

The Regulation of Probiotics

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Abstract

Probiotics are defined by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (FAO/WHO, p. 2, 2006). To meet this definition of probiotics, survivability of bacteria in the gastrointestinal tract and health benefit of the host should be demonstrated to be qualified as ‘probiotic’. However, WHO’s definition is too broad by mentioning ‘live microorganisms,’ without specifying the microorganism species. Currently, conventional lactic acid bacteria, such as *Bifidobacterium Lactobacillus* and *Streptococcus*, as well as *Enterococcus faecium*, *Enterococcus faecalis*, and even the yeast *Saccharomyces boulardii* are claimed as probiotics. Although various live bacterial strains have been grandfathered in and deemed safe for consumption due to a history of use, newly developed probiotics could benefit from a risk-based evaluation for future regulations. The FDA would benefit from evaluating the global regulatory approach to probiotics and creating new guidance for the industry. Potential approaches would be defining ‘probiotics and their specifications, in particular microbial purity, as well as mandating the proof for health benefits in humans. This would allow consumer confidence that the product has been thoroughly vetted. In addition, an approval process for live microbe as a drug should be accelerated to offer consumer benefits.

Introduction

Probiotics are a good bacterium that lives in the body to fight bad bacteria to maintain a healthy balance of bacteria in the body. Specifically, probiotics must be shown to survive the digestive process to reach the intestines while having a beneficial impact on a person's microbiome. When there is an imbalance of bad bacteria, it can affect the immune system and excess inflammation can occur. Probiotics can also boost digestion, prevent absorption of bad bacteria, and aid in drug metabolism (Cleveland Clinic, 2020). In 2012, only 1.4% of the US population used probiotics within the prior 30 days if the National Health Interview Survey (NHIS) (Adroit Market Research, 2020). By May 2020, about 22% of Americans use some form of probiotic (Daniells, 2020). Probiotics are projected to have a global compound annual growth rate (CAGR) of 7.7% for the next four year, with the projected market to reach \$74.3 billion by 2025. While 68% of this market is from food and beverage, yeast-based probiotics, specifically *Saccharomyces boulardii*, are on trend to have the most gains (Adroit Market Research, 2020). As far as bacteria-based probiotics, *Lactobacillus* and *Bifidobacterium* are the most common groups, though not all bacterial groups have the same outcomes based on the specific strain (NCCIH, 2019).

Probiotics are not a necessary addition to a healthy and balanced diet; they can be added through naturally occurring foods such as fermented foods, yogurts, fermented drinks, etc. They can also be added through dietary supplements, which can be delivered through pills, capsules, powders, and liquids. Not all probiotic supplements are the same. Within the same species of probiotics, different strains may exhibit different efficacy and safety profiles. However, regulations of probiotics have not been fully established in the United States. This review summarizes the current regulations, issues, and future directions related to probiotics.

Current U.S. Regulations

Current U.S. Regulations for probiotics depends largely on the intended use of the product. Probiotics usually fall under food ingredients and dietary supplements. However, probiotics can also be used as pharmaceutical treatments.

Regulations of Probiotics as a Food Ingredient

In the U.S. a food additive is defined as:

“any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the

characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use)” (21 USC §321(s), Findlaw, 2018).

However, exclusion from the definition of a food additive and the corresponding exemption from the premarket approval by the U.S. Food and Drug Administration (FDA) are afforded by the Generally Recognized as Safe (GRAS) program. Under the program, GRAS status can be obtained by one of 2 procedures: 1) history of use (a substance used in food prior to January 1, 1958) or 2) scientific procedures (consensus among qualified experts (21 USC §321(s)).

Although “experience based on common use in food” can be used to establish the Generally Recognized as Safe (GRAS) use of a food ingredient in some cases, there is no official list of grandfathered probiotics prior to 1958. The International Dairy Federation (IDF) has compiled a list of organisms with documented safe history of use in foods in its Bulletin No. 377, ‘Inventory of Microorganisms with a Documented History of Use in Food’ (Mogensen et al., 2002). The IDF list may be the only credible compendium documenting such uses. However, the IDF list does not differentiate microorganisms used in USA in or prior to 1958. Thus, the grandfathered list of probiotics used prior to 1958 is not available.

Currently, most probiotics are exempt from the premarket approval process via scientific procedures of GRAS, either self-affirmed GRAS or GRAS notice to FDA when used as food ingredients. General recognition of safety based upon scientific procedures requires a similar quantity and quality of scientific evidence as those required for approval as a food additive (21 CFR §170.30(b) – FDA, 2018a). However, a GRAS substance is distinguished from a food additive in that a common knowledge element, in addition to technical element, is required in the safety evaluation of a substance for its intended use. Several bacterial species of *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* have obtained the GRAS status at the strain level in the U.S. (FDA, 2021).

Regulations of Probiotics as Dietary Supplements

According to the Dietary Supplement Health and Education Act (DSHEA), a "new dietary ingredient" means “a dietary ingredient that was not marketed in the United States before October 15, 1994 and does not include any dietary ingredient which was marketed in the United States before October 15, 1994.” By this provision, dietary ingredients already in use as of October 15, 1994 were ‘grandfathered’ in under DSHEA. The several bacterial species of

Bifidobacterium, *Lactobacillus*, and *Streptococcus* are included in the Old Dietary Ingredient (ODI) list and are thus grandfathered under the DSHEA (CRN, 1998). The Council for Responsible Nutrition (1998) and other organizations have developed the list of ingredients that are grandfathered under the DSHEA, but the FDA has never officially granted such lists. To be grandfathered under the DSHEA, the same strains marketed on or prior to October 15, 1994, must be manufactured using the same manufacturing methods used on or prior to October 15, 1994. In addition, the ODI list prepared by CRN does not specify the strains in each species of bacteria.

New strains isolated recently may not be grandfathered under the DSHEA and may be considered as New Dietary Ingredient (NDI). In 2016, the FDA specified *Enterococcus faecium*, *Enterococcus faecalis*, and *Escherichia coli* as bacteria to be avoided in its 'Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry' (FDA, 2016a). Despite the FDA guidance, dietary supplements containing *Enterococcus faecium* and/or *Enterococcus faecalis* are still marketed as 'probiotics' in the U.S.

Probiotics as Pharmaceuticals

While probiotics can hypothetically be used as pharmaceuticals to treat illnesses or disorders and have been safely used as components of fermented foods and dietary supplements, there have been no approved therapeutics to date despite the FDA commissioner's 2018 statement: "the FDA is convening a workshop co-hosted with the National Institutes of Health on September 17 that will discuss microbiome-based products and how manipulation of the microbiome may potentially be used to prevent or treat a variety of different diseases," (FDA, para. 8, 2018d). An expert panel disapproved of probiotics being regulated as biologics because they are meant to support health rather than act as a cure to a disease.

As of now, probiotics cannot be legally claimed for prevention or treatment of disease when used as a component of foods and dietary supplements. Probiotics must adhere to FDA biologic guidelines by conducting clinical trials to prove both safety and efficacy before being marketed (American Gastroenterological Association, N.D.). Under the no approval status for a probiotic-based therapy for treating or preventing certain disease conditions, consumers may miss the opportunity for efficacious therapy if probiotics do have various health benefits in preventing or treating diseases. If human clinical studies of a particular probiotic strain prove clear benefits in treating a disease condition, such as treatments of *Clostridium difficile* infection, preventing necrotizing enterocolitis and sepsis in premature babies, treating symptoms of colic in babies,

periodontal disease, or ulcerative colitis, etc. (NCCIH, 2019), the FDA should accommodate the approval of such bacterial strain as a drug for efficacious therapy as long as the safety of such a strain is proven.

To accommodate the use of probiotics as drugs, the case of omega-3 fatty acids is worth considering. Humans have consumed for omega-3 fatty acids for centuries through food. Due to known health benefits of omega-3 fatty acids-rich foods, dietary supplements containing omega-3 have been developed. Subsequently, several drugs whose main components are omega-3 fatty acids have been developed and received the FDA approved as drugs for lowering blood triglyceride and cholesterol levels (OmegaQuant, 2019). Because physicians recommend such drugs as therapies, patients can take omega-3-fatty acids more confidently to improve their disease conditions.

Likewise, approval of probiotics as a drug, if the efficacy and the safety are proven, will benefit American population. For example, the administration of certain probiotics can help prevent a serious disease in premature infants necrotizing enterocolitis, which has been associated with systemic infection and death. Because these preventative effects cannot be legally marketed, physicians may have less confidence in prescribing the regiment, which could result in serious consequences. An accelerated program for approving probiotic strains on a strain-by-strain basis as a drug will benefit Americans in prevention or treating certain diseases.

Regulation of Probiotics in Europe

In Europe, probiotics fall under the Food Products Directive and Regulation (regulation 178/2002/EC; directive 2000/13/EU). In addition to a safe history of use in foods and dietary supplements, regulatory agencies outside the U.S. have evaluated the safety of LAB and other organisms in the food supply. The European Food Safety Authority (EFSA) has critically evaluated the components of the International Dairy Federation (IDF) list and developed a list of bacterial species suitable for the Qualified Presumption of Safety (QPS) approach for safety assessment (EFSA, 2007, 2010). Uses of any of the organisms on the list as food ingredients in the European Union do not require premarket approval from EFSA as long as the new strains meet the QPS criteria.

The QPS approach is a generic assessment system used within EFSA to harmonize premarket safety assessments of selected groups of microorganisms used in food and food production (EFSA, 2007). The QPS approach establishes the safety of a defined taxon (genus or group of related species) based on four 'pillars': (a) established identity, (b) body of knowledge, (c)

possible pathogenicity, and (d) end use. Exclusion or qualification of safety concerns should result in granting QPS status for a given taxonomic group (EFSA, 2007). Those applying for EFSA approval of such “new” strains are required to provide proof of the absence of transferable resistance to therapeutic antibiotics. Other primary criteria for functionality are a strain’s ability to survive passage through the upper gastrointestinal tract and its interaction under typical conditions in the small intestine. There are currently 22 strains that have established a QPS status (De Simone, 2019).

However, EFSA has not approved any health claims (corresponding to structure-function claims in the U.S.) related to the use of probiotic due to the stringent rules, though companies can still manufacture and sell products with little oversight as long as they don’t make health claims (De Simone, 2019).

Issues Related to Labeling of Probiotics for Food and Dietary Supplements Packages

In the current marketplace, there are many products labeled as ‘probiotics’ with no proven health benefits because there are no regulations prohibiting the misuse of the term ‘probiotics.’ Due to perceived health benefits by consumers, many companies now claim *Enterococcus faecium*, *Enterococcus faecalis*, and even the yeast *Saccharomyces boulardii* as probiotics in addition to conventional lactic acid bacteria such as *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* species. In addition, heat-killed bacteria are also marketed as probiotics. Heat-killed bacteria may not meet the WHO definition of ‘live microorganisms,’ (FAO/WHO, p.6, 2006). More importantly, many microorganisms whose health benefits have not been proven are currently marketed as probiotics although the proof for ‘health benefit on the host’ is required to meet the WHO definition of probiotics. Although the FDA (2016b) has issued the guidance for “Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information,” the proof for health benefits is not mandated for labelling live microbes as probiotics.

Issues Related to Standardization of Probiotics

Labeling issues also arise due to a lack of standardization. Although FDA has issued a draft policy regarding quantitative labeling of dietary supplements containing live microbials (FDA, 2018b). Some labels will list only a bacteria group while leaving out specific strain information. Because of the fact that different strains may have different efficacy and safety profile, it is important to label strain names.

In addition, there are no standard specifications regarding the microbial purity for live microbes, resulting in adverse effects in some consumers. For example, in late 2014, premature infant was given ABC Dophilus Powder for a week from birth. After the baby died, sealed bottles of the probiotic were examined and *Rhizopus ozryzae* was found – this is a mold that can lead to mucormycosis. Upon in depth review, it was most likely that the infant had died due to the extra organism that was contained in the probiotic, which was marketed directly for use by children and babies (Vallabhaneni et al., 2015).

Until issues surrounding regulations on probiotics are set (including working definition, efficacy, safety evaluation, and quality assurance parameters, etc.), physicians may not be able to confidently recommend probiotics as efficacious therapy and consumers would have less confidence in using probiotics to maintain health, even if probiotics are used as a component of food or dietary supplements only.

Safety Concerns

It is generally believed that probiotics do not harbor the potential for translocation (Hempel et al., 2011). As a result, the absence of virulence and allergenic genes, biogenic amine production, and hemolytic and mucolytic activities as well as susceptibility to antibiotics are the commonly used tests when evaluating the safety of probiotics for food and dietary supplement applications. However, opportunistic infections have been reported in many *Lactobacillus* species, in particular, *L. rhamnosus* species (Salminen et al., 2006). Bacterial translocation has not been mandated by FDA for proving the safety of dietary supplements or foods containing live microbes. For bacterial species which have been associated with higher frequencies of opportunistic infections, it is desirable to include bacterial translocation tests under desirable test conditions as part of safety evaluation.

However, the FDA has no standards for required tests for when evaluating the safety of new probiotic strains. Thus, some notifiers of GRAS or NDI notices may withhold undesirable or complicated data. For example, some notifiers may not present susceptibility of their probiotics to certain antibiotics when the minimum inhibitory concentration (MIC) values go over the commonly used cutoff points. More importantly, there are so many probiotics whose safety have not been fully evaluated at the marketplace. FDA should mandate all manufacturers of probiotics to market the product only after passing a set of safety tests on a strain basis.

Potential Future Directions

To control this type of misleading claim, the FDA should establish a new labeling regulation related to probiotics to specify qualified bacterial species and qualified list of health benefits to be demonstrated in the host (human studies for foods or dietary supplement applications; or animal studies for relevant animal feeds). Microorganisms with no proven health benefits should be labelled by the name of the microorganism without using the term, 'probiotics.'

A similar issue related to dietary fiber labeling was resolved by the 2018 'The Declaration of Certain Isolated or Synthetic Non-Digestible Carbohydrates as Dietary Fiber on Nutrition and Supplement Facts Labels: Guidance for Industry' issued by FDA (FDA, 2018c). Total fiber was initially defined as polysaccharides and lignin that are not hydrolyzed by human alimentary enzymes and many research papers reported health benefits of dietary fiber (Trowell, 1976). Due to perceived health benefits of dietary fiber by consumers, many ingredient companies started to produce synthetic fibers to claim them as dietary fiber (non-digestible carbohydrates). Examples include polydextrose and resistant dextrin which are manufactured via acidic heat treatments of starch, a digestible carbohydrate. Then, the Institute of Medicine (IOM) introduced a new term, 'total fiber' which was defined as the sum of dietary fiber and added fiber. Dietary fiber is defined as nondigestible carbohydrates and lignin that are intrinsic and intact in plants, and added fiber is defined as isolated, nondigestible carbohydrates that have beneficial physiological effects in humans (IOM, 2001). In 2017, the FDA mandated the proof for health benefits to label added as 'fiber' on food packages. This FDA guidance has stimulated the research in the synthetic or isolated fibers, resulting in consumer benefits because food manufacturers are able to use fiber ingredients which exert health benefits in humans.

Likewise, to meet the commonly used WHO definition of probiotics from the perspective of 'health benefit on the host,' the FDA should mandate the proof for health benefits per each of probiotic strain. However, WHO's definition has a problem because the definition of probiotics is too broad by mentioning 'live organism' that may include bacteria, yeast, fungi, etc. FDA can narrow down the microorganism species to be qualified as 'probiotic' for food and dietary supplement applications. Alternatively, IOM may develop a new definition of 'probiotics' while developing the safety parameters to be tested.

Conclusion

Although various live bacterial strains have been grandfathered in and deemed safe for consumption due to a history of use, newly developed probiotics could benefit from efficacy and risk-based evaluation for future regulations. The FDA would benefit from evaluating the global regulatory approach to probiotics and creating new guidance for the industry.

Potential approaches for FDA would be defining 'probiotics', their specifications, in particular microbial purity, and the list of required safety tests as well as mandating the proof for health benefits in humans. This would allow consumer confidence that the product has been thoroughly vetted. In addition, an approval process for live microbe as a drug should be accelerated to offer consumer benefits, so that physicians can prescribe probiotics with more confidence.

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