Food Science and Technology | Bulletin

Functional foods in the USA: emphasis on probiotic foods

Mary Ellen Sanders* and James T Heimbach†

*Dairy and Food Culture Technologies, 7119 S. Glencoe Ct., Centennial, CO 80122-2526, USA. Tel. 303-793-9974. Email MES@mesanders.com. Website http://www.mesanders.com

†JHEIMBACH LLC, 4530 Broad Branch Road, NW, Washington, DC 20008, USA. Tel. 202-237-8406. Fax 202-478-0986 fax. Email Jim@jheimbach.com. Website http://www.jheimbach.com

Abstract

The role that functional foods might play in enhancing human health is continuing to develop. Comprehensive approaches, which will enable scientists both to understand the total human physiological response to diet (through application of human genomics and metabolomics) and evaluate health maintenance rather than disease incidence, will advance this field greatly. In the United States, functional foods remain of interest to consumers, although there is currently no legal definition of a functional food. One functional ingredient, probiotics, shows much promise as a health-promoting addition to foods, or as a basis for dietary supplements. A growth industry in the United States, the probiotics industry must develop a proactive policy in order to bolster consumer confidence in commercial probiotic products. Many publications suggest that commercial probiotic products do not comply with label claims. This article seeks to examine probiotics as functional food ingredients and the regulatory framework for labelling and describing the benefits of functional foods, as well as dietary supplements.

Keywords: probiotic, functional food, regulatory, dietary supplement, *Lactobacillus*, *Bifidobacterium*

1. Introduction

Quit worrying about your health. It'll go away.

American humorist, Robert Orben.

There is a fundamental awareness among all cultures that what we eat matters. Unfortunately, the dietary advice received by modern Americans is anything but clear, since emerging science is reported in the media as established fact and public health policy is frequently influenced by politics (Taubes 2001). 'A consistent feature of news about food...has been a lack of context in the reporting of food news, an absence of perspective necessary for consumers to actually make use of the information', states a report by the International Food Information Council (IFIC) regarding US food news coverage (IFIC 2003).

In all fairness, however, making general dietary recommendations to the public today is a difficult undertaking, with the focus for nutrition having shifted from concentration on single nutrient deficiency diseases to sustaining health and preventing chronic disease. German *et al*. (2003) state that 'the importance of diet to health has become even more obvious with the realization that many of life's modern diseases are the results of subtle but chronic metabolic imbalances related in part to diet'. The question of optimal diet is complicated by matters such as food consumption patterns, food synergy, interactions between food components, and the impact of sustaining dietary patterns over the long term. The effect of interventions for all metabolic functions, and not for just a single physiological parameter, is rarely understood. Finally, of paramount importance is the genetic and physiological status of the individual. These issues converge when attempting to assist the public on decisions regarding healthy food choices.

The value of understanding an individual's response to a particular dietary intervention can be clearly illustrated with diets that are low in saturated fat. Such diets have been recommended as part of US public health policy in order (HHS 2004) to reduce the risk of cardiovascular disease (CVD). However, studies have shown that for a significant portion of the public, such a diet can lead to worsening of serum lipid profiles and hence increasing the risk of CVD (Krauss 2001a, 2001b).

Embedded in the discussion of diet and health is the concept of *functional foods*, frequently defined as foods that offer health benefits beyond basic nutrition. Although the term functional foods has no legal definition in the US, it has not deterred the public's interest in the topic. For

Food Science and Technology Bulletin: Functional Foods **1** (8) 1–10
DOI: 10.1616/1476-2137.13616. Published 2 November 2004
ISSN 1476-2137

example, US food news coverage in 2003, as reported in the fifth annual 'Food for Thought' survey carried out by IFIC (IFIC 2003) indicated that, although obesity and weight management stories were most numerous, 11% of all 2003 US food news topics covered functional foods.

The existence of such a term suggests that there are easily defined groupings of foods which can be labelled as functional or non-functional; this is clearly not the case. However, for the sake of this general discussion, we will posit that such distinct groupings exist. A wide range of compounds naturally present in some foods (which can be added to others) has been identified as having compelling effects on health status. Compounds such as fibres, prebiotics, fatty acids, flavonoids, plant stanols and sterols, bioactive peptides, and carotenoids are widely known. One area which is growing in scientific substantiation, commercial potential and public awareness is probiotics. Probiotics have been defined as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' (FAO 2001). The potential, as well as challenges associated with this category of functional food ingredients in the US is the focus of this article.

2. Probiotics – the potential

The evaluation of the role that probiotics may play in human health has been the subject of research for decades. There is no shortage of reviews written on the topic, which focus on the effect of probiotics on regulation of immune function and prevention of infection (Bengmark 2003; Tamboli *et al*. 2003; Gill 2003). Compelling effects in well-controlled studies document the impact of probiotics on reducing conditions such as inflammatory bowel disease (Gionchetti 2003), infectious diarrhoea in infants (Van Niel *et al*. 2002), onset of atopic dermatitis in high-risk infants (Kalliomaki *et al*. 2001, 2003), and control of symptoms associated with lactose intolerance (de Vrese *et al*. 2001). Less dramatic, albeit statistically significant, results have shown the ability of certain probiotic bacteria to decrease the incidence of dental caries (Nase *et al*. 2001), as well as antibiotic use (Hatakka *et al*. 2001), respiratory infections (Hatakka *et al*. 2001) and antibiotic-associated diarrhoea (Cremonini *et al*. 2002). It must be remembered that the benefits reported should be considered specific to the strain(s) used and the levels of viable microbes consumed. Some animal studies have characterized potentially beneficial activities from killed microbes (Rachmilewitz *et al*. 2004), although, by definition, these are not probiotics. The opportunity for probiotics to be genetically modified for a specific function is another area of active research (Steidler 2003).

A welcome improvement in probiotic research is that the rigour of published trials has improved with the application of placebo-controlled, randomized studies, using both well-defined and well-described products. The impact of the disciplines of genomics (the study of the genetic complement of both the human host and the microbes they harbour) and metabolomics (the study of metabolic activity in response to different conditions of both the human host and the microbes they harbour) on probiotic research is also evolving (German *et al*. 2003; Rastall *et al*., submitted).

Clearly, there is an advantage from an efficacy and safety perspective to better define the total human physiological response to any dietary intervention, including probiotics. The large array of beneficial microbe-associated characteristics attributed to the normal gut microbes emphasizes the value of understanding the human response to an externally applied microbe. Native gut microbes have been shown to be involved in immune system development and expression, epithelial cell behaviour, pathogen resistance and barrier effects (Mai and Morris 2004; Hooper *et al*. 2003). How does applying high levels of an autochthonous microbe to the already colonized human GI tract affect these attributes? For example, the effect of probiotics on immune function will be better understood when whole patterns of gene expression response are determined. It is clear that understanding the host-microbe interaction is at the heart of understanding probiotic impact (Hooper *et al*. 2003); such an understanding is possible today by use of animal models. Furthermore, genetic techniques such as terminal restriction fragment length polymorphism (TRF), which enables examination of the impact of probiotics on specific native species of the bacterial community, provides more insight into probiotic effects. With gut microbe-related diseases such as inflammatory bowel disease, antibiotic-associated diarrhoea, or perhaps irritable bowel syndrome, in which no one pathogen has been identified to account for the pathology of each condition, a systems approach to the impact of probiotics on gut microbiota will undoubtedly prove more fruitful.

We are at a time in history when many microbe-influenced situations are considered high priority with regard to public health policy. Circumstances such as the emergence of antibiotic-resistant bacteria, highly virulent foodborne pathogens and viral infections, together with rapid increases in inflammatory and allergic diseases, and the prevalence of ageing populations desiring to live longer healthier lives, have converged. Emerging science suggests that probiotics may play a role in managing such situations (Reid *et al*. 2003), with the potential of this field being reflected by a growing worldwide market for probiotics. Although the US lags behind Europe and Asia in embracing the concept of probiotics, this situation may be starting to change. A survey of US media stories on functional foods indicated that 4% of the stories in 2003 that dealt with functional foods focused on probiotics/prebiotics (IFIC 2003). This suggests a rise in awareness in the US of probiotics and prebiotics, as similar surveys conducted in 1999 and 2001 did not report any stories on this topic. However, the survey showed that improved gastrointestinal health, which is often associated with probiotics, was not featured in the top ten functional foods-related stories reported in the media.

The status of probiotic research is likely to have much in

common with that of other functional food ingredients. Research substantiating the physiological benefits of functional food ingredients is often funded by companies which stand to gain from positive results. Unbiased research generated in multiple, independent laboratories provides stronger support for efficacy. Other challenges include the need to better define mechanisms of action and to formulate products with the most efficacious and stable components. In this way, a final product may be produced which has an acceptable taste and price, is convenient for consumers, and communicates product advantages to them in a fashion that is truthful, does not mislead and complies with regulatory constraints.

The challenge also exists to understand the impact of normal gut microbes and exogenously applied live microbes to the maintenance of health in humans. Food companies which mostly fund applied, efficacy-based research on probiotics, are interested more in enhancing health than preventing disease; this is reflected by the fact that there are no approved probiotic drugs for human use in the US. However, measurement of health remains a challenge in a research system dominated by a disease-based paradigm (German *et al.* 2003).

3. Ensuring the authenticity of probiotic products

In the US, consumers may choose from a plethora of dietary supplements, yoghurts and other dairy products which claim to deliver probiotics. However, in the absence of any unbiased assessment of the quality of these products, consumers have no rational basis for their choice of probiotic product. Useful information would include third party verification of stated levels and types of viable probiotics until the end of the product shelf life. Furthermore, a physiologically meaningful level of probiotics as determined by human studies should be delivered by the product. To address the concerns relating to such commercial probiotic products, some researchers in the scientific community have conducted product surveys.

The number of publications regarding the content of commercial probiotic products is growing. Accurate labelling of the content of a probiotic product is essential; without it, the safety and efficacy of a product cannot be determined. A summary of studies addressing the levels of probiotic bacteria in commercial products (foods and supplements) is shown in Table 1. Generalizations from the studies listed in this table are complicated, since methods differ substantially among papers. However, it is noteworthy that these studies all arrive at the same conclusion – that the actual delivery of probiotic bacteria in many commercial probiotic products does not match the content claim information on their labels with regard to the level and type of probiotics contained. This situation consequently leads to an erosion of confidence in probiotics by health care professionals and consumers.

Conclusions from product evaluations, however, should not be accepted without scrutiny. For example, Huff (2004) reported that none of ten *Lactobacillus* products purchased in lower British Columbia, Canada, met label claims. Methods used were semi-quantitative, with counts estimated using streak plating from growth on blood agar. Although the authors indicate that this method provided 'rough quantitation', no comment is made on the range of error common to this technique. Enumeration of probiotic lactobacilli is usually undertaken using a quantitative dilution to extinction approach, followed by spread plating in duplicate on the surface of MRS agar; plates with 30–300 well distributed colonies are then counted. Although blood agar is considered to be a non-selective medium in the clinical laboratory and is no doubt of use for identifying the presence of lactobacilli associated with bacteraemia, it is not the growth medium of choice for those lactobacilli which have been selected as probiotics. Furthermore, no control strains of lactobacilli were plated using this procedure to ensure the validity of the methods used. Although *Lactobacillus* was not isolated from any of the ten products in this study, this is as likely to be due to use of inadequate methods as poor probiotic product quality.

Methodological problems were also apparent in a study conducted by Berman and Spicer (2003). These authors evaluated 20 dried supplements containing lactobacilli; only one product was found to contain all the microbes listed on the label. Again, a streak plating method was used to generate single colony isolates, which were picked and identified. Enumeration of colonies was not conducted. Again, no positive controls were evaluated to ensure that the different types of microbes present could be recovered using the methods described which probably isolated only the dominant microbes present in the probiotic blends.

Although it is likely that there are many probiotic products on the market that do not meet label claims, research that investigates compliance with such label claims must be based on methods which provide reliable results. Indeed, researchers provide a disservice to the probiotics industry when responsibly formulated products are judged to be inadequate by use of flawed methodology.

Although it is not true that US probiotic products are 'unregulated', it is true that no government authority currently tests or approves such products. Current US food and dietary supplement law stipulates that companies must label products in a truthful and not in a misleading fashion (see 21 USC 343(a)(1)). It is therefore incumbent on industry to adopt procedures which address the issue of eroding consumer confidence in probiotic products.

One option is for companies to submit their products to an independent laboratory for evaluation. This would provide a measure of assurance to consumers that the products are formulated as labelled. Alternatively, efforts are being made to establish meaningful standards or guidelines for probiotic products, as spearheaded by industry, regulatory and scientific groups worldwide (Table 2). Clearly, there is a need for standardized and validated analytical methods for determining the content of probiotic products.

An example of the possible confusion regarding labelling of probiotic products can be seen in yoghurt, which is the

Table 1a. Studies of the content of commercial probiotic products available to consumers

Probiotic product tested	No. of products tested	Country/region of origin of product	Methods used	Results of analysis	References
Lactobacillus supplements, some blended with bifidobacteria	20	-	16S rDNA sequencing; no enumeration of levels	1 out of 20 samples contained microbes that were consistent with product label.	Berman and Spicer 2003
Dried *Lactobacillus acidophilus* supplements	8	-	Plate counts; carbohydrate fermentation	$\leq 10^5$ lactobacilli/g in 4 products; 3 products contained *L. acidophilus*.	Brennan *et al.* 1983
Probiotic supplements	15	-	Selective plating; carbohydrate fermentation	8 products were accurately labelled with regard to their microbial content; 1 product was labelled with the correct amount of bacteria contained in the product.	Canganella *et al.* 1997
Probiotic supplements	9	South Africa	Selective plate count; DGGE	3 out of 9 products contained the correct amount of bacteria, as listed on the label.	Elliot and Teversham 2004
Dry, liquid or dairy products claiming to contain *L. acidophilus*	13	-	Selective plate count with oxgall	3 products contained *L. acidophilus*; 6 contained bile-tolerant lactobacilli $>10^6$/g or ml.	Gilliland and Speck 1977
Probiotic supplements	13	UK	Selective plating; API rapid ID kits	2 out of 13 products met label claims for species present and quantity of microbes contained; 8 out of 13 products were >1 log below the label claim for microbial counts.	Hamilton-Miller *et al.* 1996
Probiotic supplements or food products	52		API rapid ID kits; selective plating	4 out of 11 yoghurt labels declared specific microbes in product, others provided only general descriptions; no mislabelling found in yoghurts; 12 out of 29 UK probiotic supplements were accurate in terms of labelling of microbial content and quantities.	Hamilton-Miller *et al.* 1999

Table 1b. Studies of the content of commercial probiotic products available to consumers (continued)

Probiotic product tested	No. of products tested	Country/region of origin of product	Methods used	Results of analysis	References
Lactobacillus supplements	10	Canada	Semi-quantitative streak method on blood agar	0 out of 10 supplements matched label specifications.	Huff 2004
Probiotic full- and reduced-fat yoghurts with *L. acidophilus*	7 (3 of which also contained bifidobacteria)	Australia	Selective plate count; tested stability during 6 weeks storage	*L. acidophilus* levels varied widely between products ($<10^3$–10^8/g); 1 out of 4 brands had $<10^3$/g bifidobacteria.	Micanel *et al.* 1997
Probiotic yoghurts with bifidobacteria and *L. acidophilus*	50	Australia	Selective plate count	$>10^6$ *L. acidophilus* in 24% of products; $>10^6$ bifidobacteria in 14% of products.	Rybka and Fleet 1997
Probiotic food products	10 (4 dairy, 1 juice, 5 dried)		DNA-based, culture independent analysis; DGGE; culture enrichment	4 did not contain all labelled species.	Temmerman *et al.* 2003
Probiotic products	55 (30 dried supplements, 25 dairy products)	Europe	Selective plate counts	11 out of 30 supplements contained no detectable microbes; 6 out of 55 products were accurately labelled.	Temmerman *et al.* 2003
Supplements	5		Selective plate counts	3 out of 5 supplements met the label claim for species contained; 2 out of 5 products met the label claim for microbe level.	Weese 2002
Dairy products	6		Carbohydrate fermentation study; microtitre colorimetric DNA hybridization	3 out of 6 products were correctly labelled with regard to their bifidobacteria content.	Yaeshima *et al.* 1996

main probiotic food in the US. It is estimated that about 80% of the approximately $3 billion of yoghurt sold in the US each year contains additional bacteria (as well as the required *Streptococcus thermophilus* and *Lactobacillus bulgaricus* starter bacteria). These additional bacteria are added for their beneficial health effects and consist primarily of *L. acidophilus*, but may also be bifidobacteria and some other lactobacilli. Although yoghurt labels disclose the presence of these adjunct microbes, there is essentially no information on the levels, strains or, in the case of *Bifidobacterium*, even species contained in such products. Furthermore, there is little data on product labels regarding the substantiated benefits imparted by the microbes present. In some cases, information relating to the benefits of live cultures can be found on company web sites, although the specific information that consumers need is often lacking. Consumers are therefore unable to derive answers for simple questions which will enable them to assess what benefits might be derived by them or their family members from consumption of a particular yoghurt.

Consumers specifically looking for a source of probiotic bacteria may consequently turn to dietary supplements over foods as their preferred probiotic source. Probiotic supplement products, in general, provide more information to consumers about levels, types of microbes, strain designations and benefits than probiotic-containing foods. However, not all this information has either been substantiated or is accurate.

Table 2. Organizations involved in attempting to establish standards for probiotic bacteria in commercial products

Organization	Website address	Region of impact	Action
Food Agriculture Organization (FAO)/ World Health Organization (WHO)	http://www.fao.org	Worldwide	Developed guidelines for the evaluation of probiotics in foods.
International Dairy Federation	http://www.fil-idf.org	Worldwide	Has begun working on methods to determine certain functional and safety properties outlined in the FAO guidelines for the evaluation of probiotics in food.
European Food and Feed Culture Association	http://www.effca.com	Europe	Developed guidelines for use of probiotics in foods.
Codex Standard for Fermented Milks (Codex Stan 243-2003)	http://www.codexalimentarius.net	Worldwide	Among other composition stipulations, this standard specifies minimum numbers of characterizing and additional labelled microbes in yoghurt, acidophilus milk, kefir, kumys and other fermented milks.
National Yogurt Association	http://www.aboutyogurt.com	USA	Petition under consideration by the FDA which would change the standard of identity of yoghurt, including the requirement of minimum levels of live cultures in yoghurt, but not specifically levels for any additional probiotic cultures.
International Scientific Association for Probiotics and Prebiotics	http://www.isapp.net	Worldwide	Industry Advisory Committee and Board of Directors to consider method validation and establishment of laboratory sites to assess microbiological content of probiotic products.

4. Product labelling claims for probiotic products

Since the status of probiotic products as *functional* foods derives from their ability to provide health benefits, it is clearly necessary that such benefits should be conveyed to the consumer or potential consumer. There are three routes by which food companies can provide such information to consumers: food labelling; advertising; and through third parties. The claims communicated via these routes may be of three types: disease claims; health claims; or structure/function claims. These types of claims are discussed in detail below.

4.1 Prohibited disease claims

In the US, health benefit claims for food products and dietary supplements are tightly controlled by US Food and Drug Administration (FDA) regulations which prohibit any statement that an average consumer might understand as indicating that the product is useful in the cure, prevention, treatment, mitigation, or diagnosis of a disease or disorder (see 21 USC 321(g)(1)(B)). Such claims are regarded as disease claims, or drug claims, and unless the product concerned has a New Drug Application (NDA) on file with the FDA, the claim is deemed to be illegal. The truth or falsity of the claim, and the amount of substantiation available to support the claim, are irrelevant; by making such a claim, the product is considered to be a drug and, without a valid NDA, it is an illegal drug.

This limitation puts out of bounds any claims with regard to several benefits that have been demonstrated or suggested in probiotic research studies, such as reduction of the risk of relapse in inflammatory bowel conditions, treatment of infectious diarrhoea in infants, and prevention of atopic dermatitis. Furthermore, the FDA has taken the position that statements are also classed as drug claims if

they suggest utility of the product as an adjunct to therapy, or to treat, prevent, or mitigate against adverse events associated with a therapy for a disease, if such adverse events constitute diseases (see 21 CFR 101.93(g)(2)(vii and ix)). Thus, for example, a claim that a product may be useful in controlling antibiotic-induced diarrhoea would likely be regarded by FDA as an illegal drug claim.

The US Federal Trade Commission (FTC) does not operate under the same laws as the FDA, and consequently advertising is regulated differently from food labelling. Incidentally, 'food labelling' includes not only the food label itself, but also any materials such as brochures, shelf placards, and the like displayed or distributed in association with the product (FTC 2001). The FTC requires only that advertising claims be true, not misleading, and adequately substantiated. In theory, the FTC could allow advertising that included disease prevention or treatment claims for a probiotic-containing food; however, it requires that the adequacy of substantiation for claims must be evaluated based on the potential consequences of conflicting claims, as judged by experts in the field. In this case, such experts would be scientists at the FDA, and the substantiation required would be at least equal to that needed to have the product approved as a drug. Furthermore, the FDA would likely take the advertising claims themselves as demonstrating an intention to position the product as a drug and take measures against it on that basis (FTC 2001).

A third route of providing information to consumers about probiotic products is available. It is possible for a company to sponsor seminars to which physicians in private practice have been invited. At these seminars, it is permitted to present and discuss the science supporting the use of specific probiotic microorganisms in the prevention or clinical management of disease. The physicians in turn may provide direct counselling to their patients, including suggesting the use of probiotic food products.

4.2 Health claims

The Nutrition Labelling and Education Act (NLEA) of 1990 established one class of claims, health claims, as being a specific exception to the prohibition against disease-related claims for food products or ingredients (see 21 USC 343(r)). Health claims may only be used in labelling of a food or dietary supplement after they have been reviewed and authorized by the US FDA. The law defines a health claim as a statement that 'characterizes the relationship of any nutrient or other substance in a food to a disease or health-related condition' (from 21 USC 343(r)(1)(B)). However, the FDA's implementation of the law is more restrictive, taking the position that the only type of relationship that is appropriate for such health claims is a reduction in the risk of contracting a disease or health-related condition by a member of the currently healthy population. Thus, for instance, the FDA is unlikely to authorize any health claims relating to reduction of the likelihood, frequency or severity of recurrence of episodes such as those characterizing Crohn's disease, irritable bowel syndrome, or gastro-oesophageal reflux disease. Nor, of course, will it accept any claims of treatment or mitigation of these diseases as legitimate health claims.

Use of such health claims may be possible for probiotic products, assuming that adequate substantiation of the claim is available. If a probiotic product can be shown to lessen the risk of developing gastro-oesophageal reflux disease, for example (rather than mitigate recurrences), this could be used as a possible health claim. Similarly, reduction in the risk of developing colon cancer, if adequately demonstrated, is a feasible health claim, as is reduction in the likelihood of developing certain allergies.

The burden of proof that is required for the FDA to authorize a health claim is a high one: there must be *significant scientific agreement* regarding the validity of the claim. According to the FDA (FDA/CFSAN 1999) , meeting this level of significant scientific agreement requires a sufficient body of evidence that shows consistency across different studies and researchers, thus ensuring that:

- A change in the dietary intake of the substance will result in a change in a disease endpoint
- The validity of the relationship is not likely to be reversed by new and evolving science, although the exact nature of the relationship may need to be refined.

Because this required level of proof is so high, many individuals have argued that American consumers are deprived of useful information that could be provided by health claims that include appropriate disclaimers disclosing the lack of certainty of the scientific evidence available to support the claims.

This point of view found voice in a 1999 decision by the US Court of Appeals for the DC Circuit, *Pearson versus Shalala* (see 164 F.3d 650 (DC Cir. 1999)) in which the court determined that under the First Amendment, the FDA could not prohibit health claims unless they were inherently incapable of being rendered non-misleading. The court indicated that 'inherently misleading' claims might be those that have less evidence supporting them than evidence against them.

In response to this judgment, the FDA introduced an interim policy in 2003 of permitting *qualified health claims* — claims supported by the *weight of the available evidence* or, in a later formulation based on another adverse court decision, claims supported by *credible evidence*, but do not meet the standard of significant scientific agreement. These claims are authorized by the FDA only with appropriate qualifiers regarding the strength of the scientific evidence, ranging from 'there is little scientific evidence supporting this claim' to 'although there is scientific evidence supporting this claim, the evidence is not conclusive'. A number of qualified health claims have been approved under this interim policy, although to date none have been approved for probiotics (US FDA/CFSAN 2002).

The type of claim eligible for consideration as a qualified

health claim is the same as for unqualified health claims, i.e. it must deal with reduction in the risk of a disease or health-related condition among the healthy population. Cure, mitigation, and treatment claims remain illegal drug claims; this cannot be remedied by any form of disclaimer or qualification.

4.3 Structure/function claims

The benefits of a functional food product or dietary supplement may be also communicated to consumers in the form of *structure/function claims*, which are statements describing the effect of the food or ingredient on the structure or function of the body, or which describe the mechanism by which the effect is produced (US FDA/CFSAN 2004) While a structure/function claim may not state or imply any effect on a disease or disorder, this limitation is not as restrictive as it may at first appear. Structure/function claims often promise to assist in maintaining positive health that is the opposite of a disease or disorder. For example, a claim to cure or mitigate osteoarthritis is a drug claim; a claim to reduce the risk of developing arthritis would be a health claim; and a claim to help maintain healthy joints is a structure/function claim. The distinctions between different types of claims can be extremely small. For example, maintenance of sexual *potency* is a drug claim because impotence is considered a disease, but maintenance of sexual *performance* is an acceptable structure/function claim.

The only regulatory requirement for a structure/function claim is that the claim be true and not misleading; however, the FDA has never expanded on what this means in terms of the substantiation required. Generally, most observers agree that the standard is set lower for structure/function claims than for even qualified health claims. One clear difference is in the body of research that must be available since structure/function claims may be based on mechanistic and other animal studies, *in vitro* testing, epidemiological data and ethnomedical experience, and a variety of types of human data. In evaluating the evidence base for health claims, on the other hand, the FDA regards only human studies as fundamental data; indeed, a health claim petition is unlikely to be approved if it lacks multiple well-executed randomized controlled intervention trials or prospective observational cohort studies with consistent findings between studies.

Listed below are several claims that might be contemplated for a probiotic that impacts immune function:

- Helps maintain a healthy immune system
- Strengthens the body's natural defences
- Promotes production of cytokines
- Improves the body's immune response to attack
- May help protect your family against colds
- Helps provide protection against infection
- Reduces the severity of viral diarrhoea.

The first two of these, if supported with appropriate animal and/or mechanistic data, are likely acceptable structure/function claims since they describe the effect of the product on a function of the body. The following two are also probably acceptable structure/function claims, if supported by appropriate mechanistic data, because they describe the mechanism by which the product operates to produce a beneficial effect. The next two statements (or revisions of them) might form an acceptable basis for health claims, but there would clearly have to be a number of well designed and well executed clinical studies, in a variety of populations and with a variety of strains of target bacteria and viruses, showing both statistically and physiologically meaningful reductions in risk. The final statement is a drug claim and would not be approved under any circumstances.

5. Conclusions

Probiotics are a growing component of the functional foods industry in the US. The need for research to confirm physiological benefits, identify mechanisms of action and develop the technology to improve delivery of products that are attractive to the consumer is paramount. Although the broad impact of microbes on human physiology ensures that there is no shortage of potential targets for investigation into probiotic-mediated effects, the probiotics industry must be careful to recognize the importance of truthful communication about these effects to both consumers and health care professionals in order to assure growth, rather than disillusionment, in the budding US probiotics industry.

6. References

Bengmark, S. 2003. Use of some pre-, pro- and synbiotics in critically ill patients. *Best Practice and Research Clinical Gastroenterology*. **17**(5):833-848.

Berman, S. and Spicer, D. 2003. Safety and reliability of *Lactobacillus* supplements in Seattle, Washington (A Pilot Study). *Internet Journal of Alternative Medicine*. **1**(2). Available at http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijam/front.xml

Brennan, M., Wanismail, B. and Ray, B. 1983. Prevalence of viable *Lactobacillus acidophilus* in dried commercial products. *Journal of Food Protection* **46**:887-892.

Canganella, F., Paganini, S., Ovidi, M., Vettraino, A.M., Bevilacqua, L., Massa, S. and Trovatelli, L.D. 1997. A microbiological investigator on probiotic pharmaceutical products used for human health. *Microbial Research* **152**:171-179.

Cremonini, F., Di Caro, S., Nista, E.C., Bartolozzi, F., Capelli, G., Gasbarrini, G. and Gasbarrini, A. 2002. Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea. *Alimentary Pharmacology and Therapeutics* **16**(8):1461-1467.

de Vrese, M., Stegelmann, A., Richter, B., Fenselau, S., Laue, C. and Schrezenmeir, J. 2001. Probiotics -- compensation for lactase insufficiency. *American Journal of Clinical Nutrition* **73**(2 Suppl.):421S-429S.

Elliot, E. and Teversham, K. 2004. An evaluation of nine probiotics available in South Africa, August 2003. *South*

African Medical Journal **94**(2):121-124.

Federal Trade Commission (FTC). 2001. Dietary supplements: an advertising guide for industry. Available at http://www.ftc.gov/bcp/conline/pubs/buspubs/dietsupp.htm

Food and Agriculture Organization (FAO). 2001. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. *Report of a joint FAO/WHO expert consultation on evaluation of health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria*. Cordoba, Argentina, 1—4 October.

German, J.B., Roberts, M.-A. and Watkins, S.M. 2003. Genomics and metabolomics as markers for the interaction of diet and health: lessons from lipids. *Journal of Nutrition* **133**:2078S-2083S.

Gill, H.S. 2003. Probiotics to enhance anti-infective defences in the gastrointestinal tract. *Best Practice and Research Clinical Gastroenterology* **17**(5):755-773.

Gillilland, S.E. and Speck, M.L. 1977. Enumeration and identity of lactobacilli in dietary products. *Journal of Food Protection* **40**:760-762.

Gionchetti, P., Amadini, C., Rizzello, F., Venturi, A., Poggioli, G. and Campieri, M. 2003. Probiotics for the treatment of postoperative complications following intestinal surgery. *Best Practice and Research Clinical Gastroenterology* **17**(5):821-831.

Hamilton-Miller, J. M. T., Shah, S. and Smith, C.T. 1996. "Probiotic" remedies are not what they seem. *British Medical Journal* **312**:55-56.

Hamilton-Miller, J. M. T., Shah, S. and Winkler, J.T. 1999. Public health issues arising from microbiological and labeling quality of foods and supplements containing probiotic microorganisms. *Public Health and Nutrition* **2**:223-229.

Hatakka, K., Savilahti, E., Ponka, A., Meurman, J.H., Poussa, T., Nase, L., Saxelin, M. and Korpela, R. 2001. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *British Medical Journal* **322**(7298):1327.

Hooper, L.V., Midtvedt, T. and Gordon, J.I. 2002. How host-microbial interactions shape the nutrient environment of the mammalian intestine. *Annual Review of Nutrition* **22**:283-307.

Huff, B.A. 2004. Caveat emptor. "Probiotics" might not be what they seem. *Canadian Family Physician* **50**:583-587.

International Food Information Council (IFIC). 2003. Food for thought V. Reporting of diet, nutrition and food safety 1995—2003. Available at http://www.ific.org/research/upload/FFTVFullReport.pdf

Kalliomaki, M., Salminen, S., Arvilommi, H., Kero, P., Koskinen, P. and Isolauri, E. 2001. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* **357**:1076-1079.

Kalliomaki, M., Salminen, S., Poussa, T., Arvilommi, H. and Isolauri, E. 2003. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* **361**:1869-1871.

Krauss, R.M. 2001a. Dietary and genetic effects on low-density lipoprotein heterogeneity. *Annual Review of Nutrition* **21**:283-295.

Krauss, R.M. 2001b. Atherogenic lipoprotein phenotype and diet-gene interactions. *Journal of Nutrition* **131**(2):340S-343S.

Mai, V. and Morris, J.G Jr. 2004. Colonic bacterial flora: changing understandings in the molecular age. *Journal of Nutrition* **134**(2):459-464.

Micanel, N., Haynes, I.N. and Playne, M.J. 1997. Viability of probiotic cultures in commercial Australian yogurts. *Australian Journal of Dairy Technology* **52**:24-27.

Nase, L., Hatakka, K., Savilahti, E., Saxelin, M., Ponka, A., Poussa, T., Korpela, R. and Meurman, J.H. 2001. Effect of long-term consumption of a probiotic bacterium, *Lactobacillus rhamnosus* GG, in milk on dental caries and caries risk in children. *Caries Research* **35**:412-420.

Rachmilewitz, D., Katakura, K., Karmeli, F., Hayashi, T., Reinus, C., Rudensky, B., Akira, S., Takeda, K., Lee, J., Takabayashi, K. and Raz, E. 2004. Toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis. *Gastroenterology* **126**(2):520-528.

Reid, G., Sanders, M.E., Gaskins, H.R., Gibson, G.R., Mercenier, A., Rastall, R., Roberfroid, M., Rowland, I., Cherbut, C. and Klaenhammer, T.R. 2003. New scientific paradigms for probiotics and prebiotics. *Journal of Clinical Gastroenterology* **37**(2):105-118.

Rybka, S. and Fleet, G.H. 1997. Populations of *Lactobacillus delbrueckii* ssp *bulgaricus, Streptococcus thermophilus, Lactobacillus acidophilus* and *Bifidobacterium* species in Australian yoghurts. *Food Australia* **49**:471-475.

Steidler, L. 2003. Genetically engineered probiotics. *Best Practice and Research Clinical Gastroenterology* **17**(5):861-876.

Tamboli, C.P., Caucheteux, C., Cortot, A., Colombel, J.F. and Desreumaux, P. 2003. Probiotics in inflammatory bowel disease: a critical review. *Best Pract and Research Clinical Gastroenterology* **17**(5):805-820.

Taubes, G. 2001. Nutrition. The soft science of dietary fat. *Science* **291**(5513):2536-2545.

Temmerman, R., Pot, B., Huys, G. and Swings, J. 2003a. Identification and antibiotic susceptibility of bacterial isolates from probiotic products. *International Journal of Food Microbiology* **81**(1):1-10.

Temmerman, R., Scheirlinck, I., Huys, G. and Swings, J. 2003b. Culture-independent analysis of probiotic products by denaturing gradient gel electrophoresis. *Applied Environmental Microbiology* **69**(1):220-226.

US Department of Health and Human Services (HHS). 2004. Choose a diet that is low in saturated fat and cholesterol and moderate in total fat. Available at http://www.health.gov/dietaryguidelines/dga2000/document/choose.htm#lowfat

US Food and Drug Administration/Center for Food Safety and Applied Nutrition (US FDA/CFSAN). 2001. Guide for industry. Significant scientific agreement in the review of health claims for conventional foods and dietary supplements. Available at http://www.cfsan.fda.gov/~dms/ssaguide.html

US Food and Drug Administration/Center for Food Safety and Applied Nutrition (US FDA/CFSAN). 1999. Guidance for industry: qualified health claims in the labeling of conventional foods and dietary supplements. December 2002. Available at http://vm.cfsan.fda.gov/~dms/hclmgui2.html

US Food and Drug Administration/Center for Food Safety and Applied Nutrition (US FDA/CFSAN). 2004. Label claims: structure/function claims. Available at http://vm.cfsan.fda.gov/~dms/labstruc.html

Van Niel, C.W., Feudtner, C., Garrison, M.M. and Christakis, D.A. 2002. *Lactobacillus* therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics* **109**(4):678-684.

Weese, J.S. 2002. Microbiological evaluation of commercial probiotics. *JAVMA* **220**:794-797.

Yaeshima, T., Takahashi, S., Ishibashi, N. and Shimamura, S. 1996. Identification of bifidobacteria from dairy products and

evaluation of a microplate hybridization method. *International Journal of Food Microbiology* **30**(3):303-313.

About the authors

Mary Ellen Sanders is a consultant in the area of probiotic microbiology, providing services such as support for new product development, coordination of efficacy substantiation efforts, GRAS assessment, and assisting with communications efforts on probiotics. She has worked with FAO/WHO, the International Dairy Federation, and the Federal Drug Administration on pressing issues in the science of probiotics. She currently serves as President of the International Scientific Association for Probiotics and Prebiotics.

James Heimbach is President of JHeimbach LLC Food and Nutrition Consulting. He has national and international experience in a broad range of issues regarding food and nutrition policy, as well as food consumption behaviour, assessment of dietary intakes of nutrients, food additives and contaminants, safety evaluation of food and dietary supplement ingredients (including GRAS determinations and NDI notifications) and food regulation.