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COMMENTARY

Probiotic use in at-risk populations

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ABSTRACT

Objective: To inform health care providers about quality standards for manufacture of probiotic products being recommended for at-risk patient populations.

Summary: Probiotics are used in a variety of clinical settings, sometimes in at-risk populations for therapeutic endpoints. Although probiotics might not be approved as drugs, they are sometimes used for the prevention or treatment of disease. In the United States, and many regions of the world, probiotic products are marketed as dietary supplements (not drugs) and are therefore subject to different manufacturing and quality control standards than approved drugs are. Health care providers need to be assured that probiotic products used in at-risk populations are safe for this use. Pharmacists should require certificates of analysis, which document quality standards, from manufacturers of products stocked in hospital formularies or other pharmacies dispensing to at-risk people. Although responsible manufacturers use stringent quality standards on their processes and finished products, using a third party to verify compliance with manufacturing and accuracy of product labeling adds assurance to end users that the product is of high quality.

Conclusion: It is in patients' best interest to use probiotics in the prevention and treatment of conditions when the evidence is convincing. To protect high-risk patients, probiotic products should meet stringent microbiological standards. Product testing results should be available for review before recommending probiotic products to at-risk individuals. For products used in at-risk populations, manufacturers should provide this information or participate in a third-party verification program that certifies compliance.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[1] Although probiotics are often not approved as drugs, they are sometimes used for the prevention or treatment of disease.[2] As opportunities for clinical use for probiotics expand, it is prudent to consider whether quality-control standards established for the production of probiotics as foods or dietary supplements are adequate to ensure safe, clinical use in at-risk populations. Recently, a probiotic dietary supplement comprising *Bifidobacterium animalis* subsp. *lactis*, *Streptococcus thermophilus*, and *Lactobacillus rhamnosus* was administered to a premature infant who subsequently died from an infection caused by the opportunistic pathogen, *Rhizopus oryzae*. Vallabhaneni et al.[3] reported that this species of mold was recovered from unopened bottles of the probiotic supplement and from cecal tissue from the infant. The probability that this mold was a contaminant of the probiotic product led us to consider microbiological standards for probiotic products used for at-risk populations. Product contamination can occur even in the most carefully controlled processes, yet this incident highlights the need for

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Key Points

Background:

- Probiotics, although typically not sold as drugs, are sometimes used by hospitalized or other at-risk people.

Findings:

- Pharmacists should be aware of product quality when recommending probiotic dietary supplements for at-risk populations.
- Probiotic product manufacturers should, if asked, provide evidence of quality criteria and inform pharmacists on safe use of specific products in at-risk populations.
- Probiotic product manufacturers can increase confidence in safety of probiotic products through involvement in programs that provide third-party verification of quality.

manufacturers to establish, and adhere to, adequate quality standards for probiotic products used for at-risk populations. More stringent quality standards, compared with those intended for the general population, may be needed. Examples of at-risk subjects can include newborns (especially premature), patients requiring critical care, and people with a weakened immune system, such as those with AIDS or on immunosuppressant therapy.

For example, consider the use of probiotics in premature, low-birth-weight infants at risk of developing necrotizing enterocolitis (NEC). This population is characterized by a naive immune system and aberrant gut microbial colonization. A systematic review of 24 clinical trials comprising >5000 premature infants assessed the safety and effectiveness of probiotics (i.e., *Lactobacillus* sp., *Bifidobacterium* sp., and *Saccharomyces cerevisiae* var. *boulardii*) for the prevention of NEC. In addition to finding efficacy at preventing morbidity and mortality associated with NEC, this review found no reports of systemic infection with the supplemental probiotic organisms used in the intervention.[4] Commenting on this Cochrane review, the editor-in-chief for Evidence-Based Child Health concluded that, regarding probiotic use, "the concern in extremely low birth weight infants has shifted from safety to efficacy" and "further studies are required only to compare different formulations, doses and schedules."[5] This statement supports the safe use of probiotics in this at-risk population. However, safety of the product also requires sufficient manufacturing quality standards in products for such at-risk subjects. Companies targeting such at-risk subjects (through research or marketing, either formal or informal) may need to conduct additional quality control measures and testing beyond the typical standards.

It is important to distinguish between safety concerns associated with the microbiological quality of probiotic products and probiotic safety per se. Our intent is not to review probiotic safety, considering that much has already been written and many processes are in place for assessing the safety of probiotics for different uses (Table 1). An overview of probiotic safety concluded that probiotics were safe for use in otherwise healthy persons.[15] This conclusion is reinforced by the European Food Safety Authority, which considers all common species of probiotics as safe for the general population.[9] The U.S. Food and Drug Administration (FDA) operates on a case-by-case basis, but numerous probiotics have been deemed generally recommended as safe for food use.[6] Health Canada has assessed documentation of safety for many probiotics used as Natural Health Products and deemed them safe. Considering the widespread consumption of probiotics, infections linked to probiotics are rare.[16] Reported adverse incidents in clinical trials with probiotics are typically not product-related, although reporting has lacked consistency and thoroughness.[17,18] Reports of infections by common probiotic genera or species are almost exclusively limited to immunocompromised individuals. However, rarely have the microbes isolated from the infection been confirmed to be the same strain as the administered probiotic organism.[19] Reports often have not eliminated native or environmental sources of similar species as the cause of the infection. Here, we turn our focus to the microbiological quality of existing probiotic products, with the presumption that safety of the probiotic strain has been suitably assessed for the given use.

Objectives

Our objective in this commentary is to inform health care providers about quality standards for the manufacture of probiotic products being recommended for at-risk patient populations. To the extent that the strength of evidence is convincing for certain clinical uses of probiotics, such uses should be encouraged as long as safety can be assured.

In particular, we focus this article on the control of contaminating microbes through manufacturing quality standards that are both reasonable and appropriate for commercial probiotic products. We assume for the purposes of this article that manufacturers have correctly identified the probiotic strains contained in their product using current phenotypic and genotypic methods (including genomic sequencing) and have used correct nomenclature to describe them. We limit our discussion to products containing only probiotics and not those that contain other potentially functional ingredients. Such standards must take into account that probiotics by definition are not sterile; therefore, high levels of live microbes will be (and should be) present in the final product. Although probiotics are delivered in conventional foods, dietary supplements, and pharma products, we limit our discussion to those delivered as dietary supplements, natural health products, or other such non-food and non-drug formulations. Furthermore, we will not address nonmicrobial contamination concerns, such as allergens, various toxins, and heavy metals. We also will not address the microbiological quality issue of probiotic viability loss during handling after production and product storage, as this important topic has been addressed elsewhere.[20,21]

Experience from established standards and programs, such as the United States Pharmacopeial Convention (USP), NSF International (note that NSF is not an abbreviation), Health Canada's Natural and Non-Prescription Health Products Directorate, the Therapeutic Goods Association of

Table 1
Safety assessment approaches for non-drug probiotic products

Safety assessment approach	Geographic region	Applicable to	Description	Reference
GRAS	United States	Foods, medical foods	Can be self-affirmed and kept confidential, or it can be submitted to the FDA for review as a GRAS notification	6,7
New dietary ingredient notification	United States	New dietary ingredients used in dietary supplements	Requires manufacturer or distributor to provide the FDA, no later than 75 days prior to marketing, the basis for the conclusion that a dietary supplement containing a new dietary ingredient is reasonably expected to be safe under the conditions of use; must be submitted 75 days prior to marketing	8
QPS	European Union	Foods	List of microorganisms that do not require specific safety testing for use in food products,[a] with the exception of documenting that strains of species on the list do not carry transferable antibiotic resistance	9
International Dairy Federation list of safe microbes in dairy products	International	Foods	Documents the history of use of live microbes in foods	10
GMO regulation	European Union	Genetically modified bacteria	Extensive safety testing required unless the product is supported by a food authority of an E.U. member state and no-objection is waged by the European Commission or other member states	11
Novel food regulation	European Union	Genetically modified bacteria New probiotic species	Extensive safety testing required unless the product is supported by a food authority of an E.U. member state and no-objection is waged by the European Commission or other member states	12
Natural and Non-Prescription Health Products Directorate	Canada	Natural Health Products	Product license issued by Health Canada when appropriate GMPs, safety, and efficacy data are provided.	13
USP	Global	Dietary supplements	Third-party verification organization	14

Abbreviations used: GRAS, generally recognized as safe; FDA, U.S. Food and Drug Administration; GMO, genetically modified organism; E.U., European Union; GMP, good manufacturing process; USP, United States Pharmacopeial Convention; QPS, Qualified Presumption of Safety.

[a] The European Food and Safety Authority (EFSA) is requested to assess the safety of a broad range of biological agents in the context of notifications for market authorization as sources of food and feed additives, enzymes, and plant protection products. The QPS assessment was developed to provide a harmonized generic preassessment to support safety risk assessments performed by EFSA's scientific panels. The safety of unambiguously defined biological agents (at the highest taxonomic unit appropriate for the purpose for which an application is intended), and the completeness of the body of knowledge are assessed. Identified safety concerns for a taxonomic unit are, where possible and reasonable in number, reflected as "qualifications" in connection with a recommendation for a QPS status. The list of QPS recommended biological agents is reviewed and updated periodically.

Australia, and the FDA's Center for Biologics Evaluation and Research were considered. Recommendations are provided for hospital and community pharmacies to guide decisions on quality standards focused on microbiological contamination of probiotic products. We hope to heighten awareness about probiotic product safety for at-risk populations among stakeholders, including health care providers, pharmacists, and industry quality specialists.

Regulatory categories for probiotic products

The importance of the regulatory category of probiotic products might not be obvious to the end user. Probiotics are delivered through foods, dietary or nutritional supplements, drugs, infant formula, natural health products, foods for special dietary uses, medical foods, and even devices. It is important to recognize that different safety requirements exist for each product category in various geographical jurisdictions. Most important for this discussion is the difference in requirements for dietary or nutritional supplements versus drugs. Whereas premarket approval of safety is required for drugs, this might not be the case for dietary or nutritional supplements. In the United States, for example, dietary supplements, although in pill or capsule form, are not required to meet the same manufacturing and quality control standards as drugs.

The historic use of live microbes in foods and traditional medicine has led to the current circumstance that probiotics are most commonly associated with conventional foods, dietary and nutritional supplements, and foods for special dietary uses. Conventional foods and dietary and nutritional supplements are products designed for the general population. Because these products are not intended for at-risk populations, it is not required to substantiate safety in these populations. However, probiotics have been studied and used clinically for therapeutic effects in at-risk human subjects.

The juxtaposition of these 2 realities—the existence of literature that supports therapeutic use of probiotics in at-risk populations and that probiotics are commonly marketed as foods and supplements for the general population—leads to the situation in which products can be used in at-risk populations. Another complicating factor is that health care providers often erroneously assume that all probiotic strains or products are the same. This assumption can lead to the use of a clinically undocumented product that

might not have been tested in or manufactured for an at-risk patient population.

Industry approach to the control of microbiological contamination in probiotic products

Probiotic manufacturers are responsible for ensuring that their products are safe and suitable for the intended consumer. In the United States, the production of products containing probiotics is regulated by the FDA under the appropriate good manufacturing practices (GMPs) for food (21 CFR 110) and dietary supplements (21 CFR 111). The GMP requirements for food are currently being updated via a final rule with staggered implementation through 2017 based on company size. It is important to understand that GMPs do not specify what testing needs to be done to assure microbiological purity. Rather, they state that appropriate specifications for the limits of contamination or prevention of "objectionable" microorganisms must be established and that reliable testing procedures be followed. The manufacturer is responsible for identifying microorganisms that are objectionable; this determination is based on the contamination risk and the intended consuming population. The criteria can be informed by organizations such as NSF International[22] and United States Pharmacopeial Convention[14] as well as by regulatory agencies.

Dietary supplements are not required to undergo premarket approval in the United States; therefore, it is difficult for consumers or health care providers to know whether probiotic products meet quality standards for pathogen risk and product contents. Companies may elect to use a third-party verification program. For example, the USP offers a Dietary Supplement Verification program that includes a "USP Verified" seal for the finished product label. This seal communicates that the supplement: contains the ingredients listed on the label, in the declared strength and amounts; does not contain harmful levels of specified contaminants; and is made according to FDA and USP GMPs, using sanitary and well-controlled processes. Monographs currently either in final form or in development by USP on several probiotics are published in the Food Chemical Codex. The strains covered are *Bacillus coagulans* GBI-39, 6086; *Lactobacillus acidophilus* La-14; *Lactobacillus acidophilus* NCFM; *Bifidobacterium animalis* subsp. *lactis* Bi-07; *Bifidobacterium animalis* subsp. *lactis* Bl-04; *B. animalis* subsp. *lactis* HN019; *Lactobacillus rhamnosus* HN001; and *Lactobacillus paracasei* Lpc-37.[23] These monographs provide specifications for methods to identify the strain level and quantify the strains, and can be used to develop third-party verification programs for dietary supplements.

In addition to the USP program, the Natural Products Association[24] offers a GMP program that certifies adherence to current GMPs for manufacturers of dietary supplements. However, this process is less thorough than the USP verification program, which includes product testing and a chemistry, manufacturing, and controls documentation review.

Any certification program should be administered by an established, reputable organization. Some companies include seals on their products that are not associated with meaningful quality certification. A product label stating that quality is assured does not necessarily mean that the product underwent rigorous third-party verification.

All natural health products sold in Canada must have a product license issued by Health Canada. To obtain this license, appropriate GMP must be followed, and proper safety and efficacy data consistent with the recommended conditions of use must be provided for review and approval. Specific microbiological standards for at-risk populations are not specified in guidance documents and the Natural and Non-prescription Health Products Directorate typically applies limits to the following organisms: total viable aerobic plate count, contaminating fungi (yeast and mold), *Salmonella* spp., *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (Table 2). Mycotoxin testing is required for products containing ginseng or peanuts or any substance derived from these sources or other selected products where fungal contamination is considered likely. Tests for other pathogens (e.g., *Listeria monocytogenes*, specific molds) are not typically conducted.

The nonsterile pharmaceutical microbiological contaminant testing standard described in the European Pharmacopeia is also summarized in Table 2. Note that the testing requirements are almost identical to those in a natural health product standard (Canada) and dietary supplement standard (United States).

What do we recommend for a reasonable approach to safe recommendation of probiotic products for at-risk populations?

Good manufacturing practices

Companies marketing to an at-risk population may need to conduct more rigorous testing than what is sufficient for the general population. Table 2 shows microbiological standards recommended for probiotic products to be used for at-risk populations. Hospital formularies should request that all supplements on formulary have certificates of analysis that document standards. Community pharmacists should consider the same action when recommending products for at-risk patients. Some of the required microbiological limits are inappropriate for specific probiotic products (e.g., yeast limits cannot apply to a probiotic comprising probiotic yeast) and should be amended accordingly if safety can be assured.

Pathogen or toxin testing

Testing for specific pathogens or toxins might be needed if the target group has a special vulnerability. For example, pregnant women exposed to *Listeria* sp. are at risk of miscarriage. In addition, GMPs require that the manufacturer consider the production process and define microbes of concern. These concerns may differ among products, depending on ingredients used.

Seek available guidance

Guidance regarding standards for safe use for at-risk populations is available from some government authorities or organizations (e.g., NSF International or USP). Manufacturers targeting at-risk populations should apply available standards, and pharmacists should verify that products are manufactured using these standards.

Table 2
Finished microbial impurity tests for products containing live microorganisms

Product	Natural health product[a]	Infant formulas[b]	Dietary supplements[c]	Nonsterile complementary medicines[d]	Nonsterile products[e]	Nonsterile products
Country	Canada	Canada	U.S.	Australia	E.U.	U.S.
Standards-issuing organization	Health Canada	Health Canada	NSF	Therapeutic Goods Association	European Pharmacopoeia[f]	USP
Total aerobic count	$<10^4$[g]	$<10^3$	10^3	$\leq 10^4$		
Yeast & mold	$<10^2$[h]		10^2	$\leq 10^2$		$\leq 10^2$
Enterobacteriaceae and bile-tolerant Gram-negative bacteria	$<10^2$[i]		10^2	$\leq 10^2$	10^2	<10 cfu/g
Salmonella species	Absent, 10 g	Absent	Absent, 10 g	Absent, 10 g or 10 mL	Absent, 10 g	Absent, 10 g
Escherichia coli	Absent	<1.8[j]	Absent, 10 g	Absent	Absent	Absent, 10 g
Staphylococcus aureus	Absent	$<10^2$	Absent, 10 g	Absent	Absent	Absent, 10 g
Pseudomonas aeruginosa	Absent[k]					
Cronobacter sakazakii (formerly *Enterobacter sakazakii*)		Absent[l]				Absent[m]
Bacillus cereus		$<10^4$				
Clostridium perfringens		$<10^3$				Absent[n]

Blank squares indicate that no standard is imposed. All values are CFU per gram or milliliter unless specified otherwise.
Abbreviations used: USP, United States Pharmacopeial Convention.
[a] Quality of Natural Health Products Guide, Natural and Non-Prescription Health Products Directorate. May 1, 2015. Version 3.1. Health Canada.
[b] Available at: http://www.hc-sc.gc.ca/fn-an/legislation/codes/infant_formula_gmp-eng.php#a0.4. Accessed August 9, 2016.
[c] NSF International Standard/American National Standard for Dietary Supplements. 2012. NSF/ANSI 173–2012. Published by NSF International, Ann Arbor, MI.
[d] Microbiological Quality of nonsterile pharmaceutical preparations and substances for pharmaceutical use. 2011. European Pharmacopoeia 7.0. Chapter 5.1.4.
[e] Not required for products containing facultative anaerobic microorganisms (that can live and grow with or without molecular oxygen).
[f] Not required for products containing fungal microorganisms.
[g] Could exceed the 10^2 CFU/g or CFU/mL limit for products containing nonmicrobial ingredients that have not undergone or have been subject to minimal processing, such as an extraction, in which case a higher limit (or complete exclusion of testing) in line with an appropriate pharmacopeia (e.g., USP, British Pharmacopoeia, or European Pharmacopoeia), would be considered acceptable.
[h] Testing required for liquid preparations only.
[i] Ph Eur provision for oral dosage forms containing raw materials of natural origin for which antimicrobial pretreatment is not feasible.
[j] The microbial attributes of a nonsterile medicine described in either section 9 of this Order or in the pharmacopoeias mentioned in this Order should not be regarded as comprehensive microbial limit specifications. In addition to being free from the microorganisms specified in this Order, the sponsor must determine the risk to the medicine from other objectionable microorganisms.
[k] Health Canada considers this opportunistic pathogen to be of concern for infants younger than 6 months, especially if conditions after reconstitution of infant formula permit multiplication of the pathogen. The recommendation is that any sample testing positive for Enterobacteriaceae is tested for *Cronobacter sakazakii*, and lots testing positive are rejected.
[l] This value was determined using a most probable number method.
[m] USP considers this opportunistic pathogen to be of concern for infants younger than 6 months of age.
[n] USP considers this opportunistic pathogen to be of concern for infants younger than 1 year of age.

Third-party verification

Confidence in the safety that a probiotic product targeted to at-risk populations is safe can be increased if the product is subjected to a rigorous third-party verification process. Such a process should assure adherence to GMP standards, which require sanitary and well-controlled processes, and contains the ingredients listed on the label.

Be aware of potential contraindications

Probiotic products should be used with caution for immune-compromised patients, such as those with AIDS, lymphoma, short bowel syndrome, or severe pancreatitis or those undergoing long-term corticosteroid treatment. The gut microbiota was recently shown to affect drug uptake and disease treatment efficacy.[25] It has not been shown that such a risk occurs with probiotic use, but this may be a topic for future research.

Implications for pharmacists

Probiotics are increasingly being used clinically. Pharmacists may be asked to provide probiotics for consumers or patients who are not fully healthy. Most probiotic products are sold as dietary supplements, which are products categorized for use in the general population. Probiotics should be manufactured using high quality standards and (similar to any medical intervention) should be safe from risk because of microbiological contaminants. Pharmacists should work with probiotic suppliers to ensure that probiotics that are stocked or recommended can be verified to meet high-quality manufacturing standards, such as those indicated in Table 2. Furthermore, pharmacists should familiarize themselves with published guidelines and other evidence-based recommendations for probiotic use.

Conclusions

As with manufactured and well-studied drugs, supplements have the potential to cause adverse events.[26] Probiotics are generally safe for most individuals.[27] However, examples of serious adverse events have been reported,[28] and it is well-accepted that septicemia is a theoretical risk of probiotic consumption in some patients with serious underlying disease. Nevertheless, probiotic products have been used safely in preterm infants for the prevention of NEC,[4] and in patients with HIV,[29,30] cancer,[31] and other immunocompromised conditions. Some have argued that only USP-certified supplements should

be provided in hospitals.[32] Research and widespread use have demonstrated the safe use of probiotics, but physicians, consumers, and hospital systems need to be vigilant for potential rare cases of adverse events. Patients, pharmacists, and other health care providers should report any adverse incidents with dietary supplements to the FDA, through their Dietary Supplements—Adverse Event Reporting webpage.[33] To improve appropriate reporting of adverse incidents, researchers conducting probiotic studies should report adverse events using the Common Terminology Criteria for Adverse Events.[17]

For the best protection of high-risk patients, probiotic products should meet microbiological standards such as those presented in Table 2. Product testing results should be available for review before recommending probiotic products to at-risk individuals. We recommend that for products used in at-risk populations, manufacturers should provide this information or participate in a third-party verification program that certifies compliance.

The FDA requires that dietary supplements be manufactured under GMPs, and currently there is no evidence that probiotic dietary supplements in compliance with GMPs pose a risk to the general population. Standards will adapt as new testing is available and risks are identified. Many at-risk individuals are already known to consume probiotic products, but the responsibility still falls on manufacturers, physicians, and pharmacists to consider safe use for these individuals.

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