Establishing Standards for Probiotic Products: ISAPP's Role

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Background

Despite existing initiatives (Table 1), problems related to the quality of commercial probiotic-containing products abound. At least fourteen peer-reviewed papers have been published (Table 2) evaluating commercial probiotic-containing products. All conclude that such products do not adequately meet label requirements. Some arrive at this conclusion from results generated by questionable methods, but others accurately reflect a less-than-ideal situation regarding meeting label claims, responsible formulation and labeling of probiotic-containing products. Problems exist in the following areas:

1. The number of live microbes of each strain delivered through the end of shelf life is often not accurately reflected on the label;
2. Microbes contained in the product are not always named in accordance with scientifically valid nomenclature;
3. Claims of efficacy are not always adequately substantiated; and
4. Use of the term 'probiotic' on labels of products with no established record of a physiological (health) benefit in humans.

A broad range of probiotic products are marketed. Most are orally consumed, but some are delivered vaginally, rectally, applied to the skin or used as mouth or throat washes or lozenges. Formats for products include foods, supplements, over-the-counter drugs or prescription drugs. Microbes that are used in these products include a yeast, *Saccharomyces*, and bacteria of at least 6 different genera, dozens of species and many different strains.

The regulatory situation worldwide for these products is incoherent and established methods for assaying probiotic products are not consistent. Although a scientifically recognized consensus definition of the term 'probiotic' was established by an FAO Expert Consultation (http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf), the term is misused on products that lack a minimum of studies validating efficacy. Acceptance and enforcement worldwide of a "Standard of Identity" for use of the term 'probiotic' would go a long way toward bolstering consumer confidence when purchasing probiotic products, building a strong foundation for a growing industry and informing the legislation for claims.

The problems seem obvious. Less clear are the appropriate steps to address the problems. The following are some actions taken by ISAPP to address these issues.

Standard of Identity for the Term 'Probiotic'

ISAPP board members are engaged in discussion with a representative from FAO to determine if a Codex standard of identity can be developed. It is anticipated that any standard of identity would stipulate minimum criteria that a product would need to meet in order to use the term 'probiotic' on its label. Closely following the FAO Guidelines (http://www.fermented-foods.net/wgreport2.pdf), the minimum criteria would be:

1. Safe;
2. Microbiologically defined;
3. Impact on human health or physiology documented by at least one controlled study in humans of suitable size and statistical power to be considered valid by experts in the field;

4. Product labels accurately indicate the genus, species and strain of all contained types of microbes according to nomenclature accepted by the microbiological community as indicated in the Approved List of Bacterial Names (www.bacterio.cict.fr);
5. Product labels accurately indicate per serving or per dose levels of each probiotic microbe contained in the product through the end of shelf life; and
6. Any efficacy statements made on product labels or in promotional materials or websites are truthful and not misleading and are based on scientifically valid studies.

Standards for Probiotic Products

Even with the adoption of a Standard of Identity for probiotic-containing products, there is value in stipulating methods for assaying levels of probiotics in products. US Pharmacopeia (www.usp.org) would be one organization with the infrastructure and the competency to take on such a task. These standards would be voluntary standards and, at least at the start, would likely be developed on a case-by-case basis for products submitted by individual manufacturers. ISAPP representatives have met with USP to discuss this option, with a report posted on the ISAPP website (www.isapp.net). Currently, no probiotic standards are in effect.

USP has different programs that may be of interest to manufacturers. Compliance with USP standards can be indicated on a product label with the "USP" seal. In addition, manufacturers could participate in a through USP Verification Program. Under this program, compliance with standards is verified by USP-sponsored testing. Products in compliance can display a "USP Verified" seal. This program includes establishing guidelines by USP expert committees, review of manufacturing documentation, audit of manufacturing sites for GMP compliance, laboratory testing of product samples, and continuous off-the-shelf tests.

Worldwide there are likely other organizations that can perform this function. But certainly, a system whereby manufacturers can confirm that their products are certified by an independent, recognized third party would be very useful to consumers.

Table 1. Efforts relevant to establishing standards for probiotic bacteria in commercial products

Organization	Region of Impact	Action
Food Agriculture Organization/World Health Organization (www.fao.org)	Worldwide	Developed guidelines for the Evaluation of Probiotics in Food
International Dairy Federation (www.fil-idf.org)	Worldwide	Established a Joint Action Team on establishing methods to determine certain functional and safety properties of probiotics in food, as stipulated in the FAO guidelines for the evaluation of probiotics in food
European Food & Feed Culture Association www.effca.com/anglais/pages/id_links.htm)	Europe	Developed guidelines for use of probiotics in foods
Codex Standard for Fermented Milks (Codex Stan 243-2003) (http://www.codexalimentarius.net/more_info.asp?id_sta=400)	Worldwide	Among other composition stipulations, this standard specifies minimum numbers of characterizing and additional labeled microbes in yogurt,

		acidophilus milk, kefir, kumys and other fermented milks
National Yogurt Association (www.aboutyogurt.com)	US	Petition under consideration by the FDA which would change the standard of identity for yogurt, including requiring minimum levels of live cultures in yogurt, but not specifically levels for any additional probiotic cultures

Table 2. Studies of content of commercial probiotic products available to human consumers

Products tested	Results	Methods Used	Reference
20 lactobacillus supplements, some blended with bifidobacteria	1 of 20 contained microbes consistent with product label	16S rDNA sequencing; no enumeration of levels	Berman and Spicer 2003
8 dried 'L. acidophilus' supplements	10^5 or less lactobacilli/g in 4 products 3 contained L. acidophilus	Plate count Carbohydrate fermentation	Brennan et al. 1983
15 supplements	8 were accurately labeled for species; 1 contained labeled levels of all bacteria.	Selective plating Carbohydrate fermentation	Canganella et al. 1997
9 South African supplements	3 of 9 products contained labeled bacteria	Selective plate count DGGE	Elliot and Teversham 2004
13 dry, liquid or milk products claiming 'L. acidophilus'	3 contained *L. acidophilus*; 6 contained bile tolerant lactobacilli $>10^6$/g or ml	Selective plate count with oxgall	Gilliland and Speck 1977
13 UK supplements	2 of 13 met label claim for species and level; 8 of 13 >1 log below label claim for count.	Selective plating API rapid ID kits	Hamilton-Miller et al. 1996
52 supplement or food products	4 of 11 yogurts declared specific microbes in product, others provided only general descriptors; No mislabeling found in yogurts; 12 of 29 UK supplements content and levels OK.	API rapid ID kits Selective plating	Hamilton-Miller et al. 1999
10 Canadian lactobacillus	0 of 10 matched label specifications	Semi quantitative streak method on	Huff 2004

supplements		blood agar	
4 brands Australian probiotic yogurt in full and reduced fat with L. acidophilus (3 also contained bifidobacteria)	*L. acidophilus* levels varied widely between products ($<10^3$ – 10^8/g); 1 of 4 brands had $<10^3$/g bifidobacteria	Selective plate count Tested stability over 6 week storage	Micanel et al. 1997
50 Australian yogurts with bifidobacteria and L. acidophilus	$>10^6$ *L. acidophilus* in 24% $>10^6$ bifidobacteria in 14%	Selective plate count	Rybka and Fleet 1997
10 products (4 dairy, 1 juice, 5 dried)	4 did not contain all claimed species (DNA-based analysis)	DNA-based, culture independent analysis, DGGE; Culture enrichment;	Temmerman et al. 2003a
55 European probiotic products (30 dried supplements; 25 dairy products)	11 of 30 supplements contained no detectable microbes; 6 of 55 products contained all claimed microbes.	Selective plate counts	Temmerman et al. 2003b
5 supplements	3 of 5 met label claim for species and 2 met claim for levels.	Selective plate counts	Weese 2002
6 dairy products	3 of 6 products were correctly labeled with bifidobacteria	Carbohydrate fermentation study Microtiter Colorimetric DNA hybridization	Yaeshima et al. 1996
9 health food products	6 improperly labeled	Molecular typing	Zhong et al. 1998

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