

Translating the science into efficacy claims on probiotic or prebiotic products in the US market

American Dairy Science Association Annual Meeting
July 13, 2010

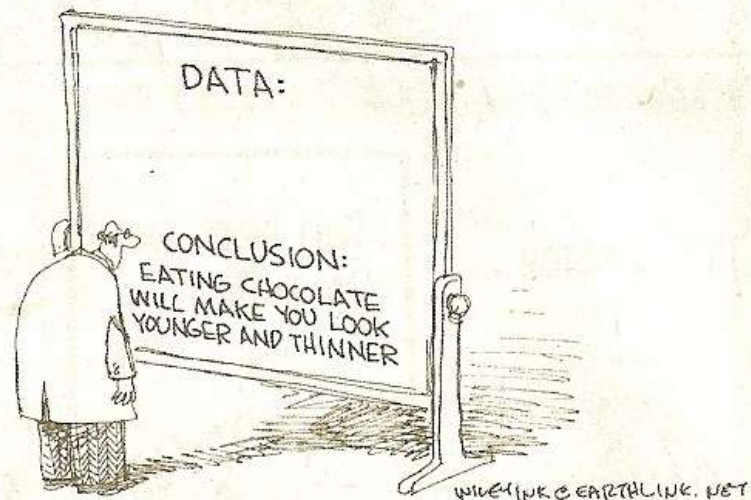
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**Dairy & Food Culture Technologies
Consulting in Science of Probiotics**

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“In the absence of effective regulation, structure/function claims have become one of the most deceptive forms of claims on food labels today.” (part I-4, 2010)

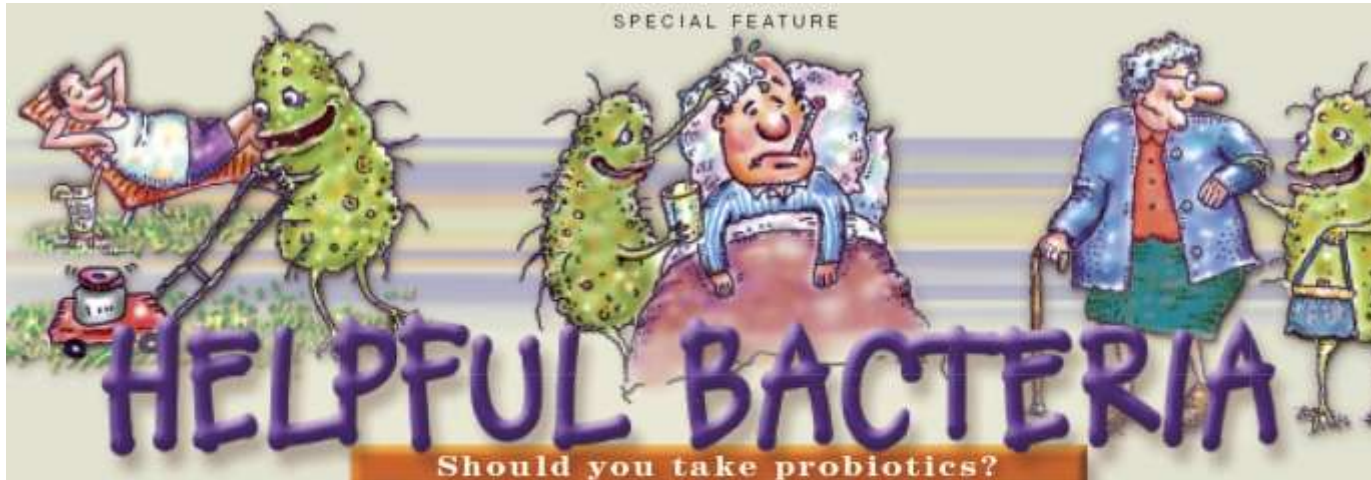


Food Labeling Chaos

The case for reform



CENTER FOR
Science IN THE
Public Interest



BY DAVID SCHARDT

You are not alone. Living on and in your body are trillions of bacteria, a good chunk of them in your gastrointestinal tract. Lay them end to end and they would circle the earth 2½ times.

While the vast majority of those bugs are harmless (the harmful ones are largely disarmed by your immune system), some are beneficial. They may crowd out disease-causing bacteria, for example, or help you digest fiber.

Not surprisingly, some companies have started adding helpful bacteria—called probiotics—to their yogurts, drinks, and supplements.

Are they worth taking?

"We believe that there might be value in adding certain living, non-disease-causing bacteria and other microbes to our diets," says Mary Ellen Sanders, president of the International Scientific Association for Probiotics and Prebiotics. (Prebiotics are ingredients that stimulate the growth of probiotic

Activia Yogurt

What's in it:

Bifidum regularis, Dannon's name for *Bifidobacterium animalis* DN-173 010.

Cost: \$20-\$60 a month for one to three 4-oz. yogurts a day.

Claims: "I'm bloated, irregular," says the young woman in the TV ad. "I eat Activia every day," says her friend. It's "clinically proven to help naturally regulate your digestive system in two weeks," adds the announcer. Sure enough, two weeks later, the young woman feels okay.

Evidence: Dannon can point to no research showing that Activia helps people who are bloated and irregular. The company has funded four studies that gave healthy men and women 4 to 12 ounces of Activia a day.¹⁻⁴ After two weeks, it took, on average, 10 to 30 fewer hours for food to travel from one end of their GI tracts to the other (called transit time).



EFSA activity on probiotic claims

Scientific opinions of the NDA

- ▶ Most claims denied for “insufficient characterization” of the probiotic
- ▶ Claims rejected based on inadequate substantiation that strains used in published studies are equivalent to strains in product
- ▶ Claims rejected based on unclear wording of the claim
- ▶ Remaining claims rejected on lack of demonstration of causality of effect

Inspections, Compliance, Enforcement, and Criminal Investigations

Nestle Healthcare Nutrition, 12/3/09



Department of Health and Human Services

Public Health Service
Food and Drug Administration
College Park, MD 20740

DEC 03 2009

David Yates
President
Nestle HealthCare Nutrition
10801 Red Circle Drive
Minnetonka, Minnesota 55343

WARNING LETTER

Re: CFSAN-OC-10-04

Dear Mr. Yates:

This is to advise you that the Food and Drug Administration (FDA) reviewed your websites at the Internet addresses <http://www.Nestle-Nutrition.com>, www.NestleNutritionStore.com, and <http://www.kidessentials.com> in November 2009. Your BOOST Kid Essentials Nutritionally Complete Drink (Vanilla, Chocolate, and Strawberry flavors) is promoted on your websites as a "medical food," and the labeling claims on your websites represent the product as a medical food for the medical condition of "failure to thrive" and also for "pre/post surgery, injury or trauma, chronic illnesses." As discussed further below, this product is misbranded under Section 403(a)(1) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 343(a)(1)], because the label is false or misleading in that the product is labeled and marketed as a medical food but does not meet the statutory definition of a medical food in the Orphan Drug Act [21 U.S.C. § 360ee(b)(3)] or the criteria set forth in 21 C.F.R. 101.9(j)(8). Furthermore, this product is promoted for conditions that cause it to be a drug under section 201(g)(1)(B) of the Act [21 U.S.C. § 321(g)(1)(B)]. The therapeutic claims on your website establish that this product is a drug because it is intended for use in the cure, mitigation, treatment, or prevention of disease. The marketing of this product with these claims violates the Act.

Specific examples of claims in your product labeling that promote your product as a drug are as follows:

- "[F]or pre/post surgery, injury or trauma, chronic illnesses"
- "Lactobacillus [an ingredient in your product] is one of the most widely studied genera of probiotics, proving numerous health benefits across many illnesses."
- "If your child has stomach problems, such as diarrhea caused by antibiotics, probiotics [an ingredient in your product] may help rebuild a healthy colony of good bacteria ..."
- "Antioxidants [found in your product] ... can help kids fight off sickness at school, the playground, at home, or anywhere on-the-go."
- "Clinical benefits include ... reducing number of days with viral diarrhea, reducing the risk of necrotizing enterocolitis (NEC)"

“...this product is promoted for conditions that cause it to be a drug...The therapeutic claims on your website establish that this product is a drug because it is intended for use in the cure, mitigation, treatment or prevention of disease.”



Can you use a scientific publication with FDA-deemed disease use to market a food or supplement?

In addition, when scientific publications are used commercially by the seller of a product to promote the product to consumers, the use of a citation of a publication or reference in the labeling of a product is considered to be a claim about disease treatment or prevention if the citation refers to a disease use and if, in the context of the labeling as a whole, the citation implies treatment or prevention of a disease..

- "Ivanov L *et al.* Probiotics for the prevention of pediatric antibiotic-associated diarrhea (review). *Cochrane Database Syst Rev* 2007;2: 1-34."
- "Szajewska H *et al.* Probiotics in gastrointestinal diseases in children: hard and no-so-hard evidence of efficacy. *J Pediatr Gastroenterol Nutr* 2006;42(5):454-75."
- "Weizman Z *et al.* Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. *Pediatrics* 2005;115:5-9."

Your product is not generally recognized as safe and effective for the above referenced uses and, therefore, it is also a

January 23, 2008 04:45 PM Eastern Time 

Health Benefits of Dannon Yogurt Exposed as False In Lawsuit Filed by Coughlin Stoia Geller Rudman & Robbins LLP and Mager & Goldstein LLP

Company's Own Studies Disprove Massive Advertising Campaign Fraudulently Touting Health Benefits of Activia and DanActive

LOS ANGELES--([BUSINESS WIRE](#))--An enormously successful marketing campaign promoting the supposed health benefits of "probiotic" yogurt products such as Activia and DanActive helped The Dannon Company, Inc. ("Dannon" or the "Company") sell hundreds of millions of dollars worth of yogurt in recent years. However, a class action filed today in the Central District of California revealed that while spending more than \$100 million to falsely claim that Activia and DanActive have "clinically" and "scientifically" "proven" health benefits not available in other yogurts, Dannon's own studies flatly disproved the Company's deceptive boasts.



FOR IMMEDIATE RELEASE

Dannon Refutes Class Action Lawsuit Alleging Misleading Claims

WHITE PLAINS, N.Y., January 24, 2008 — The Dannon Company, Inc. today provided the response below to a class-action lawsuit filed yesterday in Los Angeles, CA.

Dannon is aware of the lawsuit and we are reviewing it. Dannon proudly stands by the claims of its products and the clinical studies which support them. All of Dannon's claims for Activia and DanActive are completely supported by peer-reviewed science and are in accordance with all laws and regulations. Dannon's advertising has always been and will continue to be absolutely truthful, and Dannon will vigorously challenge this lawsuit.



Dannon pulls 'immunity' claim from probiotic drinks

By Guy Montague-Jones and Shane Starling, 21-Sep-2009

Related topics: Proteins, peptides, amino acids, Gut health, Immune system

Dannon is removing the word "immunity" from its DanActive probiotic drink on-package marketing after concluding an out-of-court settlement last week over alleged misleading probiotic claims.





DANONE

Paris, September 18th 2009

The Danone Company settles the class action filed in January 2008

Following the settlement of the class action lawsuit filed in January 2008, Danone relays the following statement issued today by its American subsidiary, The Dannon Company:

DANNON COMMENTS ON SETTLEMENT OF CLASS ACTION LAWSUIT

White Plains, NY – September 18, 2009 – The Dannon Company, Inc. today announced the settlement of a class action lawsuit filed in January 2008 regarding advertising for its Activia and DanActive products.

Under the settlement, Dannon will make certain changes and enhancements to the labeling and marketing of Activia and DanActive to, among other things, increase the visibility of the scientific names of the unique strains of probiotics that are in each of these products. This information continues to be available on the products' websites, along with the scientific substantiation for the health benefit claims. Dannon also agreed to create a fund of up to \$35 million to reimburse qualified consumers for the cost of buying the products.

"The decision to settle this case is based on the Company's desire to avoid the distraction and expense of litigation and to quickly resume 100 percent focus on making products that provide proven health benefits to millions of highly satisfied consumers. This resolves the plaintiff's concerns while affirming the essence of the claims of Activia and DanActive, which are substantiated by years of scientific research," said Michael Neuwirth, spokesperson for The Dannon Company.

Dannon is also cooperating with the Federal Trade Commission (FTC), which is currently reviewing similar claims. The FTC routinely reviews consumer advertising and Dannon is confident the matter will also be resolved soon.

So there are lots of “eyes” looking carefully at the claims you are making

- ▶ Regulatory agencies
- ▶ Consumer watchdog organizations
- ▶ Marketplace competitors
- ▶ Lawyers
- ▶ Media
- ▶ Healthcare professionals
- ▶ Consumers

Your claims must
measure up against this
scrutiny



Current situation in the US:

- ▶ The FDA has never challenged a probiotic food or dietary supplement for lack of evidence substantiating a properly worded structure/function claim
 - ▶ But if you make a claim that a reasonable consumer would interpret as a claim that your product can cure, treat, prevent, mitigate or diagnose disease – in the eyes of the FDA you are an illegal, unapproved drug.
 - ▶ Also, if you propose research *for public funding* on an endpoint that the FDA considers a disease use, the FDA will require an Investigational New Drug application on file
 - ▶ FDA is not currently distinguishing between research designed to understand the biological activity of a product and your intention to market a product
-

- ▶ The FDA has a strict interpretation of a drug
 - ▶ Reducing the risk of diarrhea in otherwise healthy day care kids – DRUG
 - ▶ Improving the ability of a drug to cure an infection – DRUG
 - ▶ Reducing the risk of developing side effects from antibiotic use – DRUG
 - ▶ Helping manage symptoms of any disease - DRUG

- ▶ FDA has legitimate concern about delayed medical care if symptoms of serious disease are masked by foods used to target disease symptoms
 - ▶ But what about dietary approaches (i.e., foods) for conditions that do NOT present such a risk?
 - ▶ Probiotics and IBS
 - ▶ Probiotics and prevention of GI or respiratory infections in healthy people

▶ **Example:**

- ▶ Clear use of food to help people avoid illness, but would be considered a drug use by FDA



Fermented milk decreases incidence of CIDs in healthy children

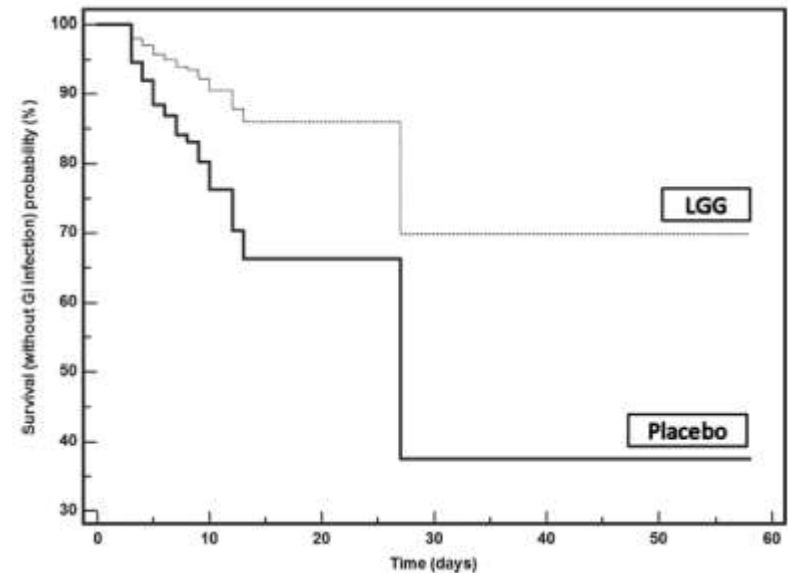
Merenstein et al. 2010. Eur J Clin Nutr. 64(7):669-77.

- ▶ Placebo controlled, double-blinded randomized (by family) controlled trial with allocation concealment
- ▶ Active: DanActive with *L. casei* DN-114 001
- ▶ Placebo: Non-cultured dairy drink
- ▶ N=638 healthy children ages 3-6 in daycare/school 5 days a week
- ▶ Duration: 3 months
- ▶ Primary outcomes as determined by parent diaries
 - ▶ Common infectious diseases (CID)
 - ▶ Change of behavior due to illness
- ▶ Results:
 - ▶ No change in behavior due to illness between active and control groups
 - ▶ ↓ incidence rate for CIDs in the active group by 19% compared to control group



L. rhamnosus GG prevents nosocomial GI and respiratory infections in hospitalized children

- ▶ RDBPC trial
- ▶ 742 hospitalized children
- ▶ *L. rhamnosus* GG at a dose of 10^9 CFU/d in 100 mL fermented milk product
- ▶ Results:
 - ▶ ↓ risk GI infections (NNT 15)
 - ▶ ↓ risk respiratory tract infections (NNT 30)
 - ▶ ↓ risk vomiting episodes
 - ▶ ↓ risk diarrheal episodes
 - ▶ No effect on hospitalization duration



Probability of no GI infection in relation to days of hospitalization

Supplementing the diet with this fermented milk could help these kids avoid additional morbidity
But the FDA views such use a “drug use”

This reflects a disconnect
between the type of research
being done on probiotics and
what the FDA deems within the
scope of food/dietary
supplement use



Requirements for substantiating claims

Product definition

- Microbiological/genomic
- Product matrix

Proper wording of claim

- Endpoint must be beneficial
- Wording must be consistent with countries' legal framework

Demonstrated causal relationship between probiotic and health benefit

- RDBPC trials
- Other evidence?



Example probiotic claims

Regardless of the claim, it must be substantiated

There are no generic probiotic claims

Claim substantiation must be based on a specific strain or combination of strains, dose and bioequivalent matrix



U.S. Regulatory Approach to Probiotics

- ▶ No legal definition of “probiotic” in the US
- ▶ Probiotics regulated on **intention of use**
 - ▶ Conventional foods: nourish generally healthy (or at-risk) population
 - ▶ Dietary supplements: supplement the diet of the generally healthy (or at-risk) population
 - ▶ Medical foods: Food administered under physician guidance to manage a medical condition
 - ▶ Drugs (including OTC): substances to cure, treat, mitigate or prevent disease (healthy or sick populations)
- ▶ Different regulations on labeling, safety and claims for each of these categories



Hierarchy of evidence: the gold standard

- ▶ RDBPC trial
 - ▶ in population that reflects the target population (general population for foods)
 - ▶ using product format and dose equivalent to that being sold (strains, other functional ingredients, delivery format – dried, yogurt, etc)
 - ▶ with endpoint appropriate for product category (normal structure/function of the human body or reduction of risk of chronic, diet related disease)
- ▶ Consistency in results among different studies
- ▶ Published in peer-reviewed journals
- ▶ Appropriately worded claim language that accurately reflects the results



Hierarchy of evidence: often the reality

- ▶ RDBPC trial that has limitations:
 - ▶ In a different target population
 - ▶ In a different product format or dose
 - ▶ With a disease endpoint
- ▶ These studies provide evidence of biological activity, but leave questions about the extent of activity that will be observed under different usage conditions than those used in the study.
- ▶ Such studies are good supportive evidence, but – without sound scientific rationale to the contrary - are not sufficient as primary substantiation of product efficacy



Example: evidence that 10^9 cfu/d Bb-12 can support immune function in adults

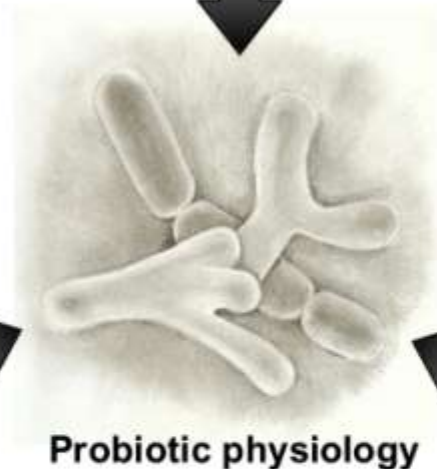
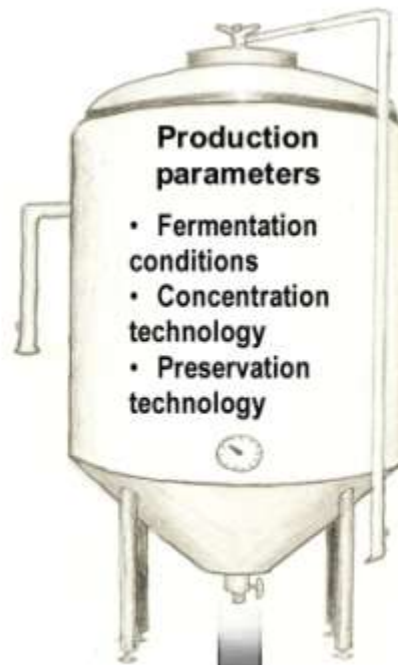
| | # published references |
|--|------------------------|
| Probiotics (minus reviews) | 4,904 |
| Probiotic clinical studies | 806 |
| <i>Bifidobacterium lactis</i> Bb12 | 113 |
| BB12 clinical trial | 35 |
| ...and immune | 17 |
| ...without any additional probiotic strains or prebiotics | 9 |
| ...and at $\leq 10^9$ cfu/d | 4 |
| ...in healthy adults* | 0 |
| *all 4 remaining studies done with either elderly or infants | |



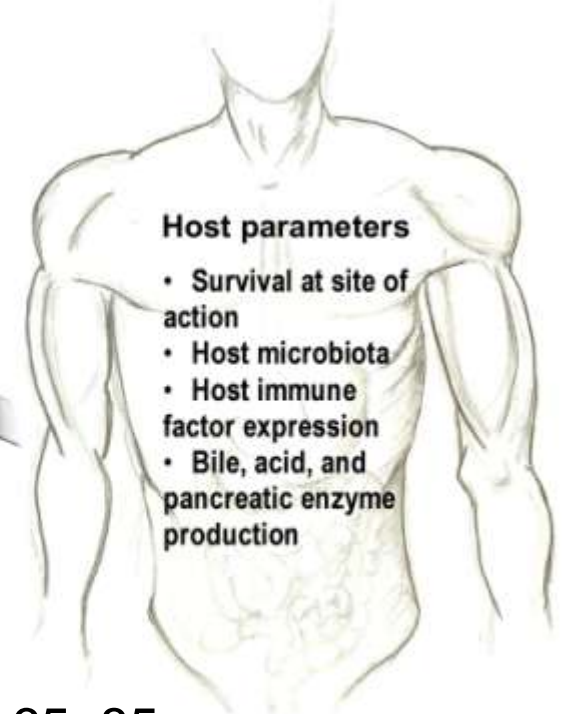
Challenges for research to substantiate claims of health benefit for foods

- ▶ How much – and what types – of evidence is enough?
- ▶ Negative studies or conflicting results
 - ▶ Better to do one properly powered study than several that are underpowered; underpowered studies are at high risk of not disproving your null hypothesis
- ▶ Statistical significance compared to biological meaningfulness
- ▶ Extrapolation from study populations to general populations
 - ▶ It can be difficult to see effects in healthy people
- ▶ Studies should match product as tested with regard to delivery matrix, CFU delivered, number of strains, method to prepare strains
 - ▶ Must develop rationale to demonstrate bioequivalency of different delivery matrices/process conditions
- ▶ Choice of endpoints and placebos
- ▶ Lack of validated biomarkers for “probiotic” endpoints
- ▶ Magnitude of effect may be small
- ▶ Confounders (background diet, host microbiota, placebo effect)
- ▶ Identifying responders/non-responders

Factors that potentially impact probiotic physiology



Probiotic physiology will in turn impact in vivo functionality and stability. The extent to which these factors influence probiotic physiology should be expected to be strain-specific.



How can we navigate probiotic health benefit claims in this regulatory environment?

- ▶ Stay committed to good, basic science
 - ▶ FTC guided by “the amount of substantiation experts in the field believe is reasonable”
- ▶ Push for high standards of evidence for any claim
- ▶ Acknowledge weaknesses in the dataset
- ▶ Craft the wording for your claims carefully
- ▶ Consider ways to nudge regulatory interpretations more favorably toward recognition of the value of foods in prevention and dietary management of disease
- ▶ Recognize that progress in understanding the human microbiome and metabolome will provide