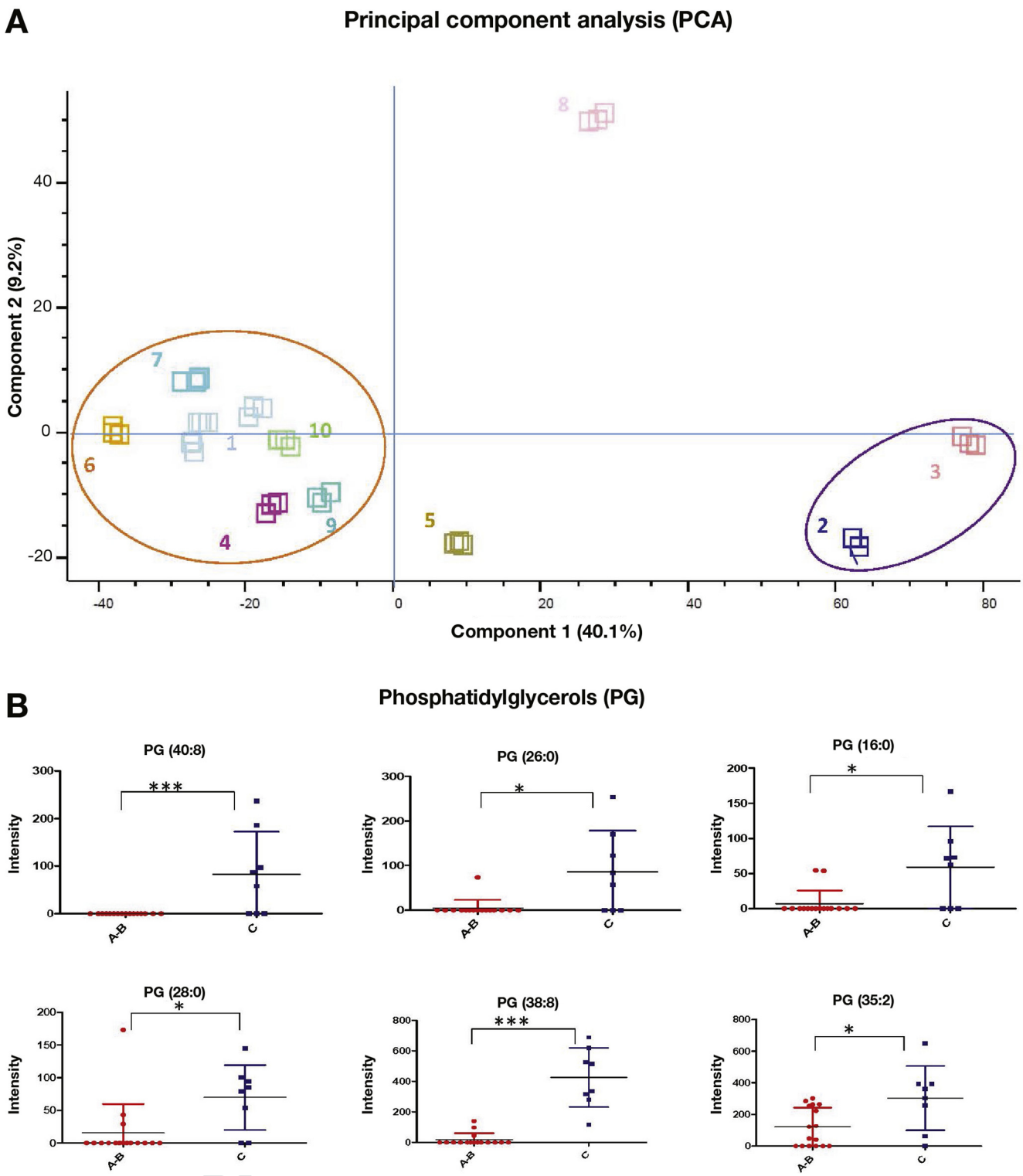

Figure 2. (*A*) Quality control of a multistrain probiotic. Proteomic analysis reveals that a number of functional group of proteins varied significantly between the U.S. product (including the expired product) and the Italian product. Lots 4, 7, 1, 10 have an expiry date in 2017 and 2018 (all U.S. made); Lots 6, 9, 5 expired in 2016, 2015, and 2014 (all U.S. made). Lots 3, 2, 8 have an expiry date of 2018 (all Italy made). The Italy-made product shows an interlot variability (Lots 3 and 2 vs Lot 8) and is always different from the U.S.-made product, independently from the expiration date. Courtesy of B. Mattei and V. Correani. (*B*) Quality control of a multistrain probiotic. The diversity in phosphatidylglycerols (PG) content may be another means of revealing differences of the same probiotic product manufactured at 2 different sites. In this case, the U.S.-made product (C) clearly shows higher levels of PG compared with the Italy-made product (A-B) (unpublished data, P. Del Boccio).

in its capability to refer to the previous studies carried out with the probiotic formulation.

Conclusions

No regulatory problems arise for probiotics that are true drugs and are therefore governed by well-consolidated regulations. However, the same cannot be said for probiotics that, although not classifiable as drugs, benefit human health and are sometimes valuable tools for the dietary management of serious pathologies such as inflammatory bowel diseases, hepatic encephalopathy and in the future, if confirmed, HIV. If there are published scientific data on a specific probiotic formulation, regardless of the name the product is referred to by, physicians must be able to clearly identity these data so that they can make the best medical judgments in the interest of their patients. Equally, patients should not be deprived of their right to continue on the tested product if this is available under a different brand, or to make an informed decision to try to the "new" formulation of the brand if they wish to.[28]

In the absence of specific and stringent regulations for probiotics, there is no appropriate protection for the interests of producers whose objectives are to identify, study and market new probiotic products benefiting human health, or for the interests of the end users, who may be misled by product labeling or trademarks and deprived of information on the true nature of the product they are using. More strict regulations specifically addressing medically beneficial probiotics that are not classifiable as drugs would be welcome.

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Conflicts of interest
The author discloses the following: Claudio de Simone owns one share of VSL Pharmaceuticals Inc, and served in the past as Director and/or Officer of VSL Inc, Actial Farmaceutics Ltda, CD Investments Srl, CD Pharma India. He is the inventor of a high concentration multistrain probiotic formulation.