Generic and Product-Specific Health Claim Processes for Functional Foods across Global Jurisdictions¹⁻³

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Abstract

Worldwide consumer interest in functional foods and their potential health benefits has been increasing over the past 10 y. To respond to this interest, regulatory bodies have developed guidelines for assessing health claims on functional foods. The objective of this article is to investigate the type and amount of evidence needed in various jurisdictions on a worldwide basis to substantiate both generic and product-specific health claims. Two types of health claims were examined using separate case studies. Analysis of generic health claims was highlighted by (n-3) fatty acids and their relation to heart health; whereas examination of product-specific health claims was conducted using probiotics and their association with gastrointestinal well-being. Results showed a common core for use of convincing high-quality human data, especially in the form of randomized controlled trials (RCT), but there was significant variability in the type and amount of scientific evidence needed to substantiate health claims, both generic and product specific, across different jurisdictions. Product-specific claims tended to use human RCT as the main basis for claims, whereas generic claims tended to base their statements on a wider spectrum of literature. J. Nutr. 138: 1228S–1236S, 2008.

Introduction

Health claims on foods impart benefits to stakeholders including regulatory bodies, industrial manufacturers, and consumers as well as to research institutions and scientists. For regulatory bodies, health claims provide a means to protect consumers from misleading or unsubstantiated information on product labels. For the food industry, health claims and nutrition labeling enable communication of health benefits of a food or food ingredient to consumers, which can also provide a strategic competitive advantage. It has recently been suggested that consumers would be 10–26% more likely to consume products with proven health claims, which may translate to a 20% increase in sales (1). In turn, health claims tend to help consumers make better food choices and gain a deeper understanding of diet-disease relations (2). Research institutions and scientists also benefit from conducting research on foods and their effects on health stimulated by the ability to develop and utilize health claims.

In response to the growing interest in functional foods by consumers and food industries, regulatory bodies in a number of countries have developed policies governing issuance of health claims for foods over the past 10 y (3–13) (Table 1). Such policies permit structure-function and risk reduction claims, both generic and product specific, to be implemented under these various legislative environments. Generic health claims are defined by the International Life Sciences Institute as claims based on a consensus within the scientific community regarding a well-established, generally accepted diet-disease or diet-health relation (14). In contrast, product-specific health claims are those that imply that a given food product possesses certain positive physiological effects when that specific entity is consumed in realistic amounts (14).
The level of evidence required to permit a given health claim differs markedly across various regulatory bodies; thus, it is possible that a health claim that is permitted in 1 country may be prohibited in another. Additionally, the degree of evidence required for generic vs. product-specific claims varies, posing challenges for international manufacturers wishing to launch a given product possessing a specific health claim across different countries. To better understand how much and what type of evidence is required to substantiate a health claim, the objective of this article is to investigate the extent of evidence required by various national food agencies for establishment of both generic and product-specific claims.

Case studies were used to investigate types and levels of evidence required to obtain a generic and product-specific health claim existing for different agencies. For generic health claims, the relation of (n-3) fatty acids and cardiovascular disease (CVD) was investigated. For product-specific claims, the linkage between probiotics and gastrointestinal well-being was examined. These examples are presented as 2 separate case studies, and the similarities and differences of the 2 types of health claims are discussed.

Methods utilized in comparison of data across agencies

In 2006, Alcimed (Paris, France), an independent research agency, analyzed the existing data concerning functional food definitions, organizations dealing with functional foods, regulatory contexts, as well as recommendations and practices for the preparation of scientific dossiers supporting health claims (15). Information was obtained by contacting national food agencies and internet searches. From this search, regulatory bodies with approved generic health claims on (n-3) fatty acids and CVD and product-specific health claims on probiotics and gastrointestinal well-being were identified; and when scientific dossiers were available, these were obtained, and bibliographic references were extracted. Subsequently, an analysis grid was created to summarize key scientific evidence from the primary human intervention studies identified in the scientific dossiers. Type and quality of references used by different national food agencies for their health claim submissions were then compared.

### Analysis grid for evaluation of scientific evidence

Information required to support a valid scientific claim was extracted and assembled within a matrix grid that included 1) study design, i.e., whether the design was considered appropriate to answer the research question posed; 2) subject characteristics, i.e., whether the study group was representative of the target group; 3) intervention, i.e., whether treatment, dose, and duration of consumption were clearly defined; 4) regimen, i.e., background diet, vehicle, and frequency of consumption; and 5) results, assessed as whether endpoint markers were appropriate and what information they provided.

### Assessment of scientific quality of studies used to support intended claims

Two grading systems were established to rate the quality of the studies. The first used was a star system to identify the type of study design, where 4 stars corresponded to a randomized, placebo-controlled, double-blind trial, 3 stars identified a randomized, placebo-controlled but not double-blinded study, 2 stars were designated for a randomized study with a defined control group but no placebo, and 1 star was given for a study that was not randomized and had no defined control group.

A second grading system was used to evaluate whether the key criteria to support the research were achieved taking into consideration study groups and characteristics, duration and dose, matrix, compliance, statistical power, and side effects. The following quality symbols were then allocated to each trial, a positive rating (+) was assigned to studies where all criteria were addressed in manuscript, a neutral rating (Ø) was given to studies where most but not all criteria were clearly defined, whereas a negative rating (–) was given if key information was missing regarding study design.

### Case study 1: Generic health claims for (n-3) fatty acids

**Background on (n-3) fatty acids.** (n-3) fatty acids are defined as polyunsaturated fatty acids in which the first double bond is positioned 3 carbons distal from the methyl end of the carbon chain (16). Many studies have shown that long-chain, C20–C22, (n-3) fatty acid consumption provides health benefits in preventing CVD (17–20). Benefits for cardiovascular health include antiarrhythmia (21,22) and improvement of lipid profiles, particularly in decreasing circulating triglyceride levels (23,24). Based on the level of evidence purporting the positive influences of (n-3) fatty acids, agencies from several countries have accepted health claims regarding (n-3) fatty acid consumption and cardiovascular health benefits (8,12,13).

### Generic health claim dossiers for (n-3) fatty acids and CVD available for assessment

In the search for jurisdictions currently allowing health claims related to (n-3) fatty acids and CVD, 6 national agencies were identified. Of these agencies, 2 allowed product-specific claims for (n-3) fatty acids and cardiovascular health, and 1 allowed a generic 2-step claim on (n-3) fatty acids from fish and risk of CVD, which made reference to their official national nutrition recommendations. The 3 remaining agencies established a generic health claim for (n-3) fatty acids and CVD based on specific reports (Supplemental Table 1). These national agency reports were obtained for evaluation. As described above, references used to support the above health claims were then extracted from the reports, and primary human clinical trials were further extracted for analysis.

### Analysis of official dossiers of (n-3) fatty acids and CVD generic health claims

Agency A fell short of recommending...
Fish intake in clinical studies

GISSI-Prevenzione

Burr et al. (27) X X
Marchioli et al. (26) X X

using 8 references whereas another used as many as 43 references.

bibliographic evidence varied among agencies with 1 agency C used only journal articles for their report. The range of total including both books and journal articles. Meanwhile, agency ranging from books and theses to proceedings and journal articles. Meanwhile, agency C used only journal articles for their report. The range of total bibliographic evidence varied among agencies with 1 agency using 8 references whereas another used as many as 43 references.

Analysis of all available dossiers revealed that all 3 agencies used a majority of journal articles as the basis for their scientific reports in establishing their (n-3) fatty acid generic health claim (Supplemental Table 2). Agency A utilized a variety of references ranging from books and theses to proceedings and journal articles. Similarly, agency B selected a mixture of references including both books and journal articles. Meanwhile, agency C used only journal articles for their report. The range of total bibliographic evidence varied among agencies with 1 agency using 8 references whereas another used as many as 43 references.

Human studies chosen by agencies A and B were mostly well conducted randomized controlled trials (RCT) and large cohort studies. Although agency C referred to fewer studies, these also included a blend of large RCT and cohort studies as well as a case-control and a meta-analysis. All agencies had some overlap with each other in references used for establishing their generic health claim (19,25–28), with an article by Bucher et al. (19) used by all agencies (Table 2).

The quality of the clinical trials used by agency A ranged from one-third of trials considered to be very well conducted studies, i.e., double-blinded, placebo-controlled, and randomized, 4-star rating, to studies that were conducted with less rigor and/or from which substantial information was missing, 1- or 2-star rating. Meanwhile, half of the clinical studies used by agency B were highly rated, i.e., 4 stars, whereas the other half ranked in the 1- to 3-star range. All 3 clinical studies used by agency C were rated as 2-star studies because they either were not double-blinded or did not have a placebo control group (Supplemental Table 3).

Scientific dossiers for all agencies analyzed clinical data from healthy populations as well as populations with CVD and/or showing risk factors for developing CVD, e.g., high blood lipid levels. In examining the benefits of (n-3) fatty acid intake on coronary heart health, most of the studies used (n-3) fatty acid supplements with subjects who had recently experienced a myocardial infarction or were diagnosed with angina, with dosages ranging from 100 mg/d to 6 g/d of (n-3) fatty acids across agencies (Table 3). All agencies also used at least 1 study that examined (n-3) fatty acid intake via other means such as, fish consumption with a recommendation of oily fish twice/wk or α-linolenic acid (ALA)-rich diets, with ALA dosages ranging from 1.8 g/d to 6.3 g/d. All agencies included multiple long-term studies.
with follow-up of up to 9 y, although there were also some short-term studies that were less than 1 mo in duration (Table 3).

Discussion of (n-3) fatty acids and CVD generic health claim analysis. Agencies A, B, and C based generic health claims for (n-3) fatty acids and cardiovascular health mostly on secondary prevention in individuals with established cardiovascular problems and used a variety of types of studies of which ~70% showed efficacy mostly in hard endpoints such as decreased risk of myocardial infarction or death as well as markers such as blood lipids (Table 3).

Challenges for (n-3) fatty acid health claims. Challenges remain regarding approval of generic health claims for (n-3) fatty acids. One important confounding issue is that cardioprotective benefits vary depending on the type of (n-3) fatty acid consumed. Plant sources of (n-3) fatty acids such as ALA may not be as effective as animal-source (n-3) fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Although some studies including the Lyon Heart Study (34) and the Indian Experiment of Infantar Survival Trial (36), have suggested that ALA may have cardioprotective benefits, other studies including the Mediterranean Alpha-Linolenic Enriched Groningen Dietary Intervention study (35) and the Norwegian Vegetable Oil Experiment (49) have not demonstrated a benefit from ALA consumption. Similarly, a systematic review by Wang et al. (50) recently showed that (n-3) fatty acids given in the form of fish or fish oil supplements, but not ALA, were able to improve CVD outcomes, including all-cause mortality, cardiac and sudden death, and possibly stroke. Stable isotope studies have shown that <10% of consumed ALA is converted to EPA and that an even smaller amount, 4% of ALA, is converted to DHA (51). Perhaps the low conversion of ALA to EPA and DHA may explain why less significant health benefits have been seen in experiments using ALA; however, more studies need to be performed to discover if there is a potential for ALA to have similar cardioprotective effects as EPA and DHA.

Agency B specifically mentions consumption of EPA and DHA in their generic claims, whereas agencies A and C refer to (n-3) fatty acids in general.

The safety of (n-3) fatty acid sources has also been a concern and may affect consumers’ willingness to purchase and consume foods containing these bioactive components. The main concerns regarding safety are whether the potential presence of toxins including mercury and polychlorinated biphenyls can adversely affect consumers and/or diminish the cardioprotective effect of the (n-3) fatty acids. A recent review investigated the risks and benefits of fish consumption and concluded that benefits of fish intake for reducing the risk of CVD and total mortality outweigh potential risks of exposure to mercury and polychlorinated biphenyls (52).

Conclusions regarding (n-3) fatty acids and CVD generic health claim analysis. Agencies A, B, and C used a combination of references ranging from RCT to cohort studies to meta-analyses. All agencies focused on EPA and DHA intake trials; however, some references regarding ALA intake were used as part of the scientific dossier submitted in application for a generic (n-3) fatty acids health claim. Previous reports have mentioned concern about potential contaminants from fresh fish or tainted supplements; however, it appears that the benefits of (n-3) fatty acid intake outweigh the risks. Agencies worried their generic health claims to address either maintenance of heart health or good cardiovascular function, or reduction in the risk of coronary heart disease. It is of interest to note that some experimental data are obtained from individuals with diseases; nevertheless these data have been extrapolated to support health-related claims in the population at large.

Case study 2: Product-specific health claims with probiotics as an example

Background on probiotics. Probiotics are defined as “live microorganisms when administered in adequate amounts that confer a health benefit on the host” (53). Different probiotics have been ascribed many potential health benefits with much research focused on their beneficial effects on gastrointestinal health, including relieving symptoms of irritable bowel syndrome (IBS) (54–58), improvement of intestinal flora and function (59–62), and potential benefits on inflammatory bowel diseases such as pouchitis, Crohn’s disease, colitis (63–65), and antibiotic-associated diarrhea (66–69).

Product-specific health claim for probiotic and gastrointestinal well-being available for assessment. In searching jurisdictions allowing probiotics with product-specific health claims, 6 national food agencies were identified. Only 2 of these agencies had scientific dossiers readily available for examination, with agencies D and E having 3 and 2 products, respectively, approved for a product-specific health claim (Supplemental Table 4). As previously described in the general methodology section, references were then extracted from the reports, and from these references primary human clinical trials were further analyzed.

Analysis of official dossiers of probiotic and gastrointestinal well-being product-specific health claims. Agency D states how much of the product is required to qualify for the proposed health claim and, in Product 2, provides how much probiotic bacteria can be found within that product. Similarly, labeling for agency E must include how much of the product needs to be consumed to obtain the claimed effects (Supplemental Table 4). Analysis of the various scientific dossiers submitted for product-specific health claims for probiotics shows that most claims are based on scientific journal references (Supplemental Table 5). Agency D used scientific substantiation consisting of clinical trial data, reviews, meta-analyses, some animal studies, and a few reports, whereas agency E solely used clinical trial support for their scientific dossiers. Probiotic scientific dossiers for product-specific health claims vary among agencies, with the total number of references in a dossier ranging from 3 to 39.

The publications used by agency D varied in rating with some clinical trials being assigned a 4-star rating, whereas quite a few others were given only a 1- or 2-star rating. For all agency D products, at least 40% of studies were deemed to be 4-star rated. Agency E had few clinical studies, but all studies were well designed and conducted and were all given 4-star ratings. All agencies had at least 2 clinical studies rated 4 stars to support their health claim (Supplemental Table 6).

All scientific dossiers used studies that focused on the specific probiotic bacteria seeking the health claim. In most cases the dosage of the bacteria ranged from study to study within a collective dossier (Table 4). The duration of the studies was also quite varied, ranging from a few days to more than half a year depending on the functional benefit (Table 4).

Discussion of probiotics and gastrointestinal well-being product-specific health claim analysis. Agencies D and E permit product-specific health claims for certain probiotics in relation to gastrointestinal health ranging from IBS symptoms to general gut microbiota improvement. Dossiers for the products primarily involved clinical trials specifically targeting the strain.
of probiotic seeking health claim approval; however, general reviews and reports were also used for a larger overview of probiotic efficacy. For all products, at least 80% of the RCT studies used in the scientific dossiers showed a gastrointestinal benefit from the probiotic intake (Table 4). Although a few other agencies were found to currently have probiotic products carrying a health claim, it should be noted that scientific dossiers are not easily obtained from all agencies for public domain, and thus, only 2 agencies were examined for this case study.

**Challenges for probiotics health claims.** Although several product specific health claims exist for probiotics, the issue is complicated by the many strains and subspecies that claim a specific benefit, thus generating a multitude of scientific dossiers. The health effects of probiotics appear to demonstrate strain specificity. Canani et al. (109) recently investigated 3 different probiotic strains in children with acute diarrhea and found that *Lactobacillus rhamnosus* GG and a mix of 4 strains significantly reduced the duration of diarrhea, as well as, the daily number of stools, whereas other probiotic strains failed to produce an effect. In another study, Martini et al. (110) reported that people with lactose maldigestion showed improvements in lactose digestion when given yogurts, but some other fermented milks with various strains and species of lactic acid bacteria were less or not at all efficient. All yogurts had a beneficial effect on lactose digestion, as did *Lactobacillus bulgaricus*-enriched milk.

Please refer to the accompanying article in this supplement by Farnworth (111), which presents a more in-depth discussion regarding probiotics and the various challenges in establishing health claims for probiotics and the state of probiotics health claims.

**Conclusions regarding probiotics and gastrointestinal well-being product-specific health claim analysis.** Agency D used a mixture of clinical trials, reviews, reports, and some animal trials in compiling their scientific dossier for their specific probiotic product health claim, whereas agency E solely used clinical trials for their dossiers. Most references focused, as expected, specifically on the strain of probiotics seeking health claim approval, especially for clinical trials. General reviews and reports on probiotics were also submitted for a larger overview of probiotic health benefit potential.

There are convincing examples of jurisdictions reviewing scientific evidence and concluding on the basis of at least 2 human RCT that the specific strains submitted were eligible for a valid claim.

**Conclusions from case studies: common themes and differences.** As shown in the 2 case studies, the process involved in securing a health claim, whether generic or product specific, requires substantiation with strong scientific evidence. In examining the substantiation used to establish claims, there are differences as well as similarities in establishing generic and product-specific health claims. There are also similarities and differences among agencies. There was a consensus among all agencies that data from well-designed clinical intervention trials are needed to support a health claim, whether generic or product specific.

In the example of a generic health claim supporting (n-3) fatty acids and cardiovascular health benefit, long-term studies, with cohort studies including up to 9 y of follow-up, were used to provide convincing scientific evidence. Meanwhile, for the product-specific health claims supporting specific probiotics and gastrointestinal well-being, shorter-term studies were enough to provide convincing evidence reflecting the impact of probiotics on gastrointestinal functions. However, we cannot derive conclusions from this limited set of examples because the generic health claim addressed a long-term disease risk, whereas the product-specific claim addressed short-term effects on a normal function.

Also, generic health claim scientific dossiers tended to use a greater variety of reference materials than product-specific health claims. For example, agencies A, B, and C incorporated many sources of references, including human clinical trials, in vivo and in vitro studies, as well as case-control studies and cohort studies, to support their generic health claim. Meanwhile, agency E used solely human clinical trials for their product-specific health claims, and agency D used some additional sources of reference materials including animal trials, reviews, and reports. The usefulness of in vivo and in vitro studies is also a matter of debate. Some agencies consider that these studies provide useful supporting information, as they provide information on mechanisms.

### Table 4 Breakdown of probiotics strain, dose range, and study duration from clinical trial references from scientific dossiers of agencies D and E for probiotics and gastrointestinal well-being product-specific health claims

<table>
<thead>
<tr>
<th>Agency/product</th>
<th>Dose</th>
<th>Duration</th>
<th>Clinical studies, n (references)</th>
<th>Studies showing a benefit from probiotics intake, n/total (n%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D/1</td>
<td>$10^8$–$10^{10}$ of <em>Bifidobacterium animalis</em></td>
<td>10 d to 2 wk</td>
<td>7 (70–76)</td>
<td>4/5 (80%) shorten colonic transit time</td>
</tr>
<tr>
<td>D/2</td>
<td>$10^5$–$10^7$ of <em>Lactobacillus GG</em></td>
<td>5 d to 7 mo</td>
<td>24 (77–100)</td>
<td>19/22 (86%) can help to support barrier function in various conditions</td>
</tr>
<tr>
<td>D/3</td>
<td>$10^8$–$10^{10}$ of <em>Lactobacillus casei</em></td>
<td>3 d to 4 wk</td>
<td>5 (101–105)</td>
<td>5/5 (100%) improve bowel movements and support balanced gut microbiota</td>
</tr>
<tr>
<td>E/1</td>
<td>$10^2$ of <em>Lactobacillus plantarum</em> 299v</td>
<td>3–4 wk</td>
<td>3 (106–108)</td>
<td>3/3 (100%) helps to alleviate symptoms of intestinal gas in IBS patients</td>
</tr>
<tr>
<td>E/2</td>
<td>$10^7$–$10^{10}$ of <em>Lactobacillus GG</em>, <em>Lactobacillus rhamnosus</em> &lt;br&gt; Lc705, <em>Propionibacterium freudenreichii</em> ssp. &lt;br&gt; Shermani JS, and <em>Bifidobacterium</em> strain</td>
<td>5–6 mo</td>
<td>4&lt;sup&gt;1&lt;/sup&gt; (56, K. Kajander, E. Myllyluoma, S. Kyönpalo, M. Rasmussen, A. Ristimäki, H. Vapaatalo, R. Korpela, unpublished data)</td>
<td>2/2 (100%) effective in reducing IBS symptoms</td>
</tr>
</tbody>
</table>

1. Two clinical trials were not included in the calculation of colonic transit time shortening: 1 was regarding bacterial community; the other was regarding GI survival of bacteria.
2. Note that 24 clinical studies were referenced for this health claim submission file, but data on dosage and duration were not available for 1 clinical study, as it was a Japanese language study that had limited data available for extraction; thus, data on dosage and duration of clinical study were available for only 23 clinical studies.
3. Two clinical trials were not included in the calculation of supporting barrier function: 1 was regarding colonization in a dose-response study; the other was a Japanese language study that had limited data available for extraction.
4. Note that 4 clinical trials were referenced in the health claim submission file, with 3 of the papers not yet published; 1 of the unpublished manuscripts had a summary of the dosage and duration of study within the submission dossier, and thus, this information was available for summary here, but dosage and duration information was not available for the other 2 clinical studies and thus, they were not further analyzed in this article.
of action or otherwise help to support the strength of the relation between the ingredient and the physiological effect. Some other jurisdictions consider that only human data can be used to support a health claim.

In terms of clinical study rating, product-specific health claims in agencies D and E had at least 2 clinical trials rated 4 stars. For generic health claims, although agencies A and B had at least 3 clinical trials rated 4 stars, agency C had none.

In conclusion, it is clear that for both types of health claims, generic and product specific, the amount and type of evidence required in substantiation vary widely across jurisdictions, but they have a common core, the need for convincing human data. Two examples were reviewed here, and although this is not enough to achieve a global comparison, it would be worthwhile to conduct a similar analysis in a few years’ time. At a minimum, it seems that human randomized, controlled trials provide the cornerstone for the evolution of product-specific claims, whereas generic claims tend to base their statements on a wider spectrum of literature. Further research in this area is likely to expose the nature of the effects of food on human systems biology and the necessity to redesign RCT methodology that would adequately serve the need to demonstrate the health effects of foods.

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Other papers in this supplement include references (111–120).

Literature Cited
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