CALIFORNIA STATE UNIVERSITY SAN MARCOS

PROJECT SIGNATURE PAGE

PROJECT SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE

MASTER OF BUSINESS ADMINISTRATION

PROJECT TITLE: Probiotics Research Report

AUTHORS: Michelle Carroll, Scott Morgans, Valerie Escalante

PRESENTATION DATE: December 11, 2017

THE PROJECT HAS BEEN ACCEPTED BY THE PROJECT COMMITTEE IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF BUSINESS ADMINISTRATION.

Name of Project Advisor

Glen H. Broadsky — 11/29/17

PROJECT ADVISOR | SIGNATURE | DATE

Name of Second Reader

David Grows — 12/1/17

PROJECT SECOND READER | SIGNATURE | DATE

Probiotics Research Report

Michelle Carroll

Valerie Escalante

Scott Morgans

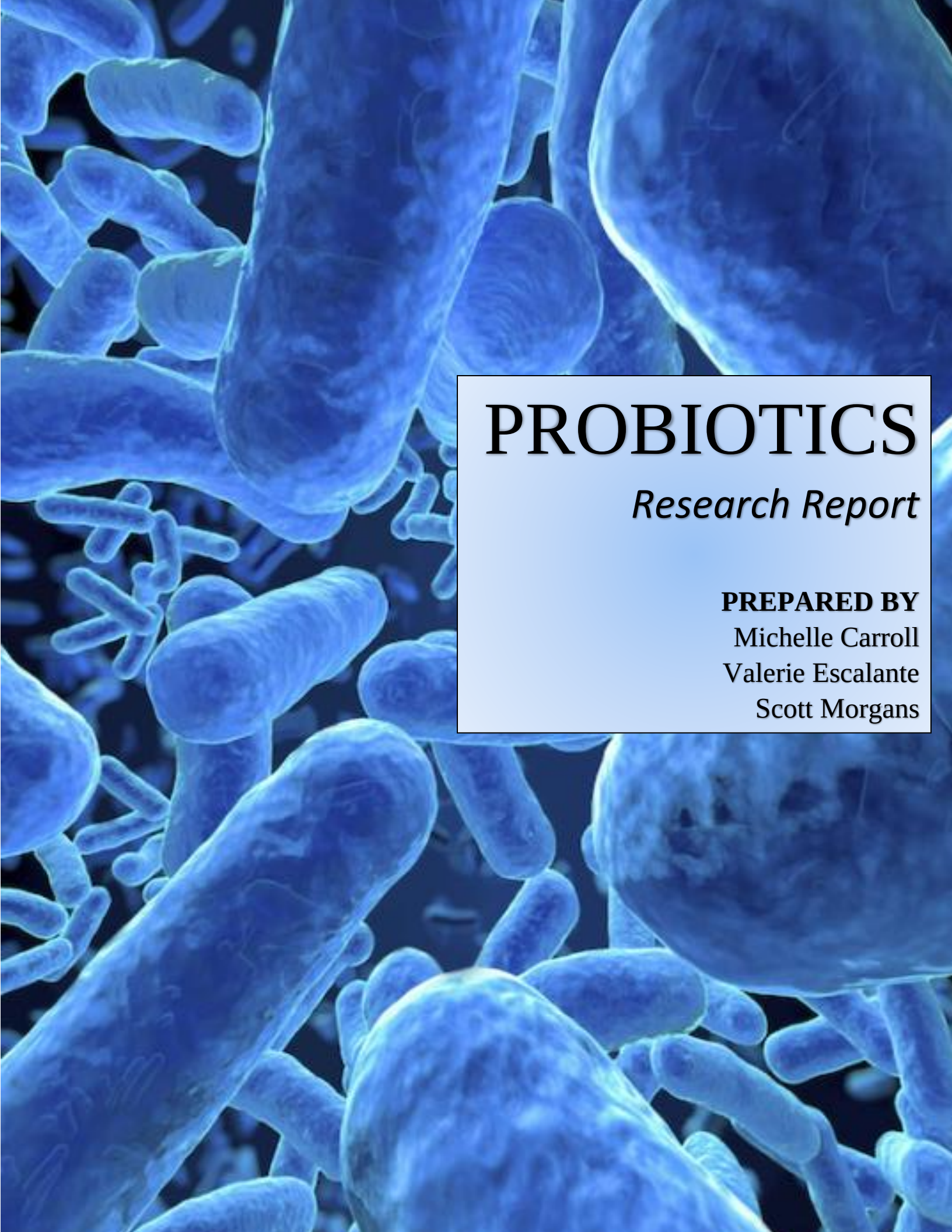
California State University, San Marcos

Author Note

This report was prepared to satisfy Nicolas & Tomasevic Law Firms's request for information surrounding the claims made by Probiotic companies in the United States.

Abstract

The probiotics industry is a booming industry, expecting to grow an additional 38% by the year 2021. Under the Food and Drug Administration regulations the majority of probiotics are marketed as dietary supplements. This categorization of dietary supplements limits companies in pursuit of claims to the labeling of their products. Probiotic companies market their products for various health reasons, mainly digestive issues. In 2009, The Dannon Company became one of the first manufacturers to endure a class action lawsuit due to its claims being made on their probiotic yogurt packaging. This suit was then followed by other lawsuits filed against other large manufacturers. These types of lawsuits have lent a hand to manufacturers becoming more cautious about their claims and adding precautions to their labels.



PROBIOTICS

Research Report

PREPARED BY
Michelle Carroll
Valerie Escalante
Scott Morgans

The human body is covered inside and out with both harmful and beneficial bacteria. The current estimate for bacteria on the human body for a 155 lb. human averages 3.8×10^{13}, or 38 trillion. In comparison, the estimated number of human cells in the body is 3.0×10^{13}, or 30 trillion cells. The nearly 1:1 ratio illustrated by these numbers provides a valuable understanding of how important bacteria are to the human body. The majority of bacteria inside the human body reside in the colon, contributing roughly 3.0×10^{13} or 79% of the total.

Probiotics are a supplement used to replenish bacteria within the human body, or in some cases to increase the health of the existing bacteria. Probiotics will typically target the gut and colon due to the number of bacteria that naturally occur in that region. Probiotics contain a variety of living microorganisms that some claim to be beneficial to the human body; Lactobacillus, Bifidobacterium and Bacillus are three of the most commonly used species in these products.

Research Objective

Nicholas & Tomasevic Law Firm is focused on evaluating the current health claims made and marketing tactics used by the manufacturers of various probiotic companies. To reach the objective, research and analysis of probiotics and the industry will be conducted. The team will draw a conclusion based on the research and its findings to further the client's understanding of marketing constraints on probiotics.

Analysis

Background

According to Google Trends, the interest in probiotics is on the rise and has been for the past 13 years. In the United States (US), the consumer spend on health products has been $210 billion with $87.4 billion of that amount being spent on vitamin and dietary supplements and another $4 billion spent on probiotic supplements. These figures are expected to grow 38% by 2021.

The US Food and Drug Administration (FDA) categorizes probiotics into four different classes, depending on their intended use. “Medical Food” products are “intended for use in dietary management of a disease or condition for which distinctive nutritional requirements have been established by a medical evaluation.” These products are meant to be administered under the supervision of a physician. “Dietary Supplements” are meant to supplement a dietary need, usually containing a dietary ingredient that is intended for ingestion and is not found in conventional food form. “Drug” products are intended for the cure, mitigation, treatment, diagnosis, or prevention of a disease. Should a probiotic be considered a drug and administered as a drug, then all probiotic drugs must be proven safe and effective for intended use before marketing (Food and Drug Administration Development & approval process (drugs), 2009).

In order for a product to be classified as a drug and not need prior approval for marketing from the FDA, the product must meet the Over The Counter (OTC) drug monograph given by the FDA. An OTC drug monograph describes the types of ingredients that are to be utilized to treat certain diseases or conditions without a prescription as well as the appropriate dosage and instructions for use. OTC products that meet a monograph’s requirements may be marketed without FDA review. OTC products that do not fit under an existing monograph must be

approved under an application similar to the applications for prescription products. Currently, probiotics do not fit into these categories positioned by the OTC monograph ("What are over-the-counter (OTC) drugs and how are they approved?", 2017).

Probiotics are widely popular because they do not need to be prescribed by a physician to be purchased by consumers. Lastly, "Biological" products contain a virus, serum or toxin meant for the prevention, treatment or cure of a disease or condition. Due to the amount of restriction and regulation, a company must follow to label a product a drug or biological product, many companies choose to market probiotics as dietary supplements. The rapid growth in this market has made it difficult for scientific research to keep up with the demand for probiotic products. At this point in time, no probiotic has been approved for preventing or treating health problems. For the reason that no probiotic has been approved for preventing or treating health problems, the probiotics that are marketed towards curing of health issues are at risk for making false claims.

With the majority of probiotics being marketed as dietary supplements, manufacturers tend to make structure/function or health claims for their products. A structure/function claim describes the process by which the supplement, food, or drug maintains normal functioning of the body. Structure/function claims require that a manufacturer's substantiation be accepted by experts in the field to show that the claim is not false or misleading, however, they do not require FDA approval. The research substantiating structure/function claims is not required to be made publicly available and there are no disclosure requirements. Additionally, when a structure/function claim is made, the manufacturer must state in a disclaimer that FDA has not evaluated the claim and that the product is not intended to "diagnose, treat, cure, or prevent any disease. "Such a claim can legally be made only with regard to a drug (Center for Drug Evaluation and Research, n.d.). In general, the level of substantiation and quality of evidence

needed to make a structure/function claim are far lower than the levels needed to make a health claim. According to the FDA, a health claim describes the relationship between a food, food component, or dietary supplement ingredient. Health claims reflect the products that reduce the risk of a disease or health-related conditions. All health claims must be approved by the FDA and undergo clinical studies. Ultimately, health claims must have scientific evidence supporting the claims before marketing is allowed. All research and data are required to be published and made available to the public.

In 2001, the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics developed several probiotic guidelines. The guidelines are intended to evaluate probiotics in food that could lead to the substantiation of health claims (Heimbach, 2008). The recommendations are as follows.

1. Identification of the genus and species of the probiotic strain by using a combination of phenotypic and genotypic tests as clinical evidence suggesting that the health benefits of probiotics may be strain specific
2. In vitro testing to delineate the mechanism of the probiotic effect
3. Substantiation of the clinical health benefit of probiotic agents with human trials
4. Safety assessment of the probiotic strain should at a minimum determine patterns of antimicrobial drug resistance
5. Metabolic activities
6. Side effects noted in humans during clinical trials and after marketing

7. Toxin production and hemolytic potential if the probiotic strain is known to possess those properties
8. Lack of infectivity in animal studies.

Although these guidelines appear comprehensive, they are largely ignored within the industry.

Regulations

Regulatory requirements differ depending upon the intended use of the probiotic, the use of a dietary supplement or the use of a drug. As stated earlier, the FDA defines a drug as having the ability to cure, mitigate, treat or prevent a disease. In the circumstance that the probiotic's intended use is for drug utilization, then the probiotic must undergo the regulatory process of a drug, which is parallel to that of a therapeutic agent. An Investigational New Drug application must be submitted and authorized by the FDA prior to administering an investigational or biological product to humans for consumption. The probiotic drug must be proven as safe and effective for its intended use prior to marketing (Venugopalan et al., 2010).

Within the US, many types of health claims for health benefits and disease prevention are authorized for functional products if the benefits have been studied and display results appropriately. Probiotics are generally considered dietary supplements and, as such, are subject to the ‘‘Dietary Supplement, Health and Education Act" (DSHEA), which was passed by Congress in 1994. DSHEA provides the framework for the regulation of dietary supplements formulated by the FDA. US restrictions enable manufacturers to sell supplements by listing the contents on the label. Probiotic products require FDA approval or Generally Recognized as Safe (GRAS) status. Thus, US regulations are not as stringent for functional foods as for the pharmaceutical products (Walker, 2006).

Probiotics that are intended for use of a dietary supplement are placed under the definition of a "food" and are then regulated by the FDA's Center for Food Safety and Applied Nutrition. A supplement, as defined by the DSHEA, is a supplement taken by mouth that includes a "dietary ingredient" intended to supplement the diet (Venugopalan et al., 2010). Manufacturers are required to notify the FDA prior to marketing a probiotic, a far lesser challenge than marketing the product as a drug. According to DSHEA, the manufacturer is responsible for determining that the dietary supplements it manufactures or distributes are safe, and that any representations or claims made about them are demonstrated by adequate evidence. The adequate evidence is to display that the representations or claims are not misleading or false (Center for food safety and Applied Nutrition, n.d.).

Additionally, in 2007, the FDA established the "Current Good Manufacturing Practice" requirements to ensure the identity, purity, quality, strength, and composition of dietary supplements. The companies that manufacture, package, or hold dietary supplements must follow these regulations. Furthermore, the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006 states that manufacturers and distributors of dietary supplements are required to record and forward to the FDA any received reporting of serious adverse effects related to the use of their products. The MedWatch Form 3500A (see appendix, Exhibit A) must be completed by the manufacturer or distributor and submitted to the FDA. The FDA encourages healthcare professionals, consumers, or patients to voluntarily report adverse events on the MedWatch Form 3500 (Commissioner, n.d.)

Product Constraints

The current challenges to establishing health claims for probiotics stem from the identification of microorganisms. In order to obtain a health claim for a probiotic product, food

manufacturers will have to precisely define their microorganism (Farnworth, 2008). Most probiotic products marketed to consumers to date contain one or more bacteria such as lactic acid bacteria (LAB), which includes Lactobacillus Acidophilus, Lactobacillus Gasseri, and Bifidobacterium Bifidum. These are the most common probiotic bacteria added to food products because LAB is presumed to impart beneficial health effects (Products with Probiotics, n.d.). In the US, a high percentage of marketed probiotic products come in the form of either food or dietary supplements. Yogurt and "Kefir" are marketed as having "beneficial cultures" and foods claiming to encompass probiotics have recently expanded to cereals, such as granola, candy bars, juice and cookies (Products with Probiotics, n.d.).

Experts have cautioned that the speed of growth in marketing and use of probiotics is far too rapid for scientific research to validate many of their proposed benefit claims. Although some probiotics have shown promise in research studies, strong scientific evidence is lacking in order to support the specific health benefits of probiotics for most health conditions. To date, the FDA has not approved any probiotics for preventing or treating any health problem (Probiotics in depth, 2017). To date there has been no evidence to support claims that probiotics can treat the common cold, diabetes, autism, or high cholesterol. Thus far, there has been no indication or study to suggest that they are effective against the flu (Probiotics come with bold health claims, but science is shaky, 2016).

Market Claims

Companies are marketing probiotics for various health reasons. Healthy digestive system (gut health), or immune health and infant health are among the most common claims of probiotics marketers. Customers purchase probiotics based on the claims made by the companies producing the products. In many cases, companies alter the bacteria's make up in order to claim

a “patented” formula that will produce far better results in one or more specific areas for which the product is marketed. For example, the company ViTAgurl by Esse Nutrition LLC targets women and their most common health concerns with probiotic supplements such as their well known, Be Balanced (Passport, 2016).

This approach of labeling a supplement as targeted toward specific customers has come increasing scrutiny leading to more regulation. In 2016, manufacturers, trade associations and regulatory bodies came together to develop new labeling standards to help mitigate the concerns that developed over poorly regulated supplements. In May 2016, the FDA announced new standards and requirements for labels containing the Nutrition Facts and Supplement Facts. Manufacturers with over $10 million in annual revenue are required to adopt the new labels by July 26, 2018, with smaller companies changing their labels within one year of that date. The revision of these labels aims to provide clearer and truer information for the consumers (Passport, 2016).

Digestive health is one of the top marketed claims of probiotic products. From 2011-2016, digestive supplements ranked third in sales amongst all other vitamins and health supplements (Passport, 2016). Probiotics claim to increase and replenish the “good bacteria” in the consumer’s digestive tract, leading to reduction in heartburn, stomach pain and irritability, Irritable Bowel Syndrome (IBS) symptoms, and constipation. According to the National Institutes of Health, “about one in five Americans suffers from digestive diseases, including GERD-style heartburn (65 million prescriptions per year), constipation (63 million cases), Irritable Bowel Syndrome (15 million cases) and Crohn's Disease (1.8 million prescriptions)” (Runestad, 2017). These numbers present probiotic manufacturers with sizable attractive target markets. However, concern remains regarding the claims made toward digestive health because a

probiotic product may not directly target the particular condition from which a consumer seeks relief. For example, consumers seeking to maintain gut health may opt for a multi-strain formulation that has a prebiotic, such as inulin or fructooligosaccharide (FOS), to increase the health of existing bacteria. However, if that consumer requires help with a specific digestive-health issue, acidophilus typically won't suffice. For example, Irritable Bowel Syndrome (IBS) is common among consumers, affecting as many as 15 percent of people worldwide (Runestad, 2017). IBS symptoms include bloating, cramping, gas, diarrhea and constipation. A consumer considering probiotics for IBS relief or any other symptom relief look for the probiotic product that is marketed to alleviate their specific symptoms. Probiotic manufacturers have begun to target these consumers by creating unique strains of various species of bacteria that target specific digestive health issues.

Probiotics for infants have become increasingly popular in recent years. Some studies have suggested that probiotics in infancy stages can lead to a reduction in skin sensitivity. Currently, dozens of studies exist to determine whether the use of probiotics during pregnancy and infancy can prevent or cure atopic dermatitis in children. There are conflicting results from these studies. For example, a study completed in 2006 resulted in no significant statistical effects of the probiotic (No benefit). A different study in 2008 found that probiotics may offer a safe means of reducing the risk of early acute otitis media and antibiotic use and the risk of recurrent respiratory infections during the first year of life (benefit). The study that identified a benefit to using probiotics asserted that the strains of probiotic had to be specific. This supports the claim that probiotics are mostly developed and even patented to target a specific health concern, not just general health (Rautava, 2008).

A study performed by Labdoor.com included the analysis of 37 best-selling probiotic supplements. Each product was examined to measure the total amount of bacteria contained as well as contaminants (mold, yeast, and pathogenic bacteria, including E. coli o157:H7, Salmonella spp., and Staphylococcus aureus). The results showed that label accuracy was problematic for these products. 16 of the 37 products recorded total viable bacteria amounts that deviated more than 50% from the label claims. Two of the 16 products deviated from their total viable bacteria claims by more than 100%. Thirty-three of the 37 products passed the product purity test, meaning they did not contain any of the harmful bacteria listed (Mcnamara, 2000).

The quantity and type of bacteria in probiotics could pose harm to individuals with prior medical conditions. A majority of the products do not list a warning on the back of the product to listing contra-indications or advice to consult a physician prior to use. A study published in the American Society for Microbiology in 1999, showed that two commercially sold preparations of B. subtilis did not actually contain the scientifically genetic and physiological characterizations of B. subtilis (Mcnamara, 2000).

Another study in 2004 in *Applied and Environmental Microbiology* was successful in characterizing five different strains of Bacillus. The study found that specific strains were responsible for promoting an immune response in the body of mice. Some of these strains are responsible for promoting the production of an immune response called TNF-alpha. TNF-alpha is important due to the role it plays in autoimmune disease. Individuals with diseases such as arthritis and diabetes, take prescriptions such as Humera to control TNF-alpha from causing inflammation. In the case that an individual consumes probiotics with these bacteria types, while on this medication, there is a great possibility that the use of the probiotic may reduce the effectiveness of the medication. To mitigate the ineffectiveness of medication, probiotic

companies should be listing warnings on the bottles to alert consumers of the antagonistic effects of probiotics with specific medications. To solidify the results and claims, more research should be conducted.

Litigation

The Squire Patton Briggs whitepaper explains that more than 65% of all US consumer food and beverage lawsuits are being filed in the state of California. The whitepaper claims California is considered to be a health-conscious state with particularly plaintiff-friendly laws favorably inclined to apply those laws to debatable health claims. Specifically, a high percentage of these food cases have been filed in the Northern District of California. These actions most frequently emphasize false claims under California's Unfair Competition Law (UCL), False Advertising Law (FAL) and Consumer Legal Remedies Act (CLRA) (Squire Patton Boggs, 2015).

Litigation has been on the rise to challenge advertisement and marketing tactics for probiotic products. Probiotic advertising claims have attracted false advertising suits and other such actions. Surveys have shown that US consumers make decisions to purchase these types of foods and dietary supplements almost exclusively on the "product labeling claims" that describe "health benefits" (Stopping Deceptive Health Claims, n.d.). The following discussion focuses on some of the litigation cases in recent years.

The Dannon Company. The article *Probiotic Advertising Class Actions: Claims Challenged & Lessons Learned* explains that although a large quantity of false advertisement claims have risen from, few have been resolved upon their accreditation (Probiotic Advertising Class Actions: Claims Challenged & Lessons Learned. (n.d.). Dannon Yogurt's advertising of its DanActive and Activia products and an ensuing lawsuit is a case in point. The suit derived from

the claims that the Dan Active and Activia probiotic yogurt products were "scientifically proven" to naturally regulate digestion. (Probiotic Advertising Class Actions: Claims Challenged & Lessons Learned, n.d). The lawsuit alleged that Dannon's clinical studies completed to validate the marketing claims indicating that DanActive®, Activia® Light, and Activia® yogurt products regulate one's digestive system didn't support the claim. The suit describes that the company charged 30% more for its probiotic yogurt and spent upwards of 100 million US dollars in advertising to convince consumers of the product's unsubstantiated benefits. The suit alleged that ads for both Activia® and DanActive® yogurt exaggerated their products' beneficial health effects. Specifically, television ads contained a voiceover claiming that Activia® is "clinically proven to help regulate your digestive system in two weeks if eaten everyday". (Lawsuit Settled: Dannon1 Yogurt Didnt Measure Up to Its Claims, n.d.).

The class-action suit against The Dannon Company alleging the company's claims that its probiotic yogurt offers clinically and scientifically-proven health benefits were false. The class action suit seeks compensation for US customers who purchased the products based on the marketing campaign. Coughlin Stoia Geller Rudman & Robbins LLP claimed that Dannon was deceptive in their advertising to target "health conscious consumers" in order to sell hundreds of millions of dollars' worth of yogurt. In 2009, Dannon settled a consumer class action suit in the US which challenged that advertisements for certain brands of its yogurt overstated their claimed health benefits. The settlement will result in $35 million paid to the affected American customers (Lawsuit Settled: Dannon1 Yogurt Didnt Measure Up to Its Claims, n.d.).

The Squire Patton Boggs whitepaper explains that to date, the primary types of probiotic-related litigation target food and beverage companies claiming health benefits in the form of products or false advertising overstating the health benefits of products labeled as "natural" The

whitepaper also describes that the verbiage “natural” on the label has become an invitation to litigation resulting from the FDA failing to clearly define the word ‘natural’ altogether despite the recent suits. The lawsuits arise from consumers alleging that industry players provide false misleading advertisement claims surrounding the “natural” (squirepattonboggs, 2015). In other words, most lawsuits arose from the mislead advertisements or the labels stating “natural” as the product may have contained genetically modified organisms (GMO) or infused with synthetic or artificial ingredients.

The Squire Patton Boggs whitepaper goes on to describe the standard defenses used by companies confronting charges of false or misleading advertisements or labels. These include focusing on technical deficiencies in the initial pleadings or challenges to class certification that threaten to dramatically reduce the value of pursuing the claims. Although few of these false advertising cases proceed to trial, it has not always been because early motion practice has been successful. Indeed, the failure to win dismissal of such cases involving health claims, coupled with the failure to avoid class certification, often results in settlement. The merits are infrequently adjudicated (squirepattonboggs, 2015).

Procter and Gamble. The Align probiotic supplement class action lawsuit, FIRST BROUGHT IN 2014, alleged that Procter & Gamble (P&G) engaged in false advertising. The suit contended that the company’s Align probiotic did not deliver the health benefits claimed in its advertising. The case focuses on P&G’s use of a trademarked phrase “GREAT DIGESTION THROUGH SCIENCE” to market the Align probiotic supplement:.” Plaintiffs Dino Rikos, Tracey Burns and Leo Jarzembrowski took issue with P&G’s claims that the Align supplement “is different because only Align contains Bifantis, a patented probiotic strain” that “brings peace to your digestive system” and provides a “restored natural balance to your digestive system.”

(Bucher, 2017). The plaintiffs stated that scientific studies have not been completed to support the health claims that P&G have declared for the Align supplement. Therefore, lacking sufficient scientific proof, Proctor and Gamble had no legitimate basis upon which to make such claims. Their probiotic class action lawsuit asserted that the Align supplement is “nothing more than a sugared capsule filled with naturally occurring bacteria.” (Bucher, 2017).

In June of 2014, the Align probiotic class action lawsuit was initially certified. Similar to other manufacturers facing class action lawsuits, P&G’s first line of defense was to file an appeal on the grounds that they believed that the district court mishandled its responsibility when it granted the plaintiffs’ motion for Class certification. The U.S. 6th Circuit Court of Appeals reviewed the case and on Aug. 20, 2015, the 6th Circuit confirmed the district court’s order certifying the Align class action lawsuit. In other words, the appeal was not granted and the lawsuit remained certified. Procter & Gamble maintains that scientific evidence exists to support the claims and denies the allegations in the Align class action lawsuit (Bucher, 2017).

Bayer Healthcare LLC. In contrast to the Dannon and P&G class action lawsuits, Bayer Healthcare LLC successfully defended itself in a class action lawsuit for allegedly falsification and misleading of dietary supplements. The product in question, Philip's Colon Health (PCH), claimed that it promoted overall digestive health. A judge ruled in favor of Bayer on all counts and concluded “In sum, plaintiffs failed to present competent evidence to create a genuine issue of material fact that Bayer’s claims that PCH promotes overall digestive health and helps defend against occasional constipation, diarrhea, gas, and bloating are actually false or misleading." (Plaintiffs File Appeal in Bayer Probiotic Lawsuit, 2017). Judge Jose Linares explained, “As two other courts have held, competent and reliable scientific evidence does not require drug-level clinical trials, and the government cannot try to reinvent this standard through expert testimony”.

The Lawyers with Sidley Austin LLP, expressed that the judgment order was an "important decision that should help to rein in the onslaught of lawsuits that improperly target dietary supplements". The attorney also stated and reinforced the point that dietary supplements are not regulated as drugs therefore do not need scientific evidence of clinical trials to indicate their structure or function. (Plaintiffs File Appeal in Bayer Probiotic Lawsuit, 2017). In order to support the PCH claims, Bayer concluded over 100 studies as described in the Plaintiffs File Appeal in Bayer Probiotic Lawsuit document.

The lawsuit judgment for Bayer that claimed that their advertisement was not substantiated, described that the burden of proof lay upon the consumers and that they could not prove that the advertisement was false. Consequently the Plaintiffs lost the case and the judgment. The judge stated that the plaintiffs did not conduct their own double blind placebo study in order to prove the false claim. Bayer has been taken to court over the falsity and misleading claims three times and each time the burden of proof is never carried out by the plaintiffs (Plaintiffs File Appeal in Bayer Probiotic Lawsuit, 2017).

Industry

The leading global probiotic supplement brand is Align, by Procter and Gamble. The company has invested heavily in making Align a highly visible, mass-facing probiotic brand in the US. Recently, the brand has developed sales in Canada, and has been pushing for global distribution. In contrast, sales of private label probiotics significantly outsell public companies. The surge in private label sales is one of the biggest trends within probiotic supplements in the US. As consumer interest in these products has soared, specialist retailers, such as GNC and Vitacost, have been quick to jump on board, turning private label into the fastest growing product offering (Passport, 2016).

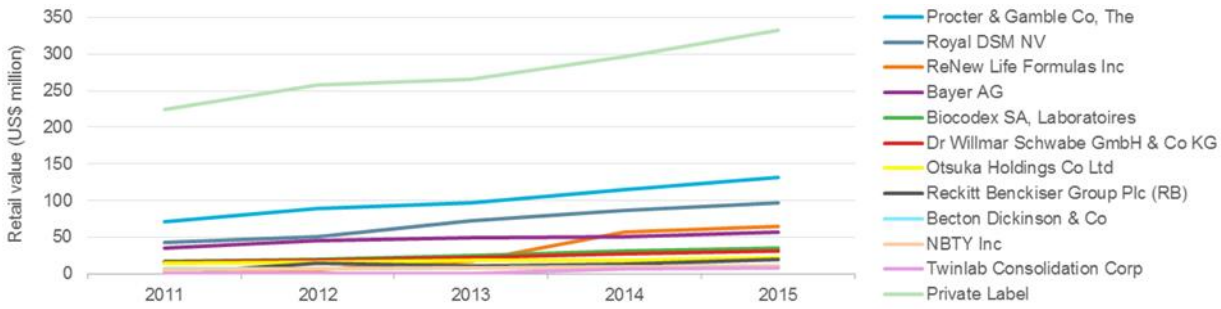


Figure 1 US: Probiotic Supplement Leaders 2011-2015

The online retail sector has been easier to track due to the "best seller" claims and the readily accessible consumer reviews. First ranked, Hyperbiotics PRO-15, does not have any packaging that makes claims to any health benefits. It does claim that the product is a natural probiotic supplement with 15 strains and five billion CFU (colony forming units). It claims the patented technology allows for the product to reach deep into your intestinal tract alive, 15x more effective than other products. The back of the label defers the consumer to their website to understand the science behind the claims. The website states that the time released pearls are uniquely formulated to repopulate the gut. The company reiterates general benefits of probiotics such as, aid in digestion, help absorbing nutrients from food and vitamins, immune system strength, an increase to energy levels, support for brain function and clarity, and the promotion of optimal body weight.

Second ranked, Garden of Life, appeared in almost every search event for probiotics. The front of the box claims that they have 16 probiotic strains. The box claims it supports vaginal, digestive and immune system health (daily value not established) and the product has 50 billion CFU and 16 raw probiotic strains. No refrigeration is required to keep the product alive, guaranteeing shelf stability. Amazon claims the following.

- DIGESTION SUPPORT: This once daily probiotic supplement contains Lactobacillus

acidophilus and Bifidobacteria for digestive health and constipation relief

- PROBIOTICS FOR WOMEN: Specially formulated probiotic for women's specific health needs contains L. reuteri and L. fermentum for vaginal health
- IMMUNE SUPPORT: This dietary supplement has 50 billion CFU and 16 probiotics for immune system health
- SHELF STABLE PROBIOTICS: This 50 billion probiotics supplement comes in 30 one daily capsules; no refrigeration required
- HYPOALLERGENIC PROBIOTIC: Our probiotic is dairy free, gluten free, soy free, and vegetarian

Third ranked, Culturelle Kids Probiotics, is focused towards supporting children's immune systems. The package claims it helps to support a healthy digestive system naturally within children's bodies. The product claims to help reduce occasional digestive upset, including diarrhea. All of these claims are followed by an asterisk, related to the statement on the back of the product that informs the consumer that these claims have not been evaluated by the Food and Drug Administration.

Overall, the claims made by these brands are non-specific to and specific disease or condition and therefore does not need to be supported by scientific research.

Conclusion

Prior to 2009, the claims made by probiotic manufactures were more specific than they are today. Previous lawsuits have given way for more stringent rules and regulations regarding the labeling and marketing of probiotics. Companies are becoming more aware of the verbiage

on their packaging and are marketing towards more generic symptoms rather than actual conditions or diseases. With the new regulations forthcoming in July of 2018, set by the FDA regarding the requirements for labels containing the Nutrition Facts and Supplement Facts, it will become more difficult for companies to make non-specific claims regarding their products. Another area of interest regarding future litigation may be the specific ingredients that are positioned into (their) products.

A study completed by Labdoor Inc, a privately held medical company, tested several probiotics and found that the actual concentrations and species of bacteria that the companies claim to be in their products, are different from the description placed on the label. As mentioned before certain species, such a Bacillus, will actually promote an immune response and create an increase in TNF-alpha, this could be disadvantageous to patients currently on TNF- alpha blockers, such as Humera.

A population analysis indicated that in California alone roughly 9 million individuals suffer from chronic joint symptoms and 2.5 million individuals suffer from diabetes. Cross referencing that total figure with approximately 2.4 million individuals that utilize or favor probiotics, opens the possibility that some of the individuals may also be taking probiotics in conjunction to their prescribed medication. Hence, the individuals that suffer from auto-immune disease may also be, unknowingly, altering the effects of their drugs and ultimately worsening their condition.

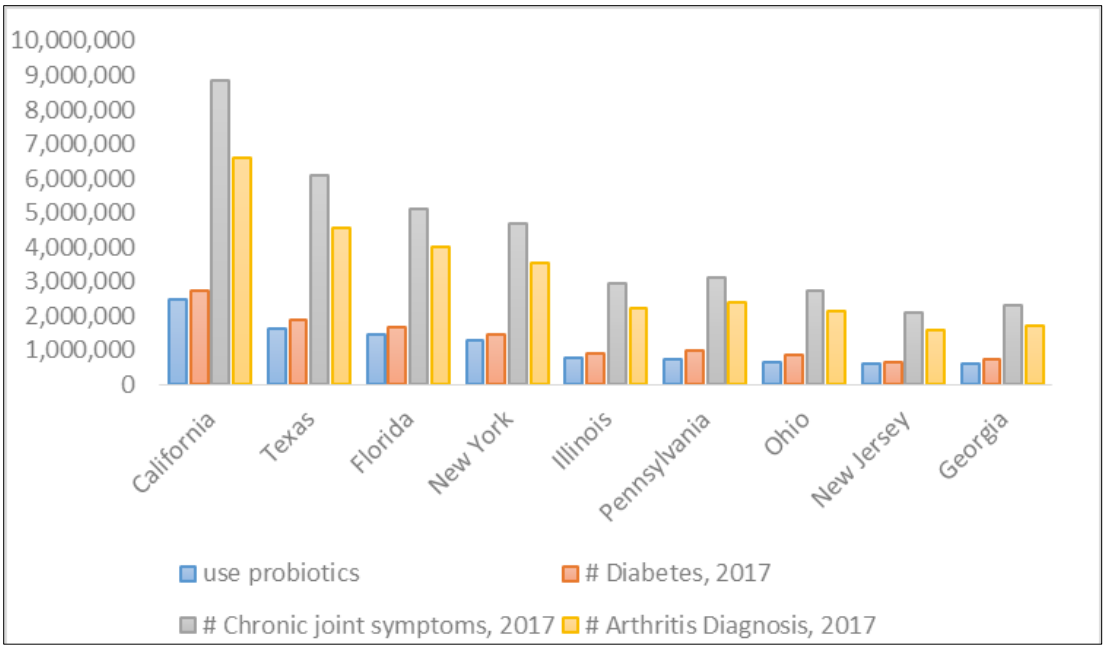


Figure 2 Probiotic Usage among those with Diabetes, Chronic Joint Symptoms, Arthritis

The actual benefits or disadvantageous that come from using probiotics is still not fully understood. More independent companies should test these products in order to validate the truthfulness of the claims. Currently, the regulations and marketing of probiotics should be proceeded with care.

Figure 3 Color Coded Map of Auto Immune Disease and Non Prescription Vitamins

References

Best Probiotics Supplements. (n.d). Retrieved December 04, 2017, from https://labdoor.com/rankings/probiotics

Brouwer, M. L., Wolt-Plompen, S. A., Dubois, A. E., Heide, S. V., Jansen, D. F., Hoijer, M. A., . . . Duiverman, E. J. (2006, June 27). *No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial*. Retrieved December 03, 2017, from http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2222.2006.02513.x/full

Bucher, Anne June 21, 2016. (2017, October 04). Trial Date Set for Align Probiotic Class Action Lawsuit. Retrieved November 06, 2017, from https://topclassactions.com/lawsuit settlements/lawsuit-news/338318-trial-date-set-align-probiotic-class-action- lawsuit/

Center for Drug Evaluation and Research. (n.d). Development & Approval Process (Drugs). Retrieved December 04, 2017, from https://www.fda.gov/Drugs/DevelopmentApprovalProcess.default.htm

Center for Drug Evaluation and Research. (n.d). FDA Basics – What are over-the-counter (OTC) drugs and how are they approved? Retrieved November 09, 2017, from https://www.fda.goc/AboutFDA/Transparency/Basics/ucm194951.htm

Center for Food Safety and Applied Nutrition. (n.d.). Dietary Supplements. Retrieved November 06, 2017, from https://www.fda.gov/Food/DietarySupplements/

Commissioner, O. O. (n.d.). Forms for Reporting to FDA. Retrieved November 06, 2017, from https://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.hm

Farnworth, E. R. (2008, June 01). The Evidence to Support Health Claims for Probiotics1,2.

Retrieved October 30, 2017, from http://jn.nutrition.org/content/138/6/1250S.full

Food and Drug Administration Development & approval process (drugs) [updated 2009 Oct 14; cited 2010 Jun 24]. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm

Heimbach J. (2008). Health-Benefit Claims for Probiotic Products .T *Clinical InfectiousDiseases. 46(S2).doi:10.1086/523327*

Joint Food and Agriculture Organization of the United Nations/World Health Organization Working Group report on drafting guidelines for the evaluation of probiotics in food, London, Ontario, Canada, April 30 and May, 2002.

Lawsuit Settled: Dannon1 Yogurt Didnt Measure Up to Its Claims. (n.d.). Retrieved November 06, 2017, from https://www.badgut.org/information-centre/a-z-digestive-topics/dannon lawsuit-settled/

Mcnamara, S. H. (2000). Food and Drug Administration Regulation of Dietary Supplements. *Regulation of Functional Foods and Nutraceuticals*, 89-100. doi:10.1002/9780470277676.ch6

P. (n.d.). Vitamins and Dietary Supplements in the US (pp. 1-12). Euromonitor International. doi:September 2016

Plaintiffs File Appeal in Bayer Probiotic Lawsuit. (2017, June 02). Retrieved November 01, 2017, from https://www.naturalproductsinsider.com/blogs/insider-law/2017/06/plaintiffs file-appeal-in-bayer-probiotic-lawsuit.aspx

Probiotic Advertising Class Actions: Claims Challenged & Lessons Learned. (n.d.). Retrieved November 06, 2017, from https://www.nutraceuticalsworld.com/contents/view_online exclusives/2013-07-22/probiotic-advertising-class-actions-claims-challenged-lessons learned/

Products with Probiotics. (n.d.). Retrieved October 30, 2017, from http://cdrf.org/home/checkoff investments/usprobiotics/products-with-probiotics/

Probiotics come with bold health claims, but science is shaky. (2016, March 09). Retrieved October 30, 2017, from https://www.statnews.com/2016/01/21/probiotics-shaky-science/

Probiotics: In Depth. (2017, January 16). Retrieved October 30, 2017, from https://nccih.nih.gov/health/probiotics/introduction.htm

Rautava, S., Salminen, S., & Isolauri, E. (2008). Specific probiotics in reducing the risk of acute infections in infancy – a randomised, double-blind, placebo-controlled study | British Journal of Nutrition. Retrieved December 03, 2017, from https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/A55DEAB5F3741361F8E33FCFF7589916

Regulations on statements made for dietary supplements concerning the effect of the product on the structure or function of the body. Food and Drug Administration, HHS. Final rule. *Fed Regist. 2000 Jan 6; 65(4):1000-50.*

Runestad, T. (2017). A gut feeling. *Delicious Living*. Retrieved October 10, 2017.

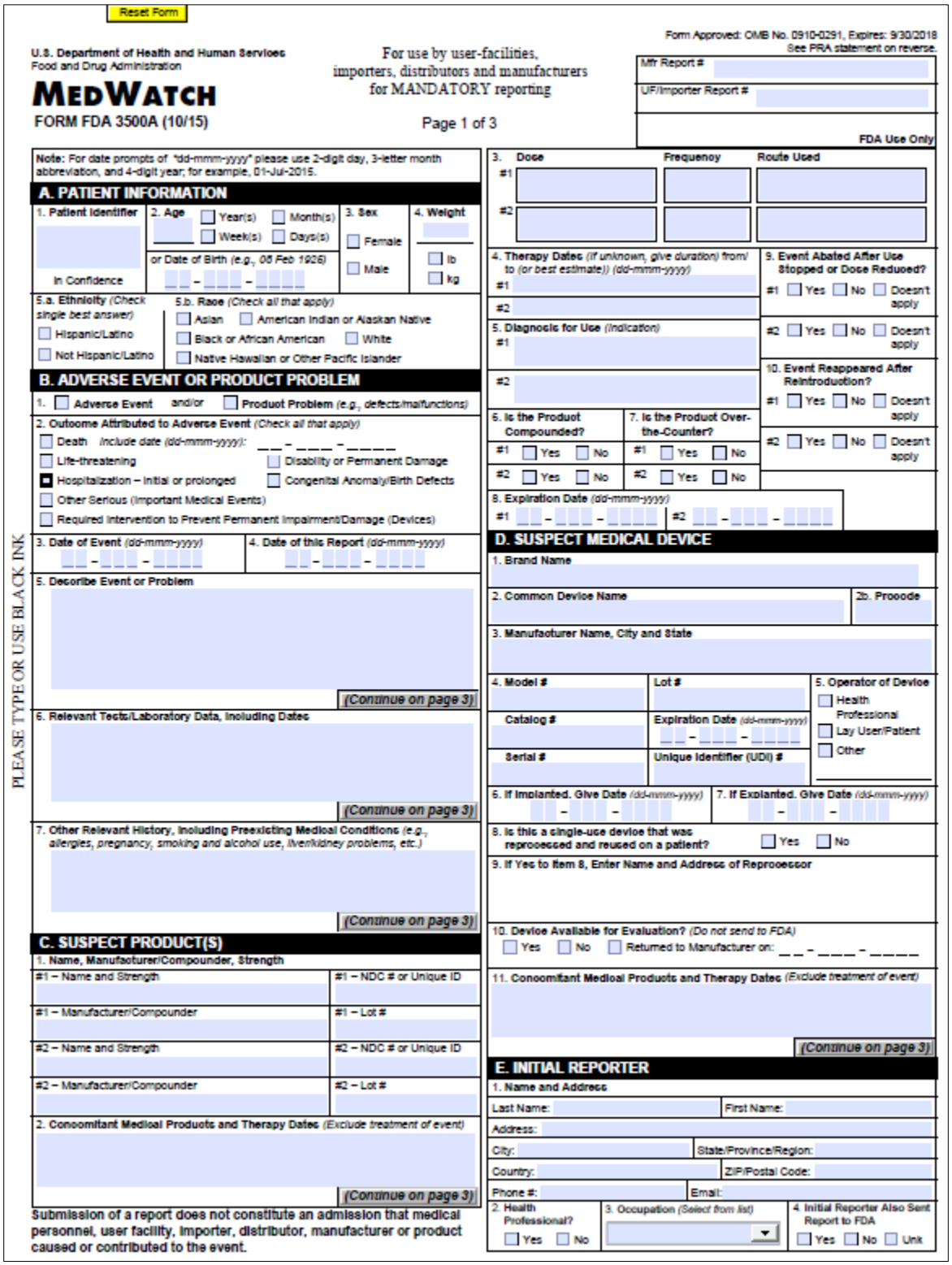
Stopping Deceptive Health Claims. (n.d.). Retrieved November 13, 2017, from http://journals.sagepub.com/doi/full/10.1177/0098858816644715

Venugopalan, V., Shriner, K. A., & Wong-Beringer, A. (2010, November). Regulatory Oversight and Safety of Probiotic Use. Retrieved November 05, 2017, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294522/

Walker, W. A., Goulet, O., Morelli, L., & Antoine, J. (2006). Progress in the science of probiotics: from cellular microbiology and applied immunology to clinical nutrition. *European Journal Of Nutrition*, *45*1-18. doi:10.1007/s00394-006-1101-1

Appendix

Exhibit A



Reset Form

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH
FORM FDA 3500A (10/15)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of 3

Form Approved: OMB No. 0910-0291, Expires: 9/30/2018
See PRA statement on reverse.

Mfr Report #
UF/Importer Report #
FDA Use Only

PLEASE TYPE OR USE BLACK INK

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2015.

A. PATIENT INFORMATION

1. Patient Identifier — In Confidence
2. Age — Year(s) Month(s) Week(s) Days(s) or Date of Birth (e.g., 05 Feb 1926)
3. Sex — Female Male
4. Weight — lb kg
5.a. Ethnicity (Check single best answer) — Hispanic/Latino; Not Hispanic/Latino
5.b. Race (Check all that apply) — Asian; American Indian or Alaskan Native; Black or African American; White; Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Adverse Event and/or Product Problem (e.g., defects/malfunctions)
2. Outcome Attributed to Adverse Event (Check all that apply)
Death Include date (dd-mmm-yyyy): ___ – ____ – _____
Life-threatening
Hospitalization – Initial or prolonged
Other Serious (Important Medical Events)
Required Intervention to Prevent Permanent Impairment/Damage (Devices)
Disability or Permanent Damage
Congenital Anomaly/Birth Defects
3. Date of Event (dd-mmm-yyyy)
4. Date of this Report (dd-mmm-yyyy)
5. Describe Event or Problem
(Continue on page 3)
6. Relevant Tests/Laboratory Data, Including Dates
(Continue on page 3)
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
(Continue on page 3)

C. SUSPECT PRODUCT(S)

1. Name, Manufacturer/Compounder, Strength

#1 – Name and Strength	#1 – NDC # or Unique ID
#1 – Manufacturer/Compounder	#1 – Lot #
#2 – Name and Strength	#2 – NDC # or Unique ID
#2 – Manufacturer/Compounder	#2 – Lot #

2. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
(Continue on page 3)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

3. Dose / Frequency / Route Used
#1
#2
4. Therapy Dates (If unknown, give duration) from/to (or best estimate)) (dd-mmm-yyyy)
#1
#2
5. Diagnosis for Use (Indication)
#1
#2
6. Is the Product Compounded? #1 Yes No; #2 Yes No
7. Is the Product Over-the-Counter? #1 Yes No; #2 Yes No
8. Expiration Date (dd-mmm-yyyy) #1 ___ – ____ – _____ #2 ___ – ____ – _____
9. Event Abated After Use Stopped or Dose Reduced? #1 Yes No Doesn't apply; #2 Yes No Doesn't apply
10. Event Reappeared After Reintroduction? #1 Yes No Doesn't apply; #2 Yes No Doesn't apply

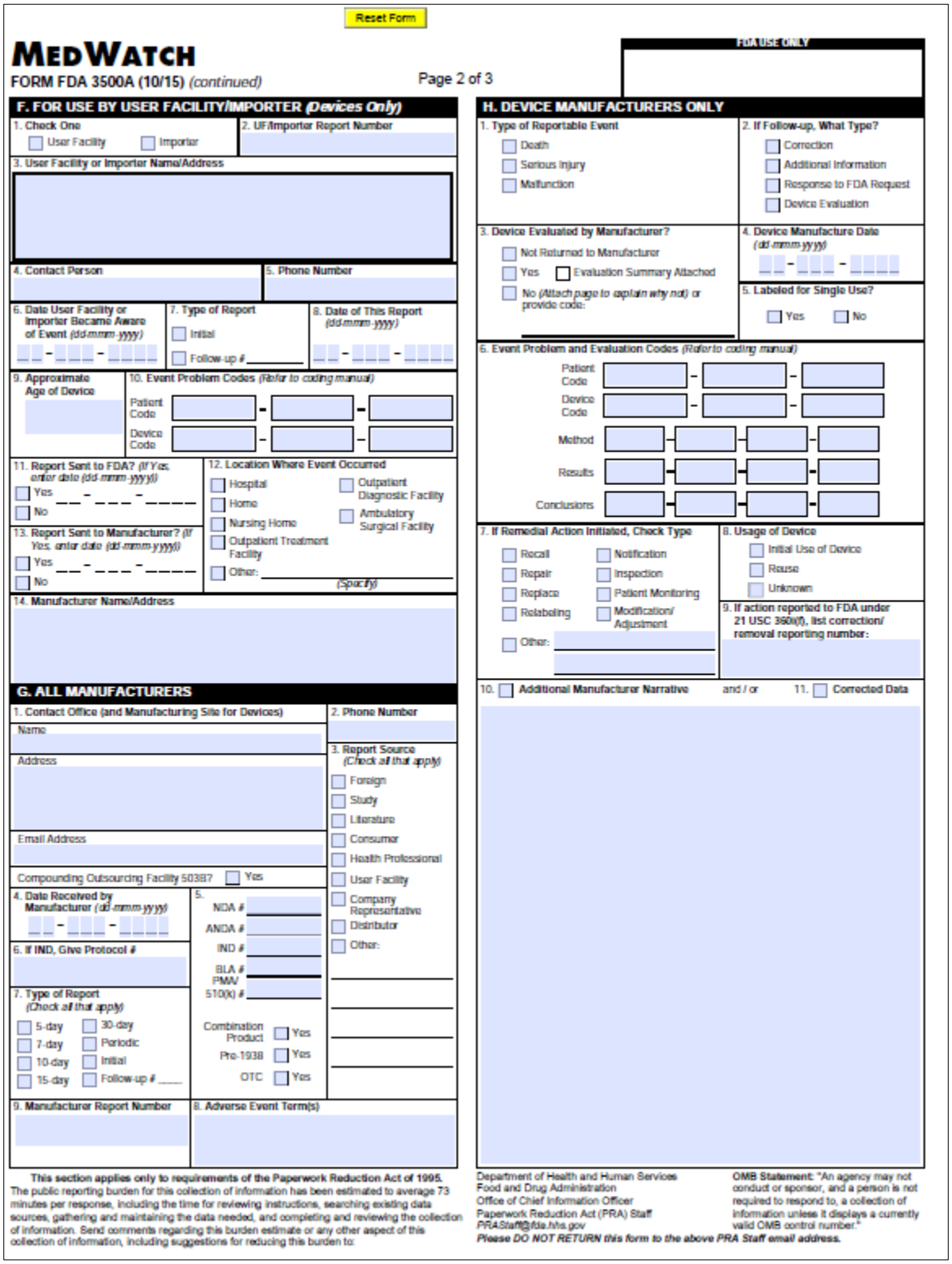
D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
2b. Prooode
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (dd-mmm-yyyy) / Serial # / Unique Identifier (UDI) #
5. Operator of Device: Health Professional; Lay User/Patient; Other
6. If Implanted, Give Date (dd-mmm-yyyy)
7. If Explanted, Give Date (dd-mmm-yyyy)
8. Is this a single-use device that was reprocessed and reused on a patient? Yes No
9. If Yes to Item 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) Yes No Returned to Manufacturer on: ___ – ____ – _____
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
(Continue on page 3)

E. INITIAL REPORTER

1. Name and Address
Last Name: First Name:
Address:
City: State/Province/Region:
Country: ZIP/Postal Code:
Phone #: Email:
2. Health Professional? Yes No
3. Occupation (Select from list)
4. Initial Reporter Also Sent Report to FDA Yes No Unk

Exhibit B



Reset Form

MEDWATCH

FORM FDA 3500A (10/15) *(continued)*

Page 2 of 3

FDA USE ONLY

F. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. Check One: User Facility; Importer
2. UF/Importer Report Number
3. User Facility or Importer Name/Address
4. Contact Person
5. Phone Number
6. Date User Facility or Importer Became Aware of Event *(dd-mmm-yyyy)*
7. Type of Report: Initial; Follow-up #
8. Date of This Report *(dd-mmm-yyyy)*
9. Approximate Age of Device
10. Event Problem Codes *(Refer to coding manual)*: Patient Code; Device Code
11. Report Sent to FDA? *(If Yes, enter date (dd-mmm-yyyy))*: Yes; No
12. Location Where Event Occurred: Hospital; Home; Nursing Home; Outpatient Treatment Facility; Outpatient Diagnostic Facility; Ambulatory Surgical Facility; Other: *(Specify)*
13. Report Sent to Manufacturer? *(If Yes, enter date (dd-mmm-yyyy))*: Yes; No
14. Manufacturer Name/Address

G. ALL MANUFACTURERS

1. Contact Office (and Manufacturing Site for Devices): Name; Address; Email Address; Compounding Outsourcing Facility 503B? Yes
2. Phone Number
3. Report Source *(Check all that apply)*: Foreign; Study; Literature; Consumer; Health Professional; User Facility; Company Representative; Distributor; Other:
4. Date Received by Manufacturer *(dd-mmm-yyyy)*
5. NDA #; ANDA #; IND #; BLA # / PMA / 510(k) #; Combination Product Yes; Pre-1938 Yes; OTC Yes
6. If IND, Give Protocol #
7. Type of Report *(Check all that apply)*: 5-day; 7-day; 10-day; 15-day; 30-day; Periodic; Initial; Follow-up # ____
8. Adverse Event Term(s)
9. Manufacturer Report Number

H. DEVICE MANUFACTURERS ONLY

1. Type of Reportable Event: Death; Serious Injury; Malfunction
2. If Follow-up, What Type?: Correction; Additional Information; Response to FDA Request; Device Evaluation
3. Device Evaluated by Manufacturer?: Not Returned to Manufacturer; Yes; Evaluation Summary Attached; No *(Attach page to explain why not)* or provide code:
4. Device Manufacture Date *(dd-mmm-yyyy)*
5. Labeled for Single Use?: Yes; No
6. Event Problem and Evaluation Codes *(Refer to coding manual)*: Patient Code; Device Code; Method; Results; Conclusions
7. If Remedial Action Initiated, Check Type: Recall; Repair; Replace; Relabeling; Notification; Inspection; Patient Monitoring; Modification/ Adjustment; Other:
8. Usage of Device: Initial Use of Device; Reuse; Unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/ removal reporting number:
10. Additional Manufacturer Narrative and / or 11. Corrected Data

This section applies only to requirements of the Paperwork Reduction Act of 1995.
The public reporting burden for this collection of information has been estimated to average 73 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

Please DO NOT RETURN this form to the above PRA Staff email address.

OMB Statement: "An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Exhibit C

Reset Form

(CONTINUATION PAGE)
For use by user facilities,
importers, distributors, and manufacturers
for MANDATORY reporting

MEDWATCH
FORM FDA 3500A (10/15) *(continued)*

Page 3 of 3

Back to Item B.5

B.5. Describe Event or Problem *(continued)*

Back to Item B.6

B.6. Relevant Tests/Laboratory Data, Including Dates *(continued)*

Back to Item B.7

B.7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)* *(continued)*

Back to Item C.2

Concomitant Medical Products and Therapy Dates *(Exclude treatment of event) (For continuation of C.2 and/or D.11; please distinguish)*

Back to Item D.11

Other Remarks