

A Review of AGA's Proposed Seal Program for Probiotic Substantiation

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Abstract

The American Gastroenterological Association recently published an article, entitled *Probiotics and the Microbiome: How Can We Help Patients Make Sense of Probiotics?* Detailing their plans to offer a seal service for companies looking to substantiate the evidence behind their probiotic product claims. The paper discussed how under the Federal Food, Drug, and Cosmetic Act (the Act), dietary supplement and food products can claim to affect the "structure or function" of the body without going through the FDA approval process required for pharmaceuticals to make such a claim. Congress' decision to treat supplements and foods differently than pharmaceuticals was undoubtedly based on the relative safety of food and supplement products, because structure/function claims do not claim that the product can treat, cure or prevent a disease, and because there are other provisions in the Act and in other laws requiring that such claims be truthful, not misleading, and substantiated. While the article cynically refers to this well-established regulatory framework as an "honor system," and use it a basis to make the case for a new "seal" program, the fact is it has given consumers access to countless safe, efficacious and affordable products that would not have been available had the manufacturers been required to go through the approval process required for pharmaceuticals.

Keywords: Probiotics • Pharmaceuticals • Dietary supplement • Health • Microorganisms

Introduction

Probiotics have been safely consumed by consumers in yogurts and other food products for centuries. While the article accurately characterizes the safety of probiotics in food and supplements, as discussed herein, it contains many inaccuracies relating to the robustness of the existing regulatory oversight over probiotics and the adequacy of the substantiation for probiotic claims. Finally, while it may be well-intentioned, the proposed "GRADE"-based evaluation scheme is contrary to current US precedent and guidelines and is far more likely to mislead consumers than to educate them [1].

Literature Review

Regulatory oversight of probiotics is robust

The article states regulatory oversight over probiotics is "lax," and "the FDA and FTC are both overburdened federal agencies that do not have adequate resources." However, it contradicts itself by discussing the "several hundred" Warning Letters issued by the FDA and the fact that the FTC takes even "significantly more enforcement actions for deceptive claims." It even highlights only two of the "high profile" cases brought by the FTC against probiotic products. The fact is that government oversight is robust.

The FDA conducts over 600 inspections of domestic food and dietary supplement companies annually and over 150 international inspections of companies exporting products to the US. The FTC has obtained well over 150 injunctions and millions of dollars in consumer refunds against food and dietary supplement products for making claims that lacked adequate substantiation.

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Like the FDA, the FTC also actively issues Warning Letters to marketers. Importantly, when the FTC initiates an investigation it is not public. An FTC investigation only becomes public when it determines claims have not been substantiated and either announces the settlement of the matter or the filing of a lawsuit. Since it is not public information, we presume the authors have no data on how many investigations the FTC initiated and closed with no public announcement. The article briefly mentions state attorneys general but does not opine on how active they have been in public and non-public investigations in this area.

To suggest, as the article does, that regulation is essentially non-existent is simply inconsistent with the facts. The government has and exercises the authority to remove non-compliant products and claims from the marketplace.

There is a robust body of scientific evidence supporting the efficacy of probiotics

The article states, without citation and without any specific evidence, that "the claims made by probiotic manufacturers generally lack adequate substantiation." That telling, unsubstantiated statement calls into question the very purpose of the proposed review scheme. If it is true, then no product will "earn" gold "seal" for its label, perhaps which is the predetermined, desired outcome of the scheme.

There have been a huge number of studies published showing the efficacy of probiotics for a wide variety of uses, but these studies do not reflect the totality of substantiating evidence. Compared to synthetic pharmaceuticals, patent protection for probiotics and other food and dietary supplement ingredients can be more difficult to obtain, and sponsors of food and dietary supplement studies may choose not to publish studies for strategic, commercial reasons. While the law requires that structure/function claims must generally be substantiated by clinical studies, there is no requirement under the law or FTC/FDA guidelines that they be published.

Experts and government agencies have reviewed the science and concluded that claims for probiotics are adequately substantiated

Expert bodies and governmental authorities around the globe have determined that claims for probiotic products are adequately substantiated.

For example, in a "Consensus Statement," the expert panel convened by the International Scientific Association of Probiotics and Prebiotics (ISAPP), opined "On the basis of the currently available literature, which includes well-designed clinical trials, systematic reviews and meta-analyses, the consensus panel concurred that certain effects can be ascribed to probiotics as a general class." It further opined based on the "accumulated evidence from the hundreds of human studies and dozens of positive meta-analyses available today," that "sufficient evidence has accumulated to support the concept of 'core' benefits of certain probiotics" [2].

As one other example, Health Canada determined that several common structure/function claims for fourteen species of "probiotics" were adequately substantiated in food formats [3]. Probiotics are also formally defined by Health Canada as microorganisms that confer a health benefit to the host.

Probiotics as a standard of care in hospitals

Members of hospital Pharmacy and Therapeutics (P&T) committees are the critical experts responsible for all matters related to the use of medications and dietary supplements in the institution, which includes development and changes made to the hospital's formulary. P&T committees review substantiating evidence on products in order to recommend them for the hospital formulary. In addition to vitamins and minerals, other dietary supplements are a standard of care in hospitals across the globe. For example, melatonin is often used as a replacement for sleep aid therapeutics in pediatrics. P&T Committees have also made probiotics available on hospital formularies as an adjunct and standard of care for certain gastrointestinal (GI) disease conditions in a majority of hospitals [4]. The AGA conditionally recommended certain probiotics for three of eight disease uses assessed in its 2020 clinical practice guidelines for probiotics and GI disorders [5]. Given the AGA recommendations for probiotics, it seems that all hospital formularies should include at least one probiotic.

While we cannot state that every claim for every probiotic is adequately substantiated, the same is the case for virtually any type of product on store shelves. The statement that "claims made by probiotic manufacturers generally lack adequate substantiation" is demonstrably false, and it, in addition to many more assertions in the article, suggests bias against the category.

The FTC and FDA have established frameworks for evaluating probiotic product Substantiation --- and it is Not a GRADE system

We will not herein critique the general usefulness of the GRADE system, or any other system, for evaluating substantiation. However, the fact is it has not been adopted by the FDA or the FTC, the federal agencies created by Congress to protect consumers from false or misleading claims for foods and dietary supplements.

Both agencies have substantial guidance on the standards they follow to evaluate substantiation for food and supplement claims, and all responsible manufacturers ensure that their claims are substantiated in accordance with those standards.

FTC guidance on claim substantiation for dietary supplements provides:

- Under FTC law, before disseminating an ad, advertisers must have a reasonable basis for all express and implied product claims. What constitutes a reasonable basis depends greatly on what claims are being made, how they are presented in the context of the entire ad, and how they are qualified. The FTC's standard for evaluating substantiation is sufficiently flexible to ensure that consumers have access to information about emerging areas of science. At the same time, it is sufficiently rigorous to ensure that consumers can have confidence in the accuracy of information presented in advertising.
- The FTC typically requires claims about the efficacy or safety of dietary supplements to be supported with "competent and reliable scientific evidence," defined in FTC cases as "tests, analyses, research, studies, or other evidence based on the expertise of

professionals in the relevant area, that have been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results." This is the same standard the FTC applies to any industry making health-related claims. There is no fixed formula for the number or type of studies required or for more specific parameters like sample size and study duration. There are, however, a number of considerations to guide an advertiser in assessing the adequacy of the scientific support for a specific advertising claim [6].

It further provides great detail on all of those considerations. FDA provides similar guidance:

- Although there is no pre-established formula as to how many or what type of studies are needed to substantiate a claim, we, like the FTC, will consider what the accepted norms are in the relevant research fields and consult experts from various disciplines. If there is an existing standard for substantiation developed by a government agency or other authoritative body, we may accord some deference to that standard [7].

The flexible approach taken by both agencies is necessary. The essentially infinite number of different structure/function claims that can be made (the article states that probiotics have a "multitude of potential objectives"), and the infinite differences in bodies of evidence to support the claims, make proscribing a specific, set standard covering all claims impossible. GRADE or any other formula-based system runs counter to that reasonable, case law-tested, flexible, and generally accepted regulatory approach in the U.S.

The proposed evaluation scheme is very unlikely to have industry participation and is very likely to mislead consumers

The proposed scheme would rely on manufacturers voluntarily submitting evidence to support claims in order to receive a gold, silver, or bronze badge from a committee that evaluates the evidence using the GRADE approach. The article suggests there will, like most "seal" programs, be a fee to participate. While apparently measures will be taken to try to ensure fair, consistent, and objective reviews, the article acknowledges that subjectivity and inconsistency are inherent risks in the scheme because ultimately "assessments made using GRADE depend on human judgment."

Why would a company voluntarily pay the fee and participate? The article recognizes that the "incentives for companies to participate in this proposed evaluation scheme are more complex . . . however, companies look for ways to increase their market share, and consumer demand may increase as a result of this type of 'seal of approval.'"

The fact is only a "Gold" ("high level of certainty") seal has a chance of increasing a product's market share. A "Silver" ("moderate level of certainty") or "Bronze" ("low level of certainty") seal would actually destroy the product. Placing a Silver or Bronze seal on a product would cause consumers to (understandably) question the product, and it would be a bright red flag for the FTC, competitors, and class action attorneys. Given the inherent subjectivity of a GRADE review, why would any manufacturer pay the fee and risk not getting "Gold"? They would not.

Discussion

Even assuming that companies were willing to pay the fee and display the Gold, Silver, or Bronze seal they receive, seals can deceive consumers and therefore this program may have the opposite of the intended effect of giving consumers useful information. The explosion of third-party seal programs like this in recent years has left very little room for additional information on the front labels of products that are already crowded with FDA-mandated information. The FTC's position, in the context of seals and otherwise, is that consumers should not be required to look elsewhere, e.g., the back label or a website, to understand the actual meaning of a seal or claim [8]. Without a detailed explanation, what will consumers think "Gold, Silver, or Bronze" seals on a probiotic product mean?

That scheme was chosen “based on the medals awarded Olympic athletes.” That is also likely to come to consumers’ minds when they see the seal, causing them to believe it signifies which product came in first, second, and third place. How will that likely be interpreted in the context of dietary supplements or foods? As a claim of comparative efficacy, if two products with the same claim are next to each other on the shelf and one has a gold seal and one has a silver seal, reasonable consumers would believe that the “Gold” product is more effective than the “Silver” product. That implication would be unsubstantiated since it had not been shown in a head-to-head clinical trial. The manufacturer of the “Gold” product could even capitalize on that misimpression and charge more for the product, to the detriment of consumers.

Similarly, if Product A and B have the same claim, and Product A has the same or better science than Product B, but only the manufacturer of product B chose to pay for the review and somehow gets a Gold seal, reasonable consumers would wrongly choose product B over A even if Product B is more expensive. Consumers will be even more confused when trying to choose between products with different seals with slightly different claims, and when competing seal programs emerge as they usually do. What will they think if a product has multiple structure/function claims each with a different seal?

Conclusion

The article states that with the proposed scheme, “ultimately, consumers will gain in availability of better products and ability to focus their resources on probiotics that will yield greater health benefits.” while that may be the laudable intention and hope, without widespread, voluntary industry participation (that will not happen for the reasons discussed above), and massive education efforts to educate consumers as to the meaning of the seals, if the proposal is implemented that hope will be very elusive. Our commentary has been reviewed and supported by the International Probiotics Association.

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