



INTERNATIONAL COMPARISON ON THE MANAGEMENT OF HEALTH CLAIMS AND NOVEL FOODS

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1.0 ABSTRACT

Both nationally and internationally, there is a growing recognition of the role of food in health among consumers, regulatory authorities, the food industry, and the scientific community. This awareness has stimulated product innovation, consumer interest in learning of food/health relationships, and the need for a regulated, compliant marketplace. In response to these advancements, regulatory bodies in Australia/New Zealand, Canada, Europe, Japan, and the United States have revised or are in the process of revising scientific requirements and regulatory frameworks for the management of health claims on foods.

Although each jurisdiction has its own definition of a health claim, generally, health claims are a statement or representation (through graphics, brand name, trade name) on a food that states, suggests, or implies that a relationship exists between a food or a component of that food and health or disease risk-reduction. Health claims do not refer to dietary information alone that quantitatively or qualitatively makes reference to the level of a nutrient in a food –*e.g.*, “zero fat” or “high in fibre”. Such claims are referred to as nutrient content claims or nutritional claims. Throughout the report, “health claims” will refer to health claims made on foods – *i.e.*, food health claims.

The management of health claims reflects a country’s level of interest in various factors including health promotion (a reflection of culture); facilitation of trade; economics; enabling food research, innovation and development; enabling industry competitiveness; public health; consumer choice; consumer protection; and civil rights (*e.g.*, freedom of speech). Health claim management is also influenced by the organizational structure and operations of regulatory bodies, which are directly affected by their capacity (human resources) and level of commitment to efficiency and effectiveness of work outputs; accountability to stakeholders and the public; and interest in ensuring transparency of decision-making processes and work outputs.

Scientific requirements for health claim substantiation address three main areas: efficacy, safety, and quality assurance. Although all jurisdictions similarly require efficacy to be addressed in health claim applications, not all require safety and quality assurance to be comprehensively addressed in health claim applications instead opting to use other routes for their assessment, such as novel food, Generally Recognized as Safe (GRAS) or food additive applications.

This report outlines and critically compares the scientific requirements in health claim applications among five jurisdictions (Australia/New Zealand, Canada, Europe, Japan, and the United States) and regulatory processes that guide the review of health claim applications. Recommendations for Canada to improve its health claim application process are also discussed.

Because a comprehensive assessment of safety of a food that is the subject of a health claim may not be included in a health claim application and other routes for its review are used, such as a novel food approval route, novel food requirements are also outlined and compared across jurisdictions.

Overall, Canada's scientific requirements for food health claim substantiation (efficacy, safety, and quality assurance) are adequate and comparable to international standards. The requirements are justified and do not pose unreasonable expectations for the applicant; in fact, they are less rigorous than other jurisdictions' requirements, such as the European Union.

In contrast, Canada's regulatory processes for health claim application reviews are not comparable to international standards. Canada would benefit from a greater commitment towards improved communication with health claim applicants; an accountability to timelines for health claim application reviews; and transparency of processes related to health claim application reviews.

Canada is not unlike other jurisdictions in being challenged by the fast pace of science, technology and food processing. Similar to most other jurisdictions (Australia/New Zealand, European Union, United States), it has not developed specific regulatory frameworks for functional foods with the opinion that the current legislation (Food Acts and Regulations) and regulatory mechanisms (e.g., approval of novel foods) provide sufficient boundaries to ensure a safe and lawful food supply.

2.0 OVERVIEW OF SCIENTIFIC REQUIREMENTS AND REGULATORY PROCESSES FOR HEALTH CLAIM MANAGEMENT IN FIVE JURISDICTIONS

2.1 Australia and New Zealand

2.1.1 Organization and Function of Relevant Regulatory Bodies

Australia (AU) and New Zealand (NZ) have a unified, bi-national agency - *Food Standards Australia New Zealand* (FSANZ) – that is an independent, expert scientific body. It was established under the *Food Standards Australia New Zealand Act* (FSANZ Act) and is responsible for developing and amending food standards (*i.e.*, food regulations) (FSANZ, 2007a, 2007e).

Food standards are mandatory legal requirements for foods sold in AU and NZ, covering food safety and the content and labelling of foods (FSANZ, 2007e). They are developed by FSANZ either by application from any agency, body, or person, or by a proposal of its own initiative (FSANZ, 2007b). In addition to the best available scientific evidence, legislative requirements of the FSANZ Act, government policies, international treaties, economic and social impacts, and risk analyses are considered in the development or amendment of a food standard (FSANZ, 2007a).

To achieve broad community support for their work and public confidence in regulatory decisions, FSANZ collaborates with various stakeholder groups. Consultation with the community is an essential part of FSANZ's decision-making process (FSANZ, 2007a).

FSANZ is comprised of 146 public service employees. Standards or variations to standards are approved by the FSANZ Board which then notifies its decisions to the *Australia and New Zealand Food Regulation Ministerial Council* (ANZFRMC). If ANZFRMC does not request to review a draft standard within 60 days, it is gazetted by FSANZ and automatically becomes law (FSANZ, 2007a).

2.1.2 Relevant Legislation

Food standards appear in the *Australia New Zealand Food Standards Code* (“the Code”) which came into effect December 2000. The Code covers all foods produced and imported into AU and NZ. It is enforced by Australian State and Territory governments and the New Zealand Government through their Food Acts and Regulations; non-compliance with the Code incurs penalties. The process for amending the Code is prescribed in the FSANZ Act. Any agency, body, or person can make an application to vary the Code (FSANZ, 2007b).

In December 2003, ANZFRMC requested that FSANZ propose a new framework for the regulation of Nutrition, Health and Related Claims (FSANZ, 2007e) and established a policy guideline to guide this process (Australia New Zealand Food Regulation Ministerial Council, 2004). The impetuses for a new management system for claims were three-fold and related to consumers and their value of nutrition, health and choice; industry and their interest in a regulatory landscape that enables product development and marketing opportunities; and inconsistency in the marketplace with claims being managed by various regulations or voluntary codes of practice (established by industry) (FSANZ, 2005a, 2007f).

Three consultations were held on FSANZ's proposed management system for nutrition, health and related claims – Standard 1.2.7 – occurring in 2004 (Initial Assessment Report), 2005 (Draft Assessment Report), and 2007 (Preliminary Final Assessment Report) (FSANZ, 2004, 2005a, 2007f). FSANZ anticipates that final recommendations on health claims will be ready for consideration by the Ministerial Council in May 2008.

2.1.3 Profile and Regulation of Health Claims

Currently, nutrient content claims (e.g., “this food is high in fibre”) and some function claims (e.g., “calcium is good for healthy bones and teeth”) are allowed while health claims are prohibited due to Standard 1.1A.2 which prohibits statements that imply the food is slimming or has weight-reducing properties; imply the food has therapeutic or prophylactic action; include the word “health” or similar words as part of the name of the food; give advice of a medical nature; or name a disease or physiological condition. Only one claim, relating folic acid to prevention of neural tube defects, is exempt from this prohibition (FSANZ, 2007c, 2007e).

Standard 1.2.7 is being proposed by FSANZ to revoke Standard 1.1A.2 (FSANZ, 2005a, 2007g). As a consequence, a wider range of health claims will be allowed (FSANZ, 2007c), including claims that mention a physiological condition. See Tables 2.1.3-1 and 2.1.3-2. Unless permitted by the Code, claims will not be allowed to refer to the prevention, diagnosis, cure or alleviation of a disease, ailment, defect or condition, or their symptoms (Australia New Zealand Food Regulation Ministerial Council, 2004). Four claims have been substantiated by FSANZ, relating foods to disease-risk reduction, which will be available for use once Standard 1.2.7 is approved (FSANZ, 2007e). See Appendix A, Table A-1.

Standard 1.2.7 proposes three categories of claims, two of the three categories considered health claims: nutrition content claims; general level health claims; and high-level health claims (FSANZ, 2007g). See Table 2.1.3-2 for a comparison of their definition and scientific requirements for claim substantiation. Unlike high-level health claims that would require pre-approval by FSANZ with an application to vary the Code, nutrition content claims and general level health claims would not; rather, evidence to support their truthfulness would have to be produced by the manufacturer upon request by an enforcement agency (FSANZ, 2005a, 2007c,e,f,g).

Table 2.1.3-1 Definition of a Health Claim in Draft Standard 1.2.7 (FSANZ, 2007g)	
Subject	Definition
Health Claim	A claim that directly or indirectly refers to a relationship between: a food or a property of the food and a health effect ¹ but does not include an endorsement, dietary information or a cause-related marketing statement.
¹ Health effect means – a) a measure of the impact of a substance on the healthy functioning of the human body; or b) a measure of the impact on the health or performance of a specific population, where the impact is associated with a particular dietary intake; and for the purposes of this definition ‘impact’ includes maintenance.	

Table 2.1.3-2 Comparison of Proposed Nutrition Content Claims, General Level Health Claims and High-level health claims in Draft Standard 1.2.7 (FSANZ, 2005b, 2007c, 2007e, 2007g)			
Type of Claim	Description of Claim	FSANZ Approval for Use	Evidence Required to Support Claim
Not classified as health claims			
Nutrition content claims	<p>A claim about the presence or absence of a property of the food, but does not include an endorsement, dietary information or a cause-related marketing statement</p> <p>Statements regarding the amount of a nutrient, energy or a biologically active substance in the food</p>	No	<p>Food manufacturers must hold evidence (<i>i.e.</i>, data from compositional analysis) to show that what is claimed on the label is present in the food; this evidence must be produced on request by enforcement agencies.</p> <p>Nutrient profiling scoring criteria <u>will not</u> apply (See Section 2.1.5)</p>
Classified as health claims			
General level health claims	<p>Refer to a function in the body; modification of a function beyond normal growth and development; performance benefits; well-being; reducing risk or helping to control a <u>non-serious</u> disease or condition (<i>i.e.</i>, does not require consultation/supervision by a health care professional for its management)</p> <p>Do not directly or indirectly refer to a serious disease¹ or a biomarker</p> <p><i>e.g.</i>, “Calcium is good for strong bones and teeth, when consumed as part of a healthy diet containing a variety of foods”</p> <p>“Exercise and a diet high in calcium helps build stronger bones when combined with a healthy diet containing a variety of foods”</p> <p>“Gives you energy, when consumed as part of a healthy diet with a variety of foods”</p> <p>“Yoghurt high in X and Y may reduce your risk of stomach upset, when consumed as part of a healthy diet with a variety of foods”</p>	No	<p>Food manufacturers must hold scientific evidence to substantiate the claim and to demonstrate the quantity of food component required to achieve health effect is present in food; this evidence must be produced on request by enforcement agencies.</p> <p>Evidence for substantiation can be a list of pre-approved nutrient function statements by FSANZ; authoritative, generally accepted information sources/scientific texts/dietary guidelines that are complemented by evidence collection to update the information; or an assessment of totality of evidence using the “Substantiation Framework”² for high-level health claims and meeting a “probable” level of evidence (See footer five in Table 2.1.4-1).</p> <p>Nutrient profiling scoring criteria will apply (See Section 2.1.5)</p>

Table 2.1.3-2 Comparison of Proposed Nutrition Content Claims, General Level Health Claims and High-level health claims in Draft Standard 1.2.7 (FSANZ, 2005b, 2007c, 2007e, 2007g)			
Type of Claim	Description of Claim	FSANZ Approval for Use	Evidence Required to Support Claim
High-level health claims	<p>Refer to reducing risk or helping to control (by reducing risk factors or improving health) a <u>serious</u> disease or condition¹</p> <p>e.g., “This food is high in calcium. Healthy diets high in calcium may increase bone mineral density, which has particular importance for women”</p> <p>“This food is low in sodium. A healthy, varied diet including foods low in sodium may assist in reducing blood pressure”</p>	Yes	<p>An application must be submitted to vary the Code. Once approved, claim can be used by all manufacturers.</p> <p>Substantiation based on assessment of totality of evidence using “Substantiation Framework”²</p> <p>Nutrient profiling scoring criteria will apply (See Section 2.1.5)</p>
<p>¹ Serious disease: A disease, ailment, defect or condition that is not appropriate to diagnose, treat, or manage without consultation/supervision by a health care professional and includes obesity but does not include being overweight (FSANZ, 2007g).</p> <p>² FSANZ’s “Substantiation Framework” (FSANZ, 2005b), described in Table 2.1.4-1, is a guide for applicants of high-level health claims. It discusses a systematic and comprehensive approach to carrying out a critical evaluation of the totality of evidence on a high-level health claim. The framework also describes the substantiation requirements for general level health claims.</p>			

2.1.4 Guidance Documents for Health Claim Substantiation

FSANZ’s *Substantiation Framework – Substantiating Nutrition, Health and Related Claims on Foods* (FSANZ, 2005b), included in FSANZ’s Draft Assessment Report (FSANZ, 2005a), is a guidance document for food manufacturers interested in primarily substantiating high-level health claims although the guidance can also be used to substantiate general level health claims; evidence required to support nutrition content claims is also outlined in the framework. See Table 2.1.4-1.

Claim substantiation pertains primarily to demonstration of efficacy. Information on a food’s safe intake in humans and technical information pertaining to its composition (e.g., quality assurance) are supplied in a novel food application; however, undesirable effects related to food intake, from the literature considered for demonstration of efficacy, are reviewed.

Proof of substantiation (i.e., efficacy) varies depending on whether authoritative reviews or generally accepted information sources exist on the claim of interest. In AU and NZ, other processes exist for the evaluation of safety and quality of foods that are the subject of health claims. An application to vary the Code, pertaining to novel foods, is submitted to FSANZ. It includes meeting information requirements related to safety and quality (FSANZ, 2005b).

FSANZ states that it is not possible to offer guidance on the number of studies to be considered in substantiating a diet/disease relationship and that each relationship will be considered individually (FSANZ, 2005b).

Table 2.1.4-1 Overview of FSANZ's Guidance Provided for Health Claim Substantiation (FSANZ, 2005b)	
Steps	Details
Identifying and categorizing the evidence ¹	<p>Identifying the evidence</p> <p>Develop a search strategy that reflects research topic</p> <ul style="list-style-type: none"> - Key words/terms included and excluded in search - Search limits - Time period searched - Databases searched (search several electronic databases) - Manual searching (references of review articles or research reports; research registers; conference proceedings) - Consult experts in research area to identify evidence potentially missed during search <p>Develop inclusion/exclusion criteria to select relevant studies</p> <p>Scan titles and abstracts for relevance</p> <p>Obtain full reports of relevant studies</p> <p>Count number of relevant studies (<i>i.e.</i>, that met inclusion criteria)</p> <p>Categorizing the evidence</p> <p>Divide evidence into four main categories and quantify number of studies in each category</p> <ul style="list-style-type: none"> - Experimental (intervention) studies (may be useful to subdivide studies according to research design, nature of intervention, population studied) - Observational studies (prospective cohort studies; case control studies) - Systematic reviews - Supporting evidence (chemical, cellular, animal studies; some observational studies – <i>e.g.</i>, case series, population monitoring statistics, cross-population studies)
Assessing and interpreting the evidence ²	<p>Assessment of study quality – general information provided on issues to be considered for quality:</p> <p>Quality of reporting - <i>e.g.</i>, of study purpose, methodology, results, quality control procedures, sample population</p> <p>Identification and description of the diet, food or food component being measured</p> <p>Measure of food or food group consumption (<i>i.e.</i>, dietary recording techniques) and dietary compliance</p> <p>Measure of intake of food component (from all foods and dietary supplements); use of validated techniques if using a laboratory for measurement</p> <p>Bioavailability of food component - <i>e.g.</i>, matrix, chemical form, individual's physiological need or nutritional status, interactions between substances in food, meal or total diet</p> <p>Relevance of studies of components administered in therapeutic form</p>

Table 2.1.4-1 Overview of FSANZ’s Guidance Provided for Health Claim Substantiation (FSANZ, 2005b)	
Steps	Details
	<p>Measure of health-related effect - <i>e.g.</i>, biological and methodological validity of biomarker</p> <p>Sample and measurement bias (in study design and conduct) - <i>e.g.</i>, selection or allocation bias; performance and measurement bias; attrition or exclusion bias</p> <p>Potential confounding variables - <i>e.g.</i>, changes in body mass; exercise; alcohol intake; smoking; changes in macronutrient intakes</p> <p>Inclusion of appropriate controls</p> <p>Study duration - <i>e.g.</i>, sufficient duration to draw conclusions about significance and sustainability of outcome; sufficient lead-in period and/or washouts</p> <p>Sample size and statistical analysis - <i>e.g.</i>, sufficient number of participants in test and control groups to reach confident conclusions of outcome (if related studies, results may be able to be pooled in a meta-analysis); statistical analysis should enable judgement about significance and magnitude of outcome measured (health effect may be significant at a population level but not at an individual level – this does not negate value of study; also, statistically significant results may not have health significance at population level)</p> <p>Assessing animal and cellular studies – <i>e.g.</i>, suitability of animal or cell model; comparability of doses and form of dose to those used in human studies; development stage of animals</p> <p>Assessing systematic reviews – <i>e.g.</i>, clearly stated aim; based on comprehensive search; inclusion/exclusion criteria stated; effect of publication bias; quality and validity of each cited study reviewed; results presented clearly; conclusions supported by data and analysis presented</p> <p>Consideration of findings of individual studies:</p> <p>Characterization of relationship between exposure and outcome – <i>e.g.</i>, identification of food and health outcome; required intake and frequency of intake; food matrix; magnitude of outcome; population group (age, gender, race, socioeconomic status, geographic location, health status)</p> <p>Circumstances under which relationship exists – <i>e.g.</i>, dietary or lifestyle factors</p> <p>Relevance of study to proposed claim and broader population</p> <p>Study type and quality and assessment of weight of study in evaluation of totality of evidence</p> <p>Identification of undesirable effects</p>

Table 2.1.4-1 Overview of FSANZ’s Guidance Provided for Health Claim Substantiation (FSANZ, 2005b)	
Steps	Details
Evaluating the totality of evidence ³	<p>Key matters addressed include:</p> <ul style="list-style-type: none"> - Type of studies - Quality of studies; greater weight placed on higher quality studies - Relationship between type and amount of food and health effect – e.g., causality⁴; intake-response relationship or required intake - Whether health effect of a nature or size that would have population health significance - Dietary patterns, lifestyle patterns, and characteristics of food associated with outcome - Comparability of populations studied to target group - Sustainability of health effect in target population and every-day circumstances - Whether required dietary pattern or intake of food achieved in practice as part of total diet and impact on this consumption pattern - Areas where lack of evidence across studies and impact of these deficiencies - Consistency of findings across study types and across and within populations - Undesirable effects identified and assessed <p>The overall circumstances associated with the food or population studied that must be in place for claimed relationship</p> <p>Overall strength of evidence in support of claim with a rating assigned – convincing, probable, possible, insufficient⁵; approval of high-level health claims likely to require “convincing” evidence</p>
<p>¹ At this stage, no studies should be excluded on basis of design or assumed quality but on their relevance to the topic. It is preferable to have two people apply stated search criteria independently. Letters or comments from researchers critiquing study findings can be used when assessing study quality. Publication of the same study findings in more than one journal paper or of the inclusion of previously published data in the results of a follow-up study should not be recorded as entirely separate studies.</p> <p>² To substantiate a high-level health claim, there must be relevant experimental and/or observational evidence. Well-designed experimental studies (blinded, randomized, placebo controlled) represent highest level of evidence and are likely to be given greatest weight in assessment of totality of evidence. In instances where high quality intervention studies are not available, it is possible that the quantity and quality of observational studies may be sufficient for claim substantiation particularly when evidence is drawn from prospective cohort studies. It is unlikely a claim could be substantiated solely on case control observational studies. Supporting evidence alone is insufficient to substantiate a diet/disease relationship for a proposed high-level health claim.</p> <p>³ Evaluation of totality of evidence recognizes collective strength of different study designs and allows for weaknesses in certain studies to be complemented by strengths in others. This step refers to evaluation of all available data of suitable quality including evidence that supports and does support relationship in question.</p> <p>⁴ Different study designs vary in their ability to show a causal relationship (i.e., consumption of food alters probability of developing a health effect) with experimental studies the most effective at establishing causality. Where only observational studies are available, causality has to be inferred through strength of measured associations. Assessment of causality will assess: strength of association and/or size of effect; independence of association; intake-response relationship; relationship in time; consistency of findings; and as many of the following: reversal of effect; specificity; biological plausibility.</p> <p>⁵ Convincing evidence: Consistent associations between food and health effect with little or no evidence to the contrary; a substantial number of human studies of acceptable quality, preferably including both observational and experimental studies and preferably conducted in different population groups; intake-response relationships supportive of a causal relationship that is biologically plausible; supporting evidence consistent with findings of human evidence.</p> <p>Probable evidence: A number of acceptable human studies, preferably including both observational and experimental studies showing associations that are either not so consistent (e.g., a number of studies that do not support association) or evidence base is insufficient to make a more definite judgement (e.g., limited number of studies; studies of limited duration; small sample size; incomplete follow-up). Some of the evidence may have only recently</p>	

Table 2.1.4-1 Overview of FSANZ’s Guidance Provided for Health Claim Substantiation (FSANZ, 2005b)	
Steps	Details
	emerged and still be subject to ongoing research. Mechanistic and laboratory evidence are usually supportive and relationship should be biologically plausible.
	Possible evidence: Studies generally indicate that a relationship exists but may be limited in number, level (e.g., only supporting evidence exists), or consistency, or may reflect predominantly emerging evidence. There may or may not be supportive mechanistic or laboratory evidence and the relationship should be biologically plausible. More studies of higher quality required to support tentative relationship.
	Insufficient evidence: Only a few studies which while consistent are not of appropriate quality to substantiate a relationship. More well-designed research needed.

2.1.4.1 High-Level Health Claims

With the proposed Standard 1.2.7 (FSANZ, 2007g), high-level health claims will require pre-approval by FSANZ.

If no authoritative reviews exist on the claim of interest, the substantiation framework can be used as guidance on a systematic process to retrieve and evaluate the totality of evidence on the diet/disease relationship. See Table 2.1.4-1.

FSANZ’s substantiation framework outlines three major steps to substantiate high-level health claims (FSANZ, 2005b): 1. identifying and categorizing evidence (e.g., developing a search strategy; filtering the literature for relevance; categorizing publications according to their publication type – intervention; observational; systematic reviews; supporting); 2. assessing and interpreting the evidence (e.g., factors to consider in assessing the quality of intervention and observational studies and systematic reviews; elements to include in a tabulation/synopses of studies); and 3. evaluating the totality of evidence of suitable quality (e.g., assessing the range of studies and consistency of their findings; causality¹; whether the magnitude of effect would have population health significance; relevance of study populations to the target group/general population; practicality of achieving effective intakes and sustaining the expected effect under every-day use conditions; adverse effects; ranking of evidence – convincing, probable, possible, insufficient). Although high level claims will be assessed on a claim-by-claim basis, FSANZ indicates that their approval will likely require “convincing”² evidence to offer “reasonable

¹ To evaluate causality, the primary focus is on demonstration of strength of association/size of effect; independence of association; intake-response relationship; relationship in time; and consistency of findings. There is a secondary focus on reversal of effect; specificity; and biological plausibility.

² Convincing evidence shows consistent associations between the food and the health effect in a “substantial number” of human studies of “acceptable quality”, preferably including both observational and experimental studies and preferably conducted in different population groups, with little or no contrary evidence. Intake-response relationships should be supportive of a causal relationship and the relationship should be biologically plausible.

certainty” that the claim is unlikely to be contradicted in the future by new evidence (FSANZ, 2005b).

For high-level claims, suitable authoritative reviews that address the diet/disease relationship of interest may be used to support claim substantiation, simplifying the claim substantiation process for the applicant (FSANZ, 2005b). FSANZ considers the following as credible sources of information: reports conducted by international governments, international agencies or internationally recognized scientific bodies (e.g., World Health Organization), where the evaluations have been conducted with a comparable degree of rigour to the FSANZ’s substantiation framework and are thus of an appropriate quality (i.e., based on a systematic or structured analysis of suitable evidence with assessment of totality of evidence); or, national diet policy publications (FSANZ, 2005b).

When authoritative reviews are used to support claim substantiation, they can streamline the substantiation process in the following way: 1. several pivotal studies from the authoritative review (e.g., likely to have been given the greatest weight due to their better quality) are independently critically appraised to determine the appropriateness of the conclusions reached in the review; 2. the evidence is checked for its comprehensiveness to ensure no significant sources of evidence were omitted and if they were, an assessment is made on whether their omission would change the review’s conclusions; 3. a detailed analysis of all relevant evidence since completion of the authoritative review is conducted according to the guidance provided in FSANZ’s substantiation framework, to assess whether the review’s findings are still valid in light of the new evidence; and 4. an assessment of the applicability of the authoritative review’s findings to the populations in AU and NZ (FSANZ, 2005b).

2.1.4.2 *General Level Health Claims*

With the proposed Standard 1.2.7, general level health claims will not require pre-approval from FSANZ, however, evidence to support their substantiation must be made available upon request by an enforcement agency. The substantiation principles underpinning general level health claims are the same as those for high-level health claims (FSANZ, 2005b).

General level health claims may be substantiated following processes outlined in the substantiation framework for high-level health claims but unlike high-level health claims that would require “convincing” evidence, general level health claims would require “probable” evidence (FSANZ, 2005b); see footer 5 in Table 2.1.4-1.

Information sources that can be used to simplify the process of substantiation include authoritative reviews (by international governments, international agencies, or internationally recognized scientific bodies); national policy documents; current scientific textbooks; and/or position papers/scientific reviews by medical, nutrition, scientific, or public health national/international non-government organizations. These information sources would have to

be relevant to populations in AU and NZ. Additionally, FSANZ’s recommendations on checking the quality of critical reviews and updating them accordingly would apply (FSANZ, 2005b).

2.1.5 Health Claim Wording and Eligibility

To ensure foods carrying general level or high-level health claims are not inconsistent with national dietary guidelines, in addition to eliminating consumer judgement on the overall healthiness of a food, FSANZ is considering implementing a “nutrient profiling” eligibility criteria for use of general and high-level health claims (FSANZ, 2007e, 2007h). Food manufacturers wanting to make general level or high-level health claims would need to score the nutrient profile of their food to ensure it meets a cut-off score based on the food belonging to one of three categories: i) beverages excluding milk; ii) cheeses and edible fats; iii) fluid, dry or condensed milk and all other foods that don’t fall into the first two categories. The scoring system would be determined using 100 g or 100 mL of the food as a reference, and assigning points based on whether the food is a fruit, vegetable, nut or legume, in addition to assigning points based on the level of calories, saturated fat, sodium, sugars, fibre, and protein in the food. An electronic calculator would be made available on the FSANZ website to carry out the nutrient profiling calculation (FSANZ, 2007h).

Proposed claim wording for general and high-level health claims includes identification of the food/food component and its health effect; the importance of a healthy diet; and the population the health effect relates to if the evidence is not generalizable to the general population (FSANZ, 2007e). See Table 2.1.5-1.

Table 2.1.5-1	Statements to be Included in General Level and High Level Claims (FSANZ, 2007e)
Property of the food and its specific health effect	The importance of a healthy diet consisting of a variety of foods
The population group to which the health effect relates to, where the evidence suggests the health effect cannot be attributed to the general population	

2.1.6 Regulatory Processes Pertaining to Health Claim Approvals

2.1.6.1 Overall Process

Nutrition content claims and general level health claims will not require approval by FSANZ before use, although food manufacturers should be able to produce sufficient evidence to support the truthfulness of the claims upon request by an enforcement agency. High-level health claims, in contrast, will require approval by FSANZ and must be accompanied by an “application” that seeks to change the Code – *i.e.*, to vary a food standard (FSANZ, 2007c).

In October 2007, FSANZ published an exemplary guidance document for applicants interested in varying the Code – *Food Standards Australia New Zealand – Application Handbook* (Commonwealth of Australia, 2007). Applications to vary the Code generally relate to an applicant’s interest in amending food standards related to labelling; substances added to food; contaminants and natural toxins; new foods; composition of food products; and food production. Health claims have not yet been included in this handbook since a standard for health claims has not yet been gazetted. Inclusion of directives in the application handbook for varying the code, pertaining to health claims, is expected for completion in 2008.

All applications to vary the Code are subject to an “administrative assessment” upon receipt by FSANZ. The purpose of the administrative assessment is 2-fold: 1. to determine whether the application meets the application requirements; and, 2. to determine the procedure under which the application should be assessed – *i.e.*, general, minor, or major (Commonwealth of Australia, 2007). See Table 2.1.6.1-1 for differences in procedures.

If an application is rejected, an applicant can apply to the Administrative Appeals Tribunal for a review of the decision within 28 days of notification to the applicant of the rejection (Commonwealth of Australia, 2007).

Once a draft regulatory food measure is approved by FSANZ, the Ministerial Council is notified. If approved by the Ministerial Council, it is gazetted – *i.e.*, it becomes law (Commonwealth of Australia, 2007).

Approval of high-level health claims for foods containing a bioactive would require two applications to FSANZ to vary the Code: the first application would relate to approval of the health claim (*i.e.*, labelling and efficacy), while the second would relate to approval of the food’s safety and its classification as a novel food.

Table 2.1.6.1-1 Comparison of Minor, General and Major Procedures for Assessment of Applications to Vary the Code (Commonwealth of Australia, 2007)					
Procedure	Time from start of assessment to approval of draft regulatory food measure	Application Fee (Canadian dollars)¹	Key features	Consultations	Examples of applications²
Minor	3 months	16, 090 based on up to 175 hours for assessment	No risk to public health	No public consultations; only one round of consultation within government agencies only	Correcting a typographical error Omitting provisions of a food regulatory measure that has ceased to have effect

Table 2.1.6.1-1 Comparison of Minor, General and Major Procedures for Assessment of Applications to Vary the Code (Commonwealth of Australia, 2007)					
Procedure	Time from start of assessment to approval of draft regulatory food measure	Application Fee (Canadian dollars)¹	Key features	Consultations	Examples of applications²
General	9 months	<p>Level 1 45, 970</p> <p>based on up to 500 hours for assessment</p> <p>Level 2 78, 149</p> <p>based on up to 850 hours for assessment</p>	<p>Level 1 Assessment of risk to public health of <u>average complexity</u></p> <p><u>Simple</u> toxicological, nutritional or microbiological assessment</p> <p>Level 2 <u>More complex</u> assessment of risk to public health</p> <p><u>Complete</u> toxicological, nutritional or microbiological assessment</p>	<p>One round of public comment</p> <p>High level advisory groups</p> <p>Consultation with key stakeholder groups</p>	<p>Level 1 <u>Extending</u> permission for use of a food or food additive</p> <p><u>Minor change</u> to a labelling or food composition requirement</p> <p>Level 2 <u>Allowing</u> a food or food additive that is currently not permitted</p> <p><u>Changing</u> a labelling or compositional requirement for a food</p>
Major	12 months (can be extended by 6 months)	96, 537 based on up to 1050 hours for assessment ³	<p>Scientific or technical complexity</p> <p>A significant change to the scope of the food regulatory measure</p> <p>Comprehensive risk management assessment</p>	<p>Two rounds of public comment</p> <p>Community meetings including public hearings</p> <p>Extensive consultation with government agencies, industry, health professionals, consumer groups</p> <p>External working groups and advisory groups</p>	<p>Development of a new standard</p> <p>Change to a labelling or compositional requirement affecting a wide range of foods</p>
<p>¹Only applies to applications with an “exclusive capturable commercial benefit” (<i>i.e.</i> amendment to Code would result in an exclusive benefit, such as a financial gain, to the applicant) or to applicants wishing to have the assessment of their application expedited.</p> <p>²It is not yet known what procedure will be followed for approval of high-level health claims</p> <p>³If application will take more than 1050 hours, a surcharge of \$92 CA will apply for each completed hour</p>					

2.1.6.2 *Transparency*

FSANZ maintains an open and transparent process with applicants that seek to amend the Code. Unless applicants make a specific request for information to be treated as confidential, all information pertaining to applications is accessible to the public *via* FSANZ's website or Public Register. All of FSANZ's scientific evaluations and reasons for making regulatory decisions are also publicly available (Commonwealth of Australia, 2007).

FSANZ's Work Plan (a list of FSANZ's work priorities) is also available on its website or can be obtained from the FSANZ Information Officer (FSANZ, 2007b).

FSANZ informs the community about processes and issues pertinent to applications and food standard proposals and welcomes stakeholder comments. FSANZ's commitment to community involvement on food standards has its basis in the FSANZ Act and reflects the need to ensure that consultation informs the assessment of applications (FSANZ, 2007a).

2.1.6.3 *Prioritizing*

In recognition of the fact that FSANZ has limited resources, it prioritizes its work through the creation of the Food Standards Development Work Plan, which is required under the FSANZ Act. FSANZ must review and update the Work Plan at least every 3 months (FSANZ, 2007b).

Once the administrative assessment for an application is complete, the application is assigned a number and placed on the Work Plan (FSANZ, 2007b).

2.1.6.4 *Timelines*

The *FSANZ Act* requires FSANZ to make its decisions related to applications within stipulated time frames depending on the procedure to be applied to the application's review (Commonwealth of Australia, 2007).

FSANZ has 15 days from receipt of an application to the completion of the administrative assessment and 20 business days to notify the applicant of FSANZ's decisions regarding the administrative assessment – *i.e.*, approval or rejection of application; procedure to be followed for application review (minor, general, major); and, fees (Commonwealth of Australia, 2007).

FSANZ has between 3 months (minor procedure), 9 months (general procedure), or 12 months (major procedure) from commencement of the assessment of an application (or receipt of fees) to the date of approval of a draft food regulatory measure; the timeframe for the major procedure can be extended up to 6 months. These timeframes do not include time taken for an applicant to provide additional information or fees; FSANZ has the right to "stop the clock" in these circumstances (Commonwealth of Australia, 2007).

Once a draft regulatory food measure is approved by FSANZ, within 10 business days the Ministerial Council must be notified. The Ministerial Council must respond to FSANZ within 60 calendar days (Commonwealth of Australia, 2007).

It is not yet determined which procedure (minor, major, general) will be applied for high-level health claim applications.

2.1.6.5 *Communication*

FSANZ keeps applicants informed of the progress of their application (for varying the Code); it is obliged to formally notify applicants in writing at specific points during the assessment process, which can be up to 7 times during the assessment process – e.g., upon receipt of application; upon completion of the administrative assessment; at approval stage (of a draft standard); when Ministerial Council makes a decision; when an amendment to the Code is to be gazetted (Commonwealth of Australia, 2007).

2.1.6.6 *Fees*

FSANZ does not charge fees for the assessment of an application (to vary the Code) unless: 1. FSANZ determines that an application has an “exclusive capturable commercial benefit” (ECCB) or 2. an applicant would like the review of the application to begin immediately rather than according to the anticipated timeframes established as part of the administrative assessment. Where an application is likely to result in an amendment to the Code that provides exclusive benefits (*i.e.*, financial gains) to the applicant, the application is considered to confer ECCB (Commonwealth of Australia, 2007).

In either of these two situations, fees are determined during the administrative assessment of the application and are payable after the applicant has been formally notified of FSANZ’s decision regarding the procedure – minor, general, or major – to be applied to the application review; fees vary depending on the type of procedure to be used. See Table 2.1.6.1-1.

2.1.7 Functional Foods

FSANZ’s guidance on health claim substantiation applies to functional foods in that the subject of general level or high-level health claims can relate to the “property” of a food.

Functional foods would likely classify as “novel foods” - foods that do not have a history of significant human consumption by the broad community in Australia or New Zealand; non-traditional foods that have features or characteristics which raise possible safety concerns (FSANZ, 2005c).

Novel foods and novel food ingredients are regulated by Standard 1.5.1 – Novel Foods – of the Code and must undergo a pre-market safety assessment before sale in Australia or New

Zealand (FSANZ, 2005c). For any food or food ingredient deemed to be novel, an application must be made to FSANZ to vary the Code since all novel foods/novel food ingredients are listed in a Table in Standard 1.5.1 (FSANZ, 2005c). Applications on novel foods or novel food ingredients require technical information (e.g., physical and chemical properties; impurity profile; manufacturing process; identity and purity; analytical method for detection); safety information (history of use in other countries; composition; method of preparation and specifications; allergenicity potential; metabolism/toxicokinetic studies; animal toxicity studies; human tolerance studies); dietary exposure to the novel food (including target groups and risk groups); nutritional impact of the novel food; impact on consumer understanding and behaviour; and impact on the food industry (Commonwealth of Australia, 2007).

2.1.8 Highlights of Australia and New Zealand’s Management of Health Claims and Related Processes

Highlights of FSANZ’s management of health claims and related processes are outlined in Table 2.1.8-1 and Table 2.1.8-2.

Table 2.1.8-1	Highlights of FSANZ’s System Pertaining to Evidence Requirements for Health Claim Substantiation
	Assessment of claim substantiation solely involves assessment of efficacy; extensive safety and quality information is provided with an application to vary the Code for novel foods/novel food ingredients.
	Claims will legally be required to be substantiated in accordance with a Standard; the Standard will make reference to a guideline (e.g., the “substantiation framework”) that includes the requirements for claim substantiation.
	Foods will need to meet a certain nutritional profile, based on a “nutrient profiling model”, to be eligible for carrying general level or high-level health claims.
	Consideration is given to authoritative and/or generally accepted information sources; a simplified approach is outlined for claim substantiation based on the existence of authoritative reviews.
	Clear and unambiguous explanation of health claim substantiation requirements.

Table 2.1.8-2 Highlights of FSANZ's System Concerning its Structure, Operations, and Processes Pertaining to Health Claims

Applicants seeking to amend the Code (*i.e.* those seeking to get approval of a high-level health claim or a novel food) are encouraged to discuss their application with FSANZ staff which can be done *via* teleconference, video link or a face-to-face meeting.

Prioritization of application reviews.

Accountability to timelines for application reviews.

Applications to vary the Code should provide as much information on impact to consumers, food industry, and government.

Applications for high-level claims would be kept confidential until the claim is approved, allowing applicants to receive a first-to-market advantage.

A “step-up” in regulation for claims from nutrition content claims to general level health claims to high-level health claims relating to criteria to support/substantiate the claims and requirement for FSANZ approval for use.

Excellent communication of contacts; an updated FSANZ organizational chart of names and roles of individuals.

Organized, user-friendly website.

Fees attached if application has an “exclusive capturable commercial benefit” or if the applicant requests expedited review; fees based on complexity of review.

Execution of research, where appropriate, to resolve uncertainties or gaps in the understanding of consumer perceptions (*e.g.* research carried out to understand consumer perceptions of claims).

Clear and unambiguous explanation of regulatory processes for health claim approvals.

2.2 Canada

2.2.1 Organization and Function of Relevant Regulatory Bodies

The *Food Directorate* within the *Health Products and Food Branch* of *Health Canada* is the federal health authority responsible for establishing policies, setting standards, and providing advice and information on the safety and nutritional value of food (Health Canada, 2005). Policies and standards for food health claims and the evaluation of food health claim petitions occur within the *Nutrition Evaluation Division* of the *Bureau of Nutritional Sciences* within the *Food Directorate*.

The *Canadian Food Inspection Agency* (CFIA) is the federal authority responsible for the development of non-health and safety food labelling regulations and policies (CFIA, 2007b). In 2003, it published a tool to assist industry in complying with food labelling and advertising requirements - *2003 Guide to Food Labelling and Advertising* (CFIA, 2007c). Among other topics, the Guide outlines the specifications or requirements for nutrient content claims, biological role claims, and health claims.

2.2.2 Relevant Legislation

Relevant legislation pertaining to foods is the *Food and Drugs Act*, the *Food and Drug Regulations*, the *Consumer Packaging and Labelling Act*, and the *Consumer Packaging and Labelling Regulations* (CFIA, 2007a). Non-compliance with Acts or Regulations incurs penalties (a fine and/or imprisonment) (Department of Health, 2006).

The *Food and Drugs Act* prohibits the advertisement and sale to the general public of any food that makes claims only allowable on drugs – *i.e.*, statements that imply or express the diagnosis, treatment, mitigation or prevention of a disease, disorder, or abnormal physical state, or its symptoms; or, restoring, correcting, or modifying organic functions. Additionally, The *Food and Drugs Act* prohibits the sale and advertising of food (and drugs and natural health products) represented as a treatment, preventative, or cure for any of the diseases, disorders, or abnormal physical states referred to in Schedule A (see Table A-4 in Appendix A for Schedule A) (Department of Health, 2006); Schedule A includes common diseases and conditions with diet-related aetiologies, including cancer, heart disease, arteriosclerosis, diabetes, obesity and hypertension. Schedule A was enacted to prevent claims directed at the general public concerning serious health problems, which should be diagnosed and treated by a medical practitioner. However, under the *Food and Drug Regulations*, a food may be exempted from any or all provisions of the Act with a regulatory amendment (Department of Health, 2006).

2.2.3 Profile and Regulation of Health Claims

In Canada, health claims do not have a specified definition in the *Food and Drug Regulations*. Rather, Health Canada regards claims that relate to parts a) and b) of Canada's definition of a

drug as health claims. See Table 2.2.3-1 for Canada's definition of a drug and Table 2.2.3-3 for health claims that relate to Canada's drug definition. Four of five of Canada's existing health claims which mention a disease (heart disease, osteoporosis, cancer) required regulatory amendments for their approval and use; they received exemptions from provisions of the Act and Regulations pertaining to drugs and from subsection 3 of the Act pertaining to Schedule A. See Table A-1 in Appendix A for a list of approved diet/disease claims in Canada.

Canada has three categories of health claims and two categories of claims not considered health claims. See Table 2.2.3-2. Health claims include structure/function claims, risk-reduction claims and therapeutic claims – all are claims related to the definition of a drug by claiming uses related to the prevention or management of a disease or abnormal physical state, including their symptoms (applies to risk-reduction claims and therapeutic claims) or the modification of organic functions beyond what is considered normal and required for the maintenance of good health (applies to structure/function claims) (Health Canada, 2002). Because such claims bring food under the definition of a drug, regulatory amendments are required to approve the use of these claims.

Nutrient content claims and biological role claims are not considered health claims since they do not bring food under the definition of a drug. As such, no regulatory amendments are required for their use. Nutrient content claims describe or imply levels of a nutrient in a food (CFIA, 2003) while biological role claims describe the function of nutrients or energy in the body for normal growth and development or health maintenance (CFIA, 2004). See Table A-3 in Appendix A for a list of Canada's biological role claims.

Canada's definition of biological role claims (generally recognized nutritional function of energy or nutrients in maintaining good health and normal growth and development) is comparable to the U.S. definition of structure/function claims (intended to affect normal structures or functions in humans or describe general well-being) and therefore the two countries' definitions of structure/function claims are not comparable. See Tables 2.2.3-2 and 2.5.2.1-2 to compare each country's definition of structure/function claims.

Table 2.2.3-1 Canada's Current and Proposed New Definitions of Health Claims and Related Terminologies (Lee, 2007; Health Canada, 2002; Department of Health, 2006)			
Current non-legal definition of a "health claim"	Legal definition of a "drug"	Proposed new definition of a "health claim"	Comparison of current vs. proposed new health claim definitions
<p>Relate primarily to paragraphs a) and b) in Canada's definition of a drug</p>	<p>A drug includes any substance or mixture of substances manufactured, sold or represented for use in:</p> <p>a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, or abnormal physical state, or its symptoms, in human beings or animals; or,</p> <p>b) restoring, correcting, or modifying organic functions in human beings or animals; or,</p> <p>c) disinfection in premises in which food is manufactured, prepared, or kept.</p>	<p>Any representation in labelling and advertising that states, suggests, or implies that a relationship exists between the consumption of foods or food constituents and <u>health</u> in the context of the total diet.</p> <p>May be specific or general and stated explicitly with words or represented implicitly (slogans, graphics, logos, symbols, or other means such as a name, trade mark, seal of approval, or by association of educational materials with advertisements).</p>	<p>Current definition represents relationship between food and disease whereas new definition represents relationship between food and health.</p> <p>Proposed new definition specifies a health claim can be expressed or implied with words or graphics.</p>

Table 2.2.3-2 Definition of Various Claim Categories in Canada (Health Canada, 2002; CFIA, 2003, 2004)	
Category of Claim	Distinguishing features of definition
Classified as Health Claims	
Structure/function claims ¹	Relate to modifying, restoring, or correcting a body structure or function <u>beyond</u> what is normal and required for the maintenance of good health
Risk reduction claims ¹	Refer to the alteration of a major risk factor for a disease/adverse health condition Not to be interpreted by consumers as disease prevention claims
Therapeutic claims ¹	Refer to the prevention, treatment, management, or mitigation of a disease, disorder, abnormal physical state or their symptoms
Not Classified as Health Claims	
Biological role claims	Refer to the generally/scientifically recognized nutritional function of energy or nutrients in maintaining good health and normal growth and development ²
Nutrient content claims	Are statements or expressions, outside the Nutrition Facts Table, which directly or indirectly describe the level of a nutrient ³ in a food - e.g., "0 g fat"; "source of"; declaration of the % Daily Value of a nutrient
<p>¹ Any biomarkers used in a health claim as a proxy for a disease, body function or body structure must be validated and generally accepted. Regulatory amendments required before these claims can be used.</p> <p>² "Generally recognized" is not officially defined but is reasonably understood to be based on a well-established prior history of a high level of scientific evidence and broad scientific agreement that is unlikely to be reversed with new data.</p> <p>"Nutrients" are not defined in the <i>Food and Drug Regulations</i>. In practice, CFIA and Health Canada consider a food substance as a nutrient if it is recognized as such by the Institute of Medicine of the National Academies (Washington, DC) for which dietary reference intakes (DRI) have been established.</p> <p>Biological role claims may not be made for other components of food, such as lycopene, lutein, anthocyanins, etc. A quantitative statement would be permitted for these other components (e.g., "14 mg of lycopene per 50 g serving.").</p> <p>³ Nutrients permitted to be declared outside the Nutrition Facts table include: nutrients required or permitted inside the Nutrition Facts table; nutrients not required or permitted inside the Nutrition Facts table (e.g., named amino acids); and, constituents of nutrients.</p>	

Table 2.2.3-3 A Comparison of Requirements and Limitations of Various Claim Categories in Canada		
	Classified as Health Claims	Not Classified as Health Claims
Categories	Structure/Function Claims Risk-Reduction Claims Therapeutic Claims	Biological Role Claims Nutrient Content Claims
Relate to Canada's definition of a drug	Yes	No
Can refer, directly or indirectly, to the treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or their symptoms	Yes	No
Can refer, directly or indirectly, to correcting, restoring or modifying organic functions beyond what can be achieved physiologically	Yes	No
Suggest an impact beyond the maintenance of good health and maintenance of body functions	Yes	No
Suggest an impact beyond normal growth and development	Yes	No
Require Health Canada's approval	Yes ¹	No ²
Eligibility criteria pertaining to nutrients <u>not</u> the subject of the claim	Risk-reduction and therapeutic claims: Yes but limited ³	Biological Role Claims: No Nutrient Content Claims: Yes but limited ⁴
<p>¹ Regulatory amendments required before these claims can be used to exempt claims from: a) provisions of the Act and Regulations pertaining to drugs; and b) provisions of the Act pertaining to Schedule A</p> <p>² For biological role claims, a list of pre-approved claims exist; additional claims would need approval by Health Canada</p> <p>³ For sodium /high blood pressure and fat/heart disease claims, the food must contain 10% of a weighted recommended nutrient intake of a vitamin or mineral per reference amount and/or serving of stated size; see Table A-1 in Appendix A for Canada's risk-reduction claims.</p> <p>⁴ Claims on saturated fat have criteria for cholesterol levels and <i>vice versa</i>; specific claims on sugars have criteria for energy; claims for saturated fat have criteria for trans fat and vice versa and may also have criteria for energy.</p>		

2.2.4 Proposed New Profile and Regulation of Health Claims

The classification of claims with the new proposed system (2007) separates health claims into a "general" and "specific" category. The "specific" health claims are further categorized into disease risk-reduction claims and function claims. As with the current system, when food relates to the definition of a drug, regulatory amendments would be required to authorize use of the claim on foods. Disease risk-reduction claims and one of the three categories of function claims will bring food under the definition of a drug, requiring regulatory amendments. See Table 2.2.4-1.

Table 2.2.4-1 Canada's Proposed New System for Categorizing Health Claims (Lee, 2007)					
	General health claims	Specific health claims			
General Feature	Do not refer to a specific health effect, disease, or health condition	Refer to a specific health effect, disease, or health condition			
Type of claim	General health claim	Disease risk-reduction claim	Function claims		
Specific feature	Promote overall health, healthy eating or provide dietary guidance e.g., "good for you"; "healthy choice"	Link consumption of food/food constituents to a reduced risk of disease in context of total diet ¹	About restoring, correcting or modifying body functions beyond what can be achieved physiologically ¹	About maintenance of body functions <u>necessary</u> for maintenance of health/normal growth and development	About maintenance/support of body functions <u>not necessary</u> for maintenance of health/normal growth and development but <u>associated</u> with good health or performance
¹ Regulatory amendments required before these claims can be used to exempt claims from: a) provisions of the Act and Regulations pertaining to drugs; and b) provisions of the Act pertaining to Schedule A					

2.2.5 Guidance Documents for Health Claim Substantiation

In 2002, Health Canada published a guidance document for petitioners of health claims - *Interim Guidance Document – Preparing a Submission for Foods with Health Claims Incorporating Standards of Evidence for Evaluating Foods with Health Claims* (Health Canada, 2002). The document outlines Health Canada's requirements for a health claim submission and addresses claim validity (*i.e.*, substantiation of efficacy), safety, and the assurance of quality. See Table 2.2.5-2.

The evidence required for demonstration of claim validity, assessment of safety, and assurance of quality differs, depending on the subject of the claim and whether the food is modified (also referred to as "altered") or unmodified. A modified food has undergone changes during its manufacturing to enhance the food's functionality such as the addition of a bioactive ingredient or modification of the levels or bioactivity of a naturally occurring component of the food (Health Canada, 2002). Unmodified foods refer to whole foods and food groups – foods that have not undergone special processing to enhance or add specific substances to the food. A higher level of evidence is required for claim substantiation of modified foods *versus* unmodified foods because modified foods increase the availability of a bioactive substance above levels normally available in, or consumed from, the food supply, increasing the potential for adverse health effects (Health Canada, 2002).

The guidance document outlines two routes for authorizing health claims – generic and product-specific. Generic claims can be used by any food manufacturers so long as their foods meet

the conditions and specifications for use of the claim – e.g., minimum/maximum levels of nutrients in the food; specified claim wording. Product-specific claims, if approved, are reserved for use by the applicant of the claim. A “claim identification number” is assigned to the claim for use on the food label (Health Canada, 2002). Product-specific claims are authorized for modified foods and demonstration of their efficacy is generally based on proprietary data.

For the evaluation of claim validity, the guidance document recommends a similar systematic approach be used to capture and evaluate the totality of evidence, favourable and unfavourable, on a food/health relationship, regardless of the subject of the claim – i.e., a modified or unmodified food. See Tables 2.2.5-3 and 2.2.5-4 for information on claim validity. The totality of evidence should demonstrate causality, be of acceptable quality (research conduct and research design), be relevant and generalizable to the target population, and should substantiate the health claim with a “high level of certainty” (i.e., reasonable assurance that the claim is unlikely to be reversed by new and evolving science). The only difference in the evaluation of claim validity for generic *versus* product-specific health claims is in the requirement for human intervention studies on the specific food as intended for sale for product-specific claims. This is not a requirement for generic health claims which can rely on a combination of human intervention studies, observational studies, and systemic reviews to support their validity. See Table 2.2.5-1 for a comparison of evidence requirements for generic and product-specific claims.

For the evaluation of safety, the breadth of required information is dependant on the degree of food modification. See Table 2.2.5-5 for information on safety. For unmodified foods, assessment of safety is more simplified and requires an evaluation of current and expected (with approval of claim) intakes of the food calculated for the target group and groups at risk. For modified foods containing a bioactive, a safety assessment would additionally include a discussion on the history of use of the bioactive; intakes (current and expected; for target group and groups at risk) of the bioactive from inclusion in a food applicable to the claim, with a comparison to current dietary recommendations; intakes (current and expected; for the target group and groups at risk) of the bioactive from all sources in the diet, with a comparison to current dietary recommendations; impact of consuming the bioactive on usual dietary patterns (i.e., the potential replacement of existing foods with the food containing the bioactive that is the subject of the claim); data on adverse effects from relevant human studies; an upper safe limit of intake of the bioactive; interactions of the bioactive with other components in the food (nutrients, dietary components), diet and drugs; potential adverse effects of the bioactive on meeting essential nutrient requirements and on the gastrointestinal tract; and population subgroups at risk of adverse effects from excessive intake of the bioactive.

For the evaluation of quality, the breadth of required information is also dependant on the degree of food modification. See Table 2.2.5-6 for information on quality assurance. For an assessment of quality of unmodified foods, analytical testing of product composition are

required to ensure expected levels of a nutrient/food component, critical to the claimed effect, are present in the food. For modified foods, additional details are required, including description of the method used to process/produce the bioactive and the food containing the bioactive; compliance with good manufacturing practices (identification of critical control points from raw materials to finished food, including packaging and labelling); evidence of good laboratory and clinical practices; stability data (on bioactive and final product containing the bioactive); for human studies, compliance with established ethical guidelines; characterization of the bioactive; compliance with specifications of the bioactive; and record retention policy and recall procedures.

Table 2.2.5-1 A Comparison of Generic Versus Product-Specific Health Claims (Health Canada, 2002)		
	Generic health claims	Product-specific health claims
Subject of claim	Food category; food; component of food Unmodified or modified foods ⁴	Component of food Modified foods ⁴
Applicable claim	Risk-reduction, structure/function, therapeutic	Risk-reduction, structure/function, therapeutic
Require a regulatory amendment	Yes	Yes
Applicable use of claim	Any food that meets specified conditions (composition, labelling) can carry the claim	Limited to use by applicant of the claim. An authorized claim identified by a "claim identification number" in product labelling
Evidence required for demonstration of claim validity	Type 2 evidence: a combination of human intervention studies (meet ranks A to C) ¹ , observational studies (meet ranks A or B) ² and systematic reviews (meet ranks 1 to 4) ³ . Animal and <i>in vitro</i> studies considered supportive data.	Type 1 evidence: controlled human intervention studies (meet ranks A to C) ¹ on the specific food being marketed. Observational studies, systematic reviews, animal, and <i>in vitro</i> studies considered supportive data.
<p>¹ Intervention studies*: A – Randomized, double-blind, placebo-controlled with sufficient power and appropriately analyzed; B – Randomized but blindness not achieved; C – Non-randomized but with good control of confounding variables and well conducted in other respects.</p> <p>² Observational studies*: A – Hypothesis or objectives specified prior to analysis, with good data and confounders accounted for; B – Hypothesis or objectives not specified prior to analysis, but with good data and confounders accounted for.</p> <p>³ Systematic reviews*: 1 - Avoidance of bias in selection of studies (based on clearly stated inclusion and exclusion criteria); 2 - Conclusion supported by data and analysis presented; 3 - Demonstration of comprehensive search for evidence; 4 - Assessment of publication bias (including many small published studies with positive effects or ignoring known unpublished studies with negative effects).</p> <p>* Additional guidance provided for assessment of study quality is: the completeness in describing study methodology; quantification of the food/substance; quantification of the health-related endpoint; sample size; sample representativeness to the general or target population.</p> <p>⁴ Modified foods have undergone changes during their manufacturing to enhance the food's functionality such as the addition of a bioactive ingredient or modification of the levels or bioactivity of a naturally occurring component of the food.</p>		

Table 2.2.5-2 Information Requirements for a Food Health Claim Submission (Health Canada, 2002)	
Item	Details
Applicant Information	Name of company, mailing address, contact person, <i>etc.</i>
General Information on health claim and product	<p>Proposed health claim</p> <p>Type of authorization (generic; product specific)</p> <p>Product (common name, brand name)</p> <p>Manufacturing location</p> <p>Ingredient list</p> <p>Reference amount, serving of stated size, recommended serving and reasonable daily intake</p> <p>Nutrient information (as sold, as consumed, per 100 g, per serving of stated size)</p> <p>Target group for product carrying claim</p> <p>Product form (as sold, as consumed)²</p> <p>Intended use of product²</p> <p>Directions for preparation; directions for use²</p>
Comprehensive Summary	<p>Summary of the evidence on safety, quality and claim validity</p> <p>Limitations of the evidence</p> <p>Proposed claim</p> <p>Method of authorization (product-specific or generic)</p> <p>Considerations in the use of the claim: food composition criteria, target group, safe use of food (directions for use, upper limit of intake, advisory or cautionary statements)</p>
General Information	<p>Data on quality if subject of claim is a modified food: manufacturing of food; manufacturing and properties of bioactive substance; specifications of raw materials</p> <p>Consumption data (see “intakes” in Table 2.2.5-5)</p>
Product Safety	See Table 2.2.5-5
Quality Assurance	See Table 2.2.5-6
Claim Validity	<p>Background Information</p> <ul style="list-style-type: none"> • Information on original research done on the product (e.g., research center, funding source, principal investigator, publication)² • If independent review of data completed on application, names and affiliations • If product and claim approved or rejection in other jurisdictions: name of country, date of approval, claim statement approved, conditions for use of

Table 2.2.5-2 Information Requirements for a Food Health Claim Submission (Health Canada, 2002)	
Item	Details
	<p>claim, postmarketing information</p> <ul style="list-style-type: none"> Objectives of original research and/or literature review <p>Literature Review</p> <ul style="list-style-type: none"> Identification of relevant studies: describe search strategy; describe inclusion/exclusion criteria Summary of studies reviewed: summarize studies in table format¹ within study design categories (experimental studies in humans; observational studies in humans; systematic reviews) <p>Health relevance of outcome measures or endpoints chosen²</p> <p>Validation of analytical method for endpoints chosen²</p> <p>Assessment of totality of evidence</p> <ul style="list-style-type: none"> Assess extent to which essential causality criteria have been met: consistency; magnitude of effect; statistical probability; temporal relationship; no equally strong opposing/neutral evidence; dose response or relevant data in support of an effective dose Assess extent to which supporting causality criteria have been met: reversal/cessation of effects; biological plausibility; alternative explanations; specificity of effect or cause; coherence Characterize the relationship between the food/bioactive substance and the claimed health effect <ul style="list-style-type: none"> Is beneficial effect achieved under controlled conditions? Is beneficial effect achieved under free-living conditions? Is magnitude of effect physiologically meaningful? Is beneficial effect sustainable? <p>What is the amount of food and bioactive substance required to achieve the claimed effect? Can the amount be reasonably consumed from foods as part of a healthy diet?</p> <p>What are the usual intakes of the food and bioactive substance?</p> <p>Who will benefit?</p>

Table 2.2.5-2 Information Requirements for a Food Health Claim Submission (Health Canada, 2002)	
Item	Details
	<p>Relevance and generalizability of the evidence to the claimed effect and target group, including limitations in data</p> <p>Other considerations</p> <ul style="list-style-type: none"> • Evidence that the composition of a food bearing the claim does not counteract the beneficial effect of the added or otherwise modified substance in the food • Safe use of the product: Whether directions for use, cautionary statements, restricted advertising, restricted channels of distribution and/or post-market surveillance are warranted <p>Reference List</p> <p>Detailed description of primary evidence (<i>i.e.</i>, protocol and data of studies conducted or sponsored by the applicant)²</p>
Supplementary Information	May include official meeting minutes, regulatory guidance or advice from other jurisdictions
<p>¹Recommended table headings: study author, year; study design and quality level; description of participants in control and intervention groups, including sample size; description of treatment and control and duration; amount of food and bioactive substance consumed; method of collecting data; identification of baseline diet and/or use of control diet; main results (provide actual data and statistical significance and include graphs where appropriate); comments (statistical analysis, other factors affecting interpretation of results, methods of analysis of intake of food and bioactive substance, outcome measures, general comments about study quality, deviations from protocol, adverse or side effects)</p> <p>²For product-specific claims</p>	

Table 2.2.5-3 Guiding Principles for the Evaluation of Claim Validity (Health Canada, 2002)	
<p>A systematic or structured approach should be used to ensure that all relevant evidence is considered and the conclusions are justified</p> <p>Consideration of the totality of evidence not just the evidence supporting the claim</p> <ul style="list-style-type: none"> • Support of a causal relationship between ingestion of the food and the claimed effect • The studies supporting the claim must be of acceptable quality (design and conduct) and conducted in accordance with current best scientific practices • Evidence supporting the claim should be relevant and generalizable to the target population • The level of certainty for claim validity should be high based on best practices in evaluating scientific evidence; a high level of certainty does not mean absolute certainty but it provides reasonable assurance that the claim is unlikely to be reversed by new and evolving science 	

Table 2.2.5-4 Requirements to Demonstrate Claim Validity Based on an Evaluation of the Totality of Evidence of “Acceptable Quality” (Health Canada, 2002)¹

Causality²

- Consistency: results reproducible in terms of direction of results (favourable or unfavourable); inconsistent results should be explained
- Magnitude of effect (intervention studies)/Strength of association (observational studies): size of effect should be statistically significant and physiologically meaningful
- Probability: statistically significant findings
- Temporality: food intake/food exposure precedes effect (proved by intervention studies)
- Opposing evidence: no equally strong opposing evidence
- Dose-response: greater effects occur with greater food intakes/exposures; lack of a dose-response should be explained and an effective intake reported (level of intake required to achieve a claimed effect)

Findings relevant and generalizable to the proposed claim (including target group)

Efficacy

- The claimed effect can be achieved under controlled conditions

Effectiveness

- The amount of food required for claimed effect can be reasonably consumed under free-living conditions without a negative effect on the diet; data can be confirmed after the product is on the market if it is not available as part of pre-market submission

Who will benefit

- If claimed effect studied in or applicable to limited population groups, such groups should be identified as part of claim statement

Sustainability of the effect

- Claimed effect should be sustainable and not due to transient adaptive response with decreasing benefit over time

¹ Acceptable quality: Ranks A to C for human intervention studies; ranks A or B for observational studies; ranks 1 to 4 for systematic reviews

Intervention studies

- A – Randomized, double-blind, placebo-controlled with sufficient power and appropriately analyzed
- B – Randomized but blindness not achieved
- C – Non-randomized but with good control of confounding variables and well conducted in other respects.

Observational studies

- A – Hypothesis or objectives specified prior to analysis, with good data and confounders accounted for
- B – Hypothesis or objectives not specified prior to analysis, but with good data and confounders accounted for.

Systematic reviews

- 1 - Avoidance of bias in selection of studies (based on clearly stated inclusion and exclusion criteria)
- 2 - Conclusion supported by data and analysis presented
- 3 - Demonstration of comprehensive search for evidence
- 4 - Assessment of publication bias (including many small published studies with positive effects or ignoring known unpublished studies with negative effects).

²The following criteria are not considered essential to demonstrate causality; however, the more of them that are met, the stronger the evidence: reversal/cessation of effects (when agent that has effect is removed, benefit should

Table 2.2.5-4	Requirements to Demonstrate Claim Validity Based on an Evaluation of the Totality of Evidence of “Acceptable Quality” (Health Canada, 2002)¹
<p>cease); biological plausibility (a biological plausible mechanism to explain why effect occurring); alternative explanations (ruling out of alternative explanations for observed effect due to confounding variables); specificity of effect (precision of association between exposure and effect); coherence (agreement with other knowledge/data).</p>	

Table 2.2.5-5	Factors to be Addressed in the Assessment of Safety for Modified¹ and Unmodified Foods (Health Canada, 2002)
Factor	Details
History of safe use ³	History of use as a food or previous human consumption in Canada or country other than Canada; describe form, preparation and range of intake
Intakes ²	<p>Current and expected intakes of food by target group and groups at risk; comparison to current dietary recommendations²</p> <p>Current and expected intakes of food and all similar sources in the diet by target group and groups at risk; comparison to current dietary recommendations²</p> <p>Current and expected intakes of bioactive from the food applicable to the claim by target group and groups at risk; comparison to current dietary recommendations</p> <p>Current and expected daily intake of bioactive from all sources in diet by target group and groups at risk; comparison to current dietary recommendations</p> <p>An upper safe limit of intake of bioactive compound (derived from intervention studies) if evidence suggests adverse health effects expected in humans at a certain level of intake</p>
Dietary, nutritional, metabolic effects ²	<p>Potential replacement of existing foods²</p> <p>Interactions of the bioactive compound with nutrients and dietary components in the food carrying the bioactive compound and in the diet</p> <p>Interactions of the bioactive compound with drugs</p> <p>Potential adverse effects of bioactive compound on meeting requirements for essential nutrients</p>
Microbial ecology ³	Microbiological organisms in the bioactive/food with bioactive that have an effect on the gastrointestinal tract; if microorganisms contained in product, data to support safety provided
Groups at risk ³	Identification of susceptible and vulnerable groups at risk of adverse effects from <i>ad libitum</i> intake of food with bioactive compound including effects related and unrelated (<i>e.g.</i> , allergenicity) to desirable effects
Data from <i>in vitro</i> , animal and human studies ³	<p><i>In vitro</i> (as needed) to demonstrate <i>in vitro</i> toxicity, mechanism of action</p> <p>Animal studies to assess metabolism of food, mechanism of action, <i>in vivo</i> toxicity</p> <p>Human studies to assess adverse effects from intake of food</p>

Table 2.2.5-5 Factors to be Addressed in the Assessment of Safety for Modified¹ and Unmodified Foods (Health Canada, 2002)	
Factor	Details
<p>¹ If a modified food may pose a nutritional or health risk to a user or non-user group (e.g., intolerance, allergenicity, metabolic susceptibility) and if there is a compelling reason to make such a food available for target users, it would be necessary to apply risk management options to ensure users and non-users are not at undue risk. Risk management options include: special labelling (cautionary statements regarding product use); restricted product distribution and/or advertising; post-marketing adverse reaction reporting.</p> <p>² Items that apply to unmodified foods; all items in table apply to modified foods.</p> <p>³Not required to be addressed if food safety has been previously reviewed (e.g., novel food approval).</p>	

Table 2.2.5-6 Factors to be Addressed in an Assessment of Quality for Modified and Unmodified Foods (Health Canada, 2002)	
Factor	Details
Method used to produce/process the bioactive and finished food containing the bioactive	<p>Description of method to manufacture, prepare, preserve, package, store bioactive and finished food with bioactive.</p> <p>If a bioactive is added to a food, its method of fractionation, purification, concentration</p>
Evidence of good manufacturing practices for manufacturing of bioactive substance and final food with bioactive	Identification of quality control procedures (identification of critical control points) for manufacturing, processing, finished product, packaging and labelling; include documentation of procedures
Stability data on bioactive and final food containing bioactive	<p>Summary of studies conducted on the bioactive and the final product containing the bioactive, including data on shelf-life and a description of methods used to obtain data (conditions, batches, analytical procedures)</p> <p>Proposed packaging, shipping and storage conditions, retest date or shelf-life, where relevant</p> <p>Stability data should support product safety and claimed effect for the entire duration of the product's shelf-life</p>
Measurement of levels of a nutrient, food component, or bioactive in a food that achieves claimed effect ¹	<p>Details of analytical method as well as sampling plan and variability of data¹</p> <p>Documentation of consistency of quantity of nutrient/food component/bioactive. If analytical method new or modified, data on standardization and validation of the method¹</p>
Compliance with established ethical guidelines	All experimental and observational studies conducted in support of health claim conducted in accordance with applicable ethical standards and guidelines
Specifications of raw materials	For raw materials used in manufacturing of bioactive and finished food with bioactive – chemical, microbiological, physical, contaminants, purity
Characterization/specifications of bioactive	<p>Characterization of bioactive, including chemical, microbiological, physical, contaminants, purity; where applicable, analytical data on biological activity of bioactive substance</p> <p>Analytical data on levels of bioactive substance in finished food</p> <p>Sampling plan and frequency of analysis of analytical data provided</p>

Table 2.2.5-6 Factors to be Addressed in an Assessment of Quality for Modified and Unmodified Foods (Health Canada, 2002)	
Factor	Details
Justification of proxy indicator	There should be a quantifiable relationship between amount of proxy indicator in food and claimed effect
Compliance with bioactive specifications	Analytical data and statistical analysis to indicate compliance with specifications Sampling plan and frequency of analysis for analytical data provided Certificate of analyses where appropriate
Good clinical practices	
Good laboratory practices	
Record retention policy	
Recall procedures	
¹ Items that apply to unmodified foods; all items in table apply to modified foods.	

2.2.6 Health Claim Wording and Eligibility

Canada does not have extensive requirements with respect to the nutrient profiles of foods for their eligibility to carry claims. See Table 2.2.3-3.

No information is provided in Canada’s guidance document regarding mandatory requirements for health claim wording. Judgement of health claim wording is likely made based on the evidence and as such is done on a case-by-case basis.

2.2.7 Regulatory Processes Pertaining to Health Claim Approvals

2.2.7.1 Overall

Upon receipt of a food health claim submission, a preliminary evaluation is conducted to assess the completeness of the submission; that all required information is provided in the required format; whether clarification and/or further information are needed; and to determine if a detailed evaluation should proceed. For product-specific applications, the applications are evaluated to determine whether the product submitted should be evaluated as a food (Health Canada, 2002)

Following the preliminary evaluation, a detailed evaluation is conducted, assessing product safety, claim validity, and quality assurance measures (Health Canada, 2002).

2.2.7.2 Timelines

Health Canada is not accountable to any timelines for the review of petitions.

2.2.7.3 *Transparency*

The Interim Guidance document for health claim submissions states that Health Canada intends to make decision summaries of approved claims publicly available (Health Canada, 2002); however, there is no commitment to ensuring public knowledge of applications received.

2.2.7.4 *Communication with petitioners*

The Interim Guidance document for food health claim submissions states that applicants are encouraged to discuss proposed claims and products in advance of submitting a formal application with the “appropriate regulatory authority within Health Canada” (Health Canada, 2002); however, no specific contact information is provided – *i.e.* contact name, telephone number.

2.2.7.5 *Fees*

No fees are attached to the application review process.

2.2.7.6 *Proposed new modernized system*

Health Canada has stated that its proposed new modernized system for managing health claims will establish a greater commitment to efficiency, transparency, and openness to support informed consumer choice whilst protecting consumers from unsubstantiated claims and supporting conditions for a fair and competitive market environment (Lee, 2007).

2.2.8 Functional Foods

Canada’s Interim Guidance Document for food health claims, specifically the information pertaining to product-specific applications, can be applied to functional foods; foods that fall under the proposal for product-specific authorization of food health claims fit with the technical concept of “functional food”. Health Canada is not pursuing a regulatory definition of functional food because a definition is not required under the current *Food and Drugs Act* to permit health claims for foods on a product-specific basis (Health Canada, 2002).

Within the *Health Products and Food Branch* of Health Canada exists the *Food Directorate* and the *Natural Health Products Directorate* (NHPD). The former regulates foods in compliance with the *Food and Drug Regulations* and the latter regulates natural health products in compliance with the *Natural Health Product Regulations*; *Natural Health Product Regulations* came into force January 2004 (Health Canada, 2007b).

Unlike functional foods which do not have a regulatory definition in Canada, natural health products (NHPs), a subcategory of drugs with their own regulations, are defined by Health Canada and refer to homeopathic and traditional medicines and other substances such as vitamins, minerals, amino acids, probiotics, essential fatty acids, and plant extracts/isolates that,

similar to drugs, are represented for use in the diagnosis, treatment, mitigation or prevention of a disease/disorder/abnormal physical state or its symptoms; or, restoring, correcting, or modifying organic functions in humans (Canada Gazette, 2006). See Table 2.2.8-1. The regulatory definition of NHPs does not specify the form or matrix of NHPs (e.g., tablets, capsules, powders, conventional food form, etc). As a result, the NHPD has received product license applications for NHPs in conventional food form – i.e., functional foods.

On October 9, 2007, the NHPD publicly notified stakeholders that NHPs in food formats/matrices (e.g., butters, juices, yogurts) that applied to the NHPD for a product license and/or approval of a claim will be reviewed by the Food Directorate while those in therapeutic dosage forms (e.g., pills, tablets, etc) will be reserved for the NHPD (Health Canada, 2007c). Although food-like products regulated as NHPs are not legally subject to food regulations and standards, Health Canada felt that consumers do not distinguish these products from other foods and thus may consume them *ad libitum*. To ensure the application of safety and efficacy standards consistent with other foods, the Food Directorate will, in addition to existing NHP guidance documents, consider the evidence requirements outlined in the *Interim Guidance Document for Preparing a Submission for Foods with Health Claims*, in their approval of health claims on food-like NHPs (Lee, 2007). Health Canada is considering a regulatory amendment that would result in food-like NHPs being regulated under food regulations (Lee, 2007).

Table 2.2.8-1 A Comparison of Health Canada’s Legal Definitions for Foods, Drugs and Natural Health Products (Canada Gazette, 2006; Department of Health, 2006)			
Definition of a “food”	Definition of a “drug”	Definition of a “natural health product (NHP)”	Comments
Any article manufactured, sold or represented for use as food or drink for human beings, chewing gum, and any ingredient that may be mixed with food for any purpose whatever	Any substance or mixture of substances manufactured, sold or represented for use in: (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, or abnormal physical state, or its symptoms, in human beings or animals; or, (b) restoring, correcting, or modifying organic functions in human beings or animals; or, (c) disinfection in premises in which food is manufactured, prepared, or kept	A substance or combination of substances set out in Schedule 1 ¹ , or a homeopathic or traditional medicine, manufactured, sold or represented for use in (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans; (b) restoring or correcting organic functions in humans; or (c) modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health A natural health product does not include a substance set out in Schedule 2 ²	NHPs are a subcategory of drugs but have their own regulations NHPs and drugs have the same representation for use (<i>i.e.</i> related to disease management and effect on body’s organic functions) Scope of what constitutes a NHP is defined (by Schedule 1 and Schedule 2) and includes homeopathic and traditional medicines, and other substances (vitamins, minerals, amino acids, probiotics, essential fatty acids, plant extracts/isolates and others) Form/matrix of a NHP is not specified
<p>¹ Schedule 1 – “Included Natural Health Product Substances”: A plant, plant material, alga, bacterium, fungus, or non-human animal material, including an extract or isolate (or their synthetic duplicate), the primary molecular structure of which is identical to that which it had prior to its extraction or isolation; vitamins (biotin, folate, niacin, pantothenic acid, riboflavin, thiamine, vitamin A, vitamin B₆, vitamin B₁₂, vitamin C, vitamin D, vitamin E) or their synthetic duplicate; mineral; amino acid or its synthetic duplicate; essential fatty acid or its synthetic duplicate; probiotic.</p> <p>² Schedule 2 – “Excluded Natural Health Product Substances”: Drugs, other than radionuclides, sold or represented for use in the preparation of radiopharmaceuticals; a substance set out in Schedule D to the <i>Food and Drugs Act</i> (exceptions exist); a substance regulated under the <i>Tobacco Act</i>; a substance set out in any of Schedules I to V of the <i>Controlled Drugs and Substances Act</i>; a substance that is administered by puncturing the dermis; an antibiotic prepared from an alga, a bacterium or a fungus or a synthetic duplicate of that antibiotic.</p>			

2.2.9 Highlights of Canada’s Management of Health Claims and Related Processes

Highlights of Canada’s management of health claims and related processes are outlined in Table 2.2.9-1 and Table 2.2.9-2.

Table 2.2.9-1 Highlights of Canada’s System Pertaining to Evidence Requirements for Health Claim Substantiation

Standards for health claims developed with the primary objectives of injury prevention and avoidance of misleading claims whilst considering practicality, flexibility, harmonization (with U.S.), industry innovation and competitiveness.

Health claim submissions require information on claim validity (*i.e.* efficacy), safety and quality; however, requirements on safety and quality differ depending on whether the food is modified and requirements for safety, specifically, differ depending on whether Health Canada has already reviewed and approved the food’s safety.

Guidance document for health claim submissions is not user-friendly – a piece-meal document that lacks organization and cohesiveness.

Not a clear distinction between generic *versus* product-specific claims in guidance document.

Safety information in a health claim submission assures there are no adverse nutritional, toxicological, or microbiological effects from ingesting the food.

Status of proposed health claim in other jurisdictions (*i.e.* whether approved or rejected) to be discussed by applicant of health claim petition.

Transparency expected regarding search strategy and selection criteria for relevant evidence to substantiate claim validity; no guidance provided on how to conduct search for literature and filtering of literature.

Appraisal of totality of evidence with tabulation of literature required for claim substantiation.

Table 2.2.9-2 Highlights of Canada’s System Concerning Its Structure, Operations, and Processes Pertaining to Health Claims

Guidance document states that Health Canada intends to make decision summaries of approved claims publicly available; however, there is no commitment to ensuring public knowledge of applications received.

Guidance document states that applicants are encouraged to discuss proposed claims and products in advance of submitting a formal application with the “appropriate regulatory authority within Health Canada”; however, no specific contact information is provided – *i.e.* contact name, telephone number.

Evaluation of a submission involves a “preliminary evaluation” followed by a “detailed evaluation”; the preliminary evaluation ensures completeness of application, allows request for further information, and determines whether a detailed evaluation should proceed.

No accountability to timelines for health claim review.

The guidance document indicates that a deviation from its suggested outline, without prior discussion with Health Canada, will be returned without review.

2.3 European Union

2.3.1 Organization and Function of Relevant Regulatory Bodies

The *European Food Safety Authority* (EFSA) is an independent European agency funded by the European Union (EU). It operates separately from the *European Commission* (EC) (the executive branch of the European Union), *European Parliament* (EP) (parliamentary body of the European Union), and 27 EU Member states (EFSA, 2007a).

EFSA is committed to providing objective, independent, science-based advice and clear communication on existing and emerging risks; it is a “risk assessor”. Scientific opinions and advice produced by EFSA are initiated by requests from the EC, EP, and Member States, or by EFSA itself. EFSA’s assessments help the “risk managers” (EC, EP, and Member States) manage risk and develop sound European policies and legislation (EFSA, 2007a).

EFSA’s activities are guided by a set of key values: openness and transparency; excellence in science; independence; and, responsiveness. EFSA’s scope of work covers nutrition; food and feed safety; animal health and welfare; and, plant protection and plant health (EFSA, 2007a).

2.3.2 Relevant Legislation

The European Parliament adopted a new regulation for nutrition and health claims on foods – Regulation (EC) No. 1924/2006 (hereafter referred to as “the regulation”) which became applicable from July 2007 (European Parliament, 2006). The impetuses for the EU regulation were many: to facilitate the free movement of foods; create equal conditions for competition (currently member states differ in their regulations of nutrition and health claims); facilitate consumer choice; and to ensure a high level of consumer protection (European Parliament, 2006). The regulation is intended to harmonize laws and regulations of Member States pertaining to nutrition and health claims (European Parliament, 2006).

2.3.3 Profile and Regulation of Health Claims

The definitions of nutrition and health claims in the regulation are outlined in Table 2.3.3-2. Claims referring to the amount or calories of a nutrient or substance in the food (*i.e.*, nutrition claims) are not considered health claims whilst those referring to health or disease, such as Article 13 and Article 14 claims, respectively, are considered health claims. Article 14 claims make reference to reduction of disease risk or to children’s development and health. Article 13 claims are claims other than those referring to the reduction of disease risk or to children’s development and health and relate to the role or a nutrient/substance in growth, development, and functions of the body; psychological and behavioural functions; slimming or weight control or a reduction in sense of hunger, increase in the sense of satiety or reduction in available energy from the diet (European Parliament, 2006).

Nutrition and health claims are approved by EFSA and their use, if not restricted (due to claim substantiation being based on proprietary data), is available to any food business operator so long as eligibility criteria are met. Evidence requirements for the approval of Article 13 claims are very different from the requirements for Article 14 claims; the latter requires a formal scientific substantiation dossier (European Parliament, 2006). See Tables 2.3.3-1 and 2.3.3-2.

Table 2.3.3-1 Definition of a Health Claim in the EU (European Parliament, 2006)	
Subject	Definition
Health Claim	Any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health

Table 2.3.3-2 Definition of Nutrition and Health Claims in the EU (European Parliament, 2006)			
Type of Claim	Definition of Claim	EFSA approval	EU requirements, where applicable
Not Classified as Health Claims			Substances for which claim made shown to have a beneficial nutritional or physiological effect Substance that is subject of claim is present/absent (in final product) at levels sufficient to produce the nutritional or physiological effect claimed Substance available for use by the body
Nutrition Claim	Any claim which states, suggests or implies that a food has particular beneficial nutritional properties due to: <ul style="list-style-type: none"> the energy (calories) it provides or does not provide and/or the “nutrients” or “other substances”¹ it contains or does not contain 	No	
Classified as Health Claims²			Significant amount of substance producing claimed nutritional or physiological effect provided by a quantity of the food that can reasonably be expected to be consumed A nutrition or health claim should not be made if inconsistent with generally accepted nutrition and health principles or if it encourages or condones excessive consumption of any food or disparages good dietary practice Nutrition labelling should be compulsory List of permitted nutrition claims and their specific conditions of use should be created Health claims authorized for use after a scientific assessment of highest possible standard; EFSA should carry out such assessments
Article 13 Claim	Claims other than those referring to the reduction of disease risk and to children’s development and health Describe or refer to: <ul style="list-style-type: none"> the role of a nutrient or other substance in growth, development and the functions of the body psychological and behaviour function slimming or weight-control reduction in the sense of hunger increase in the sense of satiety reduction of available energy from the diet 	Yes	

Table 2.3.3-2 Definition of Nutrition and Health Claims in the EU (European Parliament, 2006)			
Type of Claim	Definition of Claim	EFSA approval	EU requirements, where applicable
Article 14 Claim	Reduction of disease risk claims or claims referring to children's development and health	Yes	Health claims other than those referring to reduction of disease risk and to children's development and health, based on generally accepted scientific evidence, should undergo a different type of assessment and authorization; necessary to adopt a Community list of such permitted claims after consulting EFSA
	<p>Disease-Risk Reduction Claim</p> <ul style="list-style-type: none"> Any health claim that states, suggests or implies that the consumption of a food category, a food or its constituents significantly reduces a risk factor in the development of a human disease <p>Children's Claims</p> <ul style="list-style-type: none"> No legal definition 		<p>Use of nutrition and health claims only permitted if average consumer can be expected to understand beneficial effects as expressed in claim</p> <p>Nutrition and health claims shall refer to food ready for consumption in accordance with manufacturer's instructions</p> <p>Competent authorities of Member States may request food business operator or person placing product on market to produce all relevant elements and data establishing scientific substantiation of claims</p> <p>Scientific substantiation of claims by generally accepted scientific evidence taking into account totality of evidence and weighing the evidence; For Article 13 claims, see Tables 2.3.4.1-1 and 2.3.4.1-2; for Article 14 claims, see Table 2.3.4.2-1.</p>
<p>¹ Other substance" means a substance other than a nutrient that has a nutritional or physiological effect. "Nutrient" means protein, carbohydrate, fat, fibre, sodium, vitamins and minerals and substances which belong to or are components of one of those categories.</p> <p>² Following health claims not allowed: claims which suggest that health could be affected by not consuming food; claims which make reference to rate or amount of weight loss; claims which make reference to recommendations of individual doctors or health professionals or other associations not referred to in the regulation</p>			

2.3.4 Guidance Documents for Health Claim Substantiation

2.3.4.1 Article 13 Claims

Article 13 claims do not require a formal substantiation dossier. Member States are expected to provide the EC with a table that follows the template in Table 2.3.4.1-1 by January 31, 2008. EFSA will review the submissions and the EC shall adopt a "Community list of permitted claims" by January 31, 2010, at the latest (European Parliament, 2006).

The template to follow in Table 2.3.4.1-1 does not provide specific requirements or guidance on claim substantiation, although it is stated the totality of science and balance of evidence must be represented and the information must be in the public domain and peer reviewed.

After January 2010, information in Table 2.3.4.1-2 can be submitted to EFSA for the approval of additional Article 13 claims based on newly developed science and/or claims substantiated by proprietary data (European Parliament, 2006).

Table 2.3.4.1-1 Table Template for Article 13 Submissions to Member States for EFSA Evaluation (European Parliament, 2006)					
Food/Food component	Health Effect	Suggested Conditions of Use	Nature of Evidence	References	Example of Claim Wording
		Levels of food/food component to justify claim Frequency of consumption Warning statements	Type of evidence submitted – <i>i.e.</i> expert opinion, systematic review, randomized controlled trial, observational epidemiological study (case control, cohort), animal study	No guidance given on requirements for claim substantiation: No requirement for a specific number of references; totality of science and balance of evidence must be represented; quality of evidence more important than quantity; information must be in public domain and peer reviewed	

Table 2.3.4.1-2 Submission Requirements for Article 13 Claims Not Included on the Community List of Permitted Claims (European Parliament, 2006)
Name and address of applicant
Nutrient, substance, food, category of food, and characteristics
Copies of studies relevant to health claim
Indication of information that should be regarded as proprietary
Proposed claim wording and specific conditions for use
Summary of application

2.3.4.2 Article 14 Claims

On March 6, 2007, the EC requested that EFSA issue an opinion on scientific and technical guidance for applicants seeking authorization of nutrition and health claims. EFSA carried out this task which culminated into a final guidance document being adopted by the EC on July 6, 2007 - *Scientific and technical guidance for the preparation and presentation of the application for authorization of a health claim* (EFSA, 2007b).

The guidance document applies to the substantiation of Article 14 claims. It describes a systematic, transparent, and comprehensive approach petitioners should implement in their evaluation of a food/health relationship.

Article 14 health claim applications require information pertaining to efficacy and quality. See Table 2.3.4.2-1 for a description of required information; safety is assessed with a novel food submission.

The determination of efficacy is based on human studies – intervention and observational; animal and *in vitro* data can be submitted as supporting evidence. The totality of evidence from human studies must demonstrate causality, be relevant to the target population of the claim, and the quantity of food to achieve the intended effect should be reasonably achieved in a balanced diet (EFSA, 2007b).

Information on quality involves characterization of the food source; assurance that the food meets specifications; quality systems for the food's manufacturing; and stability information (EFSA, 2007b).

EFSA's guidance for health claim applications is very detailed, especially with regards to the evaluation of individual human studies, which requires a detailed synopsis of each study. All the factors to be addressed in the synopsis are outlined separately for intervention and observational studies. Generally the synopsis includes a description of the study population (inclusion/exclusion criteria, age, sex, setting, geographical region); study design (includes a table to summarize dose, matrix, duration); study results (includes a table to summarize pre-test and post-test outcome values and their significance); and study quality (18 quality factors for intervention studies; 22 quality factors for observational studies).

The guidance document demands transparency of process (*e.g.*, literature retrieval and filtering; tracking of number of pertinent articles; list of pertinent references) and results (*e.g.*, data tabulation and synopsis). EFSA highlights the importance of unpublished research, directly and indirectly, the latter by organizing tables in which unpublished studies are given their own column heading.

EFSA's receipt of an application (*i.e.* application summary which includes specification of the food; relationship between the food and health outcome; proposal for claim wording; conditions

of use) and its scientific opinion concerning the application will be made public, the former occurring at the time the application is received.

Table 2.3.4.2-1 Requirements for an Article 14 Health Claim Application (EFSA, 2007b)	
Part of Application	Details
Part 1 – Administrative and technical data	<p>Health claim particulars</p> <ul style="list-style-type: none"> - Claim wording - Specific conditions of use - Target population with rationale - Quantity of food and pattern of consumption to obtain claimed effect - Whether food quantity could reasonably be achieved as part of balanced diet - Warning statements – e.g., individuals who should avoid using food; concerning presentation of health risks if consumed in excess - Restrictions of use - Directions for preparation/use <p>National and international regulatory status of claim</p> <p>Inclusion of confidential/proprietary data</p>
Part 2- Characterization of food, food category, food constituent, where applicable	<p>Source and specifications (certified by laboratory)</p> <ul style="list-style-type: none"> - Composition - Physical and chemical characteristics - Microbiological constituents - Consistency; batch to batch variability <p>Quality systems in place</p> <ul style="list-style-type: none"> - Information on good manufacturing process (GMP); good laboratory practices (GLP); ISO standards <p>Manufacturing process</p> <p>Stability information</p> <ul style="list-style-type: none"> - Studies undertaken with results and conclusions regarding stability, storage and shelf-life <p>Bioavailability</p> <ul style="list-style-type: none"> - Evidence that food is in a form usable by body (e.g., absorption studies) or that food reaches target site - Data on factors that could affect absorption/utilization in body (e.g., formulation, processing)

Table 2.3.4.2-1 Requirements for an Article 14 Health Claim Application (EFSA, 2007b)	
Part of Application	Details
Part 3- Written and tabulated summaries of scientific data	<p>Detailed tabulation and synopses of human intervention and observational studies including their quality appraisal</p> <p>Written summary of human studies (of data in tables and synopses)</p> <ul style="list-style-type: none"> - Magnitude of effect and its physiological relevance; generalizability of study populations to target population of claim; study conditions (<i>e.g.</i>, free-living; controlled); sustainability of effect over time; amount of food to achieve effect; usual intakes of food in target population; whether effective amount could be reasonably consumed in balanced diet - Demonstration of causality: consistency of results across studies; statistical significance of magnitude of effect and presence/absence of equally strong opposing/neutral evidence; effective dose (if possible); biological plausibility; alternate explanations; specificity <p>Written summary of non-human studies</p> <ul style="list-style-type: none"> - How they may support food/health relationship –<i>e.g.</i>, mechanism of action <p>Conclusions</p> <ul style="list-style-type: none"> - Relevance of claimed effect to human health - Demonstration of cause and effect in humans (<i>e.g.</i>, strength, consistency, specificity, dose-response, biological plausibility) - Relevance of study groups in studies to target population of claim - Quantity of effective dose and pattern of consumption reasonably achieved in balanced diet
Part 4- Identification of scientific data	<p>Summary of search strategy for published and unpublished literature; databases and keywords used for electronic search; inclusion/exclusion criteria for literature filtering; results of literature filtering (<i>i.e.</i>, numbers of studies included/excluded); classification of studies according to their design (<i>e.g.</i>, for intervention studies: R, C; NR, C etc); summary of relevant components of non-human data (<i>e.g.</i>, of animal studies or <i>in vitro</i> studies); reference lists of relevant (or pertinent) studies (published and unpublished, human and non-human studies)</p>
Part 5- Annexes	<p>Glossary; copies of studies; scientific opinion of national/international regulatory bodies;</p>

2.3.5 Health Claim Wording and Eligibility

By January 19, 2009, the Commission shall establish specific nutrient profiles, including exemptions³, for which foods/categories of food must comply with to bear nutrition or health claims. To achieve this, the Commission has requested that EFSA provide advice, by December 2007, on: a) whether nutrient profiles should be set for food in general and/or categories of food; b) the choice and balance of nutrients to be taken into account (*e.g.*, the Commission expects to pay particular attention to fat, saturated fat, trans fat, sugars and

³ It is expected that nutrition claims will be allowed for foods that have a single nutrient that exceeds the nutrient profile, provided a statement about the specific nutrient appears in close proximity to, on the same side and with the same prominence as the claim – *e.g.*, “high in X content” where X is the name of the nutrient exceeding the profile.

salt/sodium); c) the choice of reference quantity/basis for profiles; d) the approach to the calculation of profiles; e) the feasibility and testing of a proposed system (European Parliament, 2006).

In addition to the more obvious health claim wording requirements (e.g., stating the food and the conditions for use; the health effect; relevant warnings), the EU requires health claim wording to account for the importance of a balanced diet and a healthy lifestyle. Additionally, for disease risk reduction claims, a statement must appear that indicates the disease to which the claim refers has multiple risk factors and that altering one of these risk factors may or may not have a beneficial effect (European Parliament, 2006). See Table 2.3.5-1.

Table 2.3.5-1	Statements to be Included in Health Claims (European Parliament, 2006)
	A statement indicating the importance of a varied and balanced diet and a healthy lifestyle.
	The quantity of the food and pattern of consumption required to obtain the claimed beneficial effect.
	Where appropriate, a statement addressed to persons who should avoid using the food.
	An appropriate warning for products that are likely to present a health risk if consumed to excess.
	For disease risk reduction claims, a statement indicating that the disease to which the claim is referring has multiple risk factors and that altering one of these risk factors may or may not have a beneficial effect.

2.3.6 Regulatory Processes Pertaining to Health Claim Approvals

2.3.6.1 *Timelines*

After approval of the final Community List of permitted Article 13 claims (expected by January 31, 2010), petitions can be submitted for additional claims not already on the list and based on newly developed scientific evidence and/or which include a request for the protection of proprietary data to be reviewed. The application would be submitted to a Member State which would acknowledge receipt of the application, in writing, within 14 days. Information to be included in the application is outlined in Table 2.3.4.1-2 and generally would include copies of scientific studies to support the claim; characteristics of the food; the health effect; the proposed claim wording; and specific conditions for use. EFSA would receive the application “without delay” from the Member State and conduct a scientific assessment of it, issuing an opinion within 5 months from date of its receipt with an extension up to one month if additional information is required from the applicant; in such a case, the applicant would be required to submit the requested information within 15 days from receipt of EFSA’s request. The EC shall make a decision on the application and the inclusion of the claim onto the Community list within 2 months of receipt of EFSA’s opinion, taking into account not only EFSA’s opinion but also Member State consultations, Community law and other “legitimate factors” relevant to the matter (European Parliament, 2006).

To stimulate product innovation, EFSA and the EC is committed to an expedited process of 7 months for the review and decision of an Article 13 claim based on newly developed science and/or proprietary data (European Parliament, 2006).

For Article 14 claims, following a completeness check and the formal acceptance of the validated dossiers, EFSA will assess the health claim and provide a scientific opinion within 5 months (European Food Safety Authority, 2007d).

2.3.6.2 *Transparency*

EFSA is legally obliged to be transparent. It must publish outcomes of its scientific work and management documentation (budgets, accounts, contracts) on its website. Additionally, it is to establish a “Community Register”, made available to the public, on all authorized and rejected health claims with conditions for use for the former and reasons for rejections regarding the latter. Health claims authorized on the basis of proprietary data will also be included on the Register with the name of the original applicant and the fact that the claim is restricted for use stated; a subsequent applicant can obtain authorization for the same claim assuming it does not make reference to the original applicant’s proprietary data (EFSA, 2007a).

2.3.6.3 *Marketing Opportunities*

Article 13 or 14 claims based on proprietary data are restricted for use by their applicant. However, a subsequent applicant can obtain authorization for the same claim if the original applicant has agreed that the scientific data and information marked proprietary may be used by the subsequent applicant, or, EC decides the claim could have been authorized without the submission of the data deemed proprietary. If neither of the aforementioned conditions hold, the scientific data and other information marked as proprietary in an Article 13 or 14 claim submission may not be used for a period of 5 years from the date of authorization of the health claim (European Parliament, 2006). After a 5-year period, the health claim would require re-approval and if re-approved, data would no longer be held “proprietary” and other companies would have access to the scientific data submitted.

2.3.7 Functional Foods

The subject of nutrition claims in the EU can be an “other substance”; that is, a substance other than a nutrient that has a nutritional or physiological effect (European Parliament, 2006), such as a bioactive. Moreover, the subject of Article 13 and Article 14 claims can be a food constituent (e.g., a bioactive). Functional foods thus fall into the scope of regulation of foods with health claims.

Additionally, within EFSA, there is a Panel which provides independent scientific advice on the safety of food processes excluding cooking (e.g. irradiation) and the safety of substances

deliberately added to food or used in contact with food, including “so-called functional ingredients” commonly found in functional foods (EFSA, 2007c).

2.3.8 Highlights of EU’s Management of Health Claims and Related Processes

Highlights of EU’s management of health claims and related processes are outlined in Table 2.3.8-1 and Table 2.3.8-2.

Table 2.3.8-1	Highlights of the EU’s System Pertaining to Evidence Requirements for Health Claim Substantiation
<p>Health claim substantiation for Article 14 claims requires information on efficacy and quality; safety assessed separately in a novel food submission.</p>	<p>The EU has asked EFSA to provide input on nutrient profiling as a criterion for health claims by December 2007.</p>
<p>A trademark, brand name or fancy name appearing in the labelling, presentation or advertising of a food which may be construed as a health claim may be used without undergoing authorization procedures provided that it is accompanied by a related health claim.</p>	<p>An electronic workable template for Article 14 health claim applications available.</p>
<p>Guidance document for Article 14 health claim applications detailed and ensures transparency and comprehensiveness of data evaluation.</p>	<p>Guidance document for Article 14 health claim applications requires a lot of unfavourable “back and forth” flipping from explanation of requirements to appendices (9 of them).</p>
<p>Tabulation and synopses of individual human studies in a health claim application for Article 14 claims very extensive.</p>	<p>Guidance document for Article 14 health claim applications includes a quality appraisal tool (<i>i.e.</i>, a checklist) but does not require determination of a quality score or quality rank.</p>

Table 2.3.8-2 Highlights of the EFSA’s System Concerning its Structure, Organization, and Processes Pertaining to Health Claims

EFSA is legally obliged to be transparent.

EFSA is accountable to timelines for review of health claim submissions.

EFSA coordinated a conference in 2006 to provide a forum for an interactive exchange of expert views and experiences on the scientific substantiation of health claims and nutrient profiling; participants included Member States, non-member countries, academia, European Commission, European Parliament.

Recognition that “single products” have a relative importance in the context of the total diet.

Health claim regulation attempts to strike a balance between providing a high level of consumer protection, facilitating consumer choice, creating equal conditions of competition for the food industry, and facilitating free movement of foods between nations.

Expedited review process by EFSA for health claims based on newly developed science to stimulate product innovation.

Market advantages for health claims authorized on the basis of proprietary data in that the claim is limited for use by the applicant for a defined period of time.

Evaluation of the implementation of the health claim regulation framework to be submitted by January 2013 to European Parliament and Council. It is to address: the evolution of a market in foods with health claims; consumers’ understanding of claims; proposal for amendments, if necessary; impact of regulation on dietary choices; impact on obesity and non-communicable diseases.

Monitoring guidelines of foods with health claims recommended; Member States may require manufacturer of food with health claim to notify authority of the product to be marketed, by forwarding the label used for product.

A “grace period” for meeting new health claim regulations: foods that do not comply with regulation may be marketed until their expiry date but no later than July 2009 (2 years after regulation enforced); products bearing trade marks/brand names which do not comply with Regulation may be marketed until January 2022 (14.5 years after regulation enforced).

A public register containing the lists of authorized claims to be established and updated by the Commission to avoid duplicate applications.

Consideration of the needs of small to medium-sized enterprises –e.g., recommendation that EFSA make available appropriate technical guidance and tools to help them implement Regulation on nutrition and health claims.

Provisions made for member state specific health claims used in compliance with national provisions prior to EU regulation: Member states have to communicate to Commission by January 31, 2008, at the latest, such claims and the evidence substantiating them; the Commission shall adopt decision on such claims.

2.4 Japan

2.4.1 Organization and Function of Relevant Regulatory Bodies

Within the Japanese government, the government body that regulates foods and drugs is the *Ministry of Health, Labour and Welfare* (MHLW). MHLW provides standards and regulations pertaining to food. More specifically, within the MHLW exists a *Pharmaceutical and Food Safety Bureau* within which there is a *Department of Food Safety*. The Department of Food Safety has three divisions: *Policy Planning Division*; *Standards and Evaluation Division*; and an *Inspection and Safety Division*. The Standards and Evaluation Division establishes specifications and standards for food, food additives, food labelling, pesticide residues, and animal drug residues. Within the Standards and Evaluation Division is the *Office of Health Policy on Newly Developed Food* which is responsible for nutrition labelling standards, foods with health claims, dietary supplements, and the safety assessment of genetically modified foods (MHLW, 2006d).

2.4.2 Relevant Legislation

In Japan, products are classified as food or drugs; there is no in-between category for products considered as dietary supplements. See Table 2.4.2-1 for Japan's definition of a drug. Thus relevant legislation is food-related and pharmaceutical-related, to address issues pertaining to conventional foods, and products in non-conventional food form (e.g., tablets, capsules) that are not considered drugs. Relevant legislation includes the *Food Safety Law*, *Food Sanitation Law* and the *Pharmaceutical Affairs Law* (Ohama *et al.*, 2006).

Based on the *Pharmaceutical Affairs Law*, two lists are issued by MHLW that identifies substances as "drugs" or "non-drugs". Each of these lists is subcategorized into substances of plant origin, animal origin, or others (e.g., food additives). Vitamins, minerals, and 23 amino acids are excluded from the drug category (Ohama *et al.*, 2006).

The *Health Promotion Law* prohibits exaggerated and misleading claims on foods and requires claims to be substantiated by scientific evidence. Non-compliance with the *Health Promotion Law* results in imprisonment for up to 6 months or a fine (Ohama *et al.*, 2006).

Table 2.4.2-1 Definition of a Drug in Japan (Ohama *et al.*, 2006)

<p>Items recognized in the Japanese Pharmacopoeia;</p> <p>Items (other than quasi-drugs) that are intended for use in the diagnosis, cure, or prevention of disease in man and animal, and which are not equipment or instruments;</p> <p>Items (other than quasi-drugs and cosmetics) that are intended to affect the structure or functions of the body of man or animal</p>
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2.4.3 Profile and Regulation of Health Claims

Foods with health claims include “Foods with Nutrient Function Claims” (FNFC) and “Foods for Specified Health Uses” (FOSHU). They are regulated by the *Health Promotion Law* and are thus prohibited from making exaggerated, misleading claims and claims that are not substantiated by scientific evidence. “Nutrient Function Claims” on FNFC are pre-approved claims by MHLW. “Specific health uses” for FOSHU require approval by MHLW through a standard, qualified, or individual route of approval. See Table 2.4.3.2-1 and Table 2.4.3.2-2.

“So-called health foods” are another category of foods that make claims that are exaggerated and misleading and have led to consumer contamination with toxic substances, over-dosing, and contraindicated drug interactions. Reasons for this are twofold: 1. So-called health foods are not regulated by the Health Promotion Law; their regulation depends on various laws; and, 2. So-called health foods do not require approval by MHLW (Ohama *et al.*, 2006). See Table 2.4.3.2-1.

Japan ranks the scientific evidence to support claims on FNFC or FOSHU according to A, B, or C ranks, in order of decreasing scientific support. Weak science (Rank C) is sufficient to approve FOSHU products through a qualified FOSHU route of approval. See Tables 2.4.3.2-1 and 2.4.3.2-2 (Ohama *et al.*, 2006; MHLW, 2006c).

2.4.3.1 Foods with “Nutrient Function Claims” (FNFC)

“Nutrient function claims” (NFC) on FNFC are based on rank A (the highest) scientific evidence and are structure/function claims for 17 nutrients -12 vitamins and 5 minerals. They describe the function of vitamins or minerals in the maintenance of healthy skin and mucosa; vision; utilization of energy from protein or carbohydrates; red cell production; calcium absorption from the gut and growth of bone; protection of body fat from oxidation; cell health; normal foetal growth; maintenance of taste; development of bone and teeth; function of enzymes; bone formation; blood circulation; and energy generation (MHLW, 2006b). See Table A-2 in Appendix A.

For manufacturers to use NFCs, they must follow specifications regarding levels of the vitamins/minerals to be added in the food and must include warning statements on the foods (MHLW, 2006b).

2.4.3.2 Foods for “Specified Health Uses” (FOSHU)

Unlike NFCs which are claims that refer to the function of nutrients (vitamins and minerals), FOSHU carry claims that refer to the function of nutrients and other food ingredients. Also unlike NFCs which are structure/function claims, FOSHU includes claims on structure/function or disease-reduction. The claims can be supported by ranks A, B, or C levels of scientific evidence (Ohama *et al.*, 2006).

A product seeking FOSHU status must demonstrate safety, quality and efficacy, although with different rigor depending on whether the product is seeking FOSHU status through “individual”, “standardized”, or “qualified” routes; the “individual” route of approval is for disease-risk reduction claims, of which two have been approved – folic acid and neural tube defects; and calcium and osteoporosis (MHLW, 2006c). Safety, quality, and efficacy are evaluated by different bodies within MHLW (Ohama *et al.*, 2006).

The manufacturers of FOSHU are generally companies with strong research and development that can absorb the costs of demonstrating safety, quality, and efficacy of their products. As of December 2005, ~569 products were approved as FOSHU with specified health effects on intestinal conditions; cholesterol/triglycerides; blood sugar; blood pressure; teeth; bone; and iron supply (Ohama *et al.*, 2006). The 2 most popular health effects are regarding intestinal conditions (~45% of FOSHU claim this effect) and on cholesterol/triglycerides levels (~20.6% of FOSHU claim this effect). See Table 2.4.3.2-3.

Table 2.4.3.2-1 A Comparison of FNFC, FOSHU, and “so-called health foods” (MHLW, 2006b, 2006c; Ohama <i>et al.</i>, 2006)			
	Foods with “Nutrient Function Claims” (FNFC)	Foods for “Specified Health Uses” (FOSHU)	“So-called health foods”
Definition	Refers to all food that is labelled with the nutrient function claims specified by the MHLW	Refers to food containing ingredients with functions for health and officially approved to claim its physiological effects on the human body	No formal or informal definition exists
Subject of claim	Nutrients	Nutrients or ingredients in a food	Nutrients or ingredients in a food
Health effect in claim	On structure or function of body	On structure or function of body or disease risk reduction	Prohibited but statements on nutrient content allowed
Approval by MHLW	No – they are essentially pre-approved claims available for use assuming nutrient content specifications met and warning/advisory statements included on food	Yes – product-specific approval	No – products not regulated
Level of scientific evidence required	Rank A scientific evidence	Ranks A, B, or C scientific evidence	None – products not regulated

Table 2.4.3.2-2 A Comparison of FOSHU Routes of Approval (MHLW, 2006c; Ohama et al., 2006)	
FOSHU Route of Approval	Details
Individual – Reduction of disease risk	Reduction of disease risk is clinically and nutritionally established in an ingredient Rank A scientific evidence: Evidence is medically and nutritionally established from scientific point of view
Standardized	Standards and specifications are established; products must meet standards and specifications Rank A scientific evidence: Evidence is medically and nutritionally established from scientific point of view Rank B scientific evidence: Accumulation of scientific evidence
Qualified	Food with health function which is not substantiated on scientific evidence that meets level of FOSHU – e.g., food has a certain effectiveness but mechanism of effect not established; see footer 4 in Table 2.4.4-1 Rank C scientific evidence: evidence not established but efficacy is suggested

Table 2.4.3.2-3 Profile of “Specified Health Uses” Approved for Products Classified as FOSHU (Ohama et al., 2006)		
Specified health use	Number of FOSHU products approved (%)	Approved ingredients
Intestinal condition (improving balance of enterobacterium; promoting regular bowel movements)	254 (44.6%)	Oligosaccharides, lactobacillus, bifidobacterium, psyllium husk, indigestible dextrin, wheat bran, low molecular sodium alginate, partially hydrolyzed guar gum
Cholesterol/triglycerides	117 (20.6%)	Soy protein, chitosan, low molecular sodium alginate, peptides, diacylglycerol, plant sterol/stanol (esters), green tea catechin, middle chain fatty acid, DHA, EPA, degradation of products of globin protein, psyllium husk
Blood sugar	71 (12.5%)	Indigestible dextrin, L-arabinose, wheat albumin
Blood pressure	64 (11.2%)	GABA, peptides
Teeth (maintenance of strong and healthy teeth)	34 (6.0%)	Xylitol, polyols, tea polyphenols, CPP-ACP
Bone (calcium absorption; maintenance of calcium in bone)	26 (4.6%)	Soy isoflavone
Iron supply (for susceptibility to anaemia)	3 (0.5%)	Heme iron
Total	569 (100%)	

2.4.4 Guidance Documents for Health Claim Substantiation

MHLW’s website does not provide any information on the requirements for a FOSHU submission nor does it have guidance documents or application forms for FOSHU submissions. However, the *Japan Health Food and Nutrition Food Association (JHFNFA)* has materials available to guide FOSHU submissions and provides assistance with applications for FOSHU.

JHFNFA is a public corporation founded by the MHLW; it is supported by industry companies (JHFNFA members). Its aim is to heighten the quality of dietary supplements and to protect consumer health (Food Chemical Newspaper, 2006). In March 2006, it published a manual and a separate question/answer booklet, available in Japanese only, to guide applicants of FOSHU. Unfortunately, JHFNFA’s website is only available in Japanese.

The *National Center of Excellence in Functional Foods* has, however, published a 5-page document that includes a summary of JHFNFA’s recommendations for applicants of FOSHU (National Center of Excellence in Functional Foods, 2004). See Table 2.4.4-1. Efficacy, safety, and quality data are required for a FOSHU application; data from human clinical studies are a critical requirement for the assessment of efficacy of a FOSHU product.

Table 2.4.4-1 Details Required by MHLW in the Approval of a FOSHU Product (Ohama <i>et al.</i>, 2006; National Center of Excellence in Functional Foods, 2004)	
Item to be Evaluated	Requirements²
Safety ¹	<p>Absence of safety issues; documentation to support safety of product or its functional components.</p> <p>Safety confirmed by demonstrating historical diet uses in Japan and foreign countries and conducting toxicity tests that include using an overdose (3 to 5-fold) of the established dosage level and appropriate statistical analyses.</p> <p>Toxicity studies include acute, sub-acute, chronic toxicity tests. Reproductive toxicity, carcinogenicity or teratogenicity studies may be required depending on results of toxicity studies or if the product contains a new ingredient not previously found in the list of approved FOSHU products.</p> <p>Use of nutritionally appropriate ingredients (<i>e.g.</i>, no excessive salt, <i>etc.</i>)</p> <p>All toxicity tests must be performed under GLP conditions.</p>

Table 2.4.4-1 Details Required by MHLW in the Approval of a FOSHU Product (Ohama <i>et al.</i>, 2006; National Center of Excellence in Functional Foods, 2004)	
Item to be Evaluated	Requirements²
Quality	<p>Description of product formulation/compositional analysis</p> <p>Physicochemical properties</p> <p>Manufacturing procedure</p> <p>Factory equipment used</p> <p>Accurate determination of active constituent</p> <p>Guarantee of compatibility with product specifications at time of consumption</p> <p>Established quality control methods such as specifications of products and ingredients, processes, and methods of analysis</p> <p>Stability of ingredients and formulated product</p> <p>Shelf-life</p> <p>Use and description of relevant test methods³</p> <p>Certificate of nutrient analysis and energy calculation</p>
Efficacy	<p>Effectiveness in human body clearly proven</p> <p>Data from human clinical studies crucial for determining approval as a FOSHU product</p> <p>Clinical studies must be approved by ethics committee; should be R, PC, DB; should use appropriate statistical analyses; results must show statistical significance against the control at $p < 0.05^4$; subjects for studies should be healthy or borderline between health and illness</p> <p>Discussion of mechanism of action and established dosage level</p> <p>Documentation that shows clinical and nutritional proof of product's functional effects for maintenance of health</p> <p>Documentation that shows clinical and nutritional proof of intake amount of product or its functional components</p>

Table 2.4.4-1 Details Required by MHLW in the Approval of a FOSHU Product (Ohama <i>et al.</i>, 2006; National Center of Excellence in Functional Foods, 2004)	
Item to be Evaluated	Requirements²
Other	Scientific documentation demonstrating the medical or nutritional basis for a health claim Objective of developing product Rationale of how product makes contribution to the improvement of one's diet and maintenance of health of entire population Consumer needs satisfied with product Samples of the entire package with labels and claims List of ingredients and composition percentage Instructions for preparation, storage, or intake Daily intake amount Considerations and precautions at intake
¹ Clinical studies to demonstrate safety may not be required. ² The amount of scientific documentation that manufacturers must submit has been reduced. A requirement that all studies be published in a scientific journal; an industry-sponsored journal has been deemed acceptable by MHLW. Additionally, much of the responsibility for reviewing applications has been turned over by the MHLW to local authorities. ³ MHLW eliminated requirement that products be tested by the National Health and Nutrition Laboratory; now, the manufacturer's own analytical tests are accepted by MHLW. ⁴ For qualified claims: acceptable statistical significance is <0.10. If the clinical study is R, C, mechanism of action may not need elucidation; if clinical study is NR, C, mechanism of action needs elucidation.	

2.4.5 Regulatory Processes Pertaining to Health Claim Approvals

MHLW's website does not provide any information pertaining to regulatory processes concerning FOSHU; however, the *National Center of Excellence in Functional Foods* indicates that the application process for FOSHU takes approximately one year (National Center of Excellence in Functional Foods, 2004). No information on transparency, fees or other relevant topics is provided by MHLW or related agencies.

2.4.6 Health Claim Wording and Eligibility

Japan does not have requirements concerning the nutritional profile of foods for them to be FOSHU although their labels must include a table of nutritional values and calories in addition to the product's effect on health and other statements as indicated in Table 2.4.6-1 (Ohama *et al.*, 2006; National Center of Excellence in Functional Foods, 2004).

Table 2.4.6-1	Required Information in the Labelling of a FOSHU Food (Ohama <i>et al.</i> , 2006; National Center of Excellence in Functional Foods, 2004)
Effect on health	General health guidelines – <i>i.e.</i> product should be consumed as part of a balanced diet
Table of nutritional values and calories	Indication that product is a “Food for Specific Health Use”
Recommended intake	Warning against excessive intake
Special cautions relating to intake, cooking or storage	Name and address of person (corporation) to whom the approval was granted if this person (corporation) is not the manufacturer

2.4.7 Functional Foods

Although Japan has been credited with coining the term “functional foods” in 1984, the government prohibited the use of this term since it implied “drug-like” effects. As a result, the term “health foods” became widely used. Health foods refer to foods with health claims (FNFC and FOSHU) in addition to “so-called health foods” (Ohama *et al.*, 2006).

Japan permits health foods to be sold as tablets, capsules, powders, liquids, *etc.*, although sublingual tablets and sprays into the oral cavity are prohibited. Foods with health claims (*i.e.*, FNFC, FOSHU) are generally functional foods in conventional food form and not in a form typical of dietary supplements (tablets, capsules), whereas “so-called health foods” are generally dietary supplements and mostly include herbal or botanical products (Ohama *et al.*, 2006).

Japan’s regulation of functional foods has been criticized. Although products approved as FOSHU indicate such an approval on the product’s label, the *Japan Health Food and Nutrition Food Association* offers its own “seal of approval” of product, increasing consumer confusion (National Center of Excellence in Functional Foods, 2004).

2.4.8 Highlights of Japan’s Management of Health Claims and Related Processes

Highlights are outlined in Table 2.4.8-1 and Table 2.4.8-2.

<p>Table 2.4.8-1</p>	<p>Highlights of Japan’s System Pertaining to Evidence Requirements for Health Claim Substantiation</p>
<p>Safety, quality and efficacy addressed in a FOSHU submission.</p> <p>No guidance provided by MHLW on the expected content of FOSHU submissions. Guidance documents/application information for FOSHU published by the <i>Japan Health Food and Nutrition Food Association</i>; however, their website and the supportive materials are only available in Japanese.</p>	

<p>Table 2.4.8-2</p>	<p>Highlights of Japan’s System Concerning Its Structure, Operations, and Processes Pertaining to Health Claims</p>
<p>MHLW has a non-user friendly website with no guidance provided on the application process for FOSHU submissions. Guidance documents/application information for FOSHU published by the <i>Japan Health Food and Nutrition Food Association</i>; however, their website and the supportive materials are only available in Japanese. Regulated and unregulated environments for health foods: FNFC and FOSHU are regulated while “so-called health foods” are not.</p> <p>Much of the responsibility for reviewing FOSHU applications has been turned over by the MHLW to local authorities.</p> <p>Products classified as either foods or drugs; there is no in-between legal category and products in non-conventional food forms (tables, capsules) are regulated as foods</p> <p>Although products approved as FOSHU indicate such an approval on the product’s label, the <i>Japan Health Food and Nutrition Food Association</i> offers its own “seal of approval” of products, increasing consumer confusion.</p>	

2.5 United States

2.5.1 Organization and Function of Relevant Regulatory Bodies

The *Office of Nutritional Products, Labeling, and Dietary Supplements* (ONPLDS), *Center for Food Safety and Applied Nutrition, Department of Health and Human Services, United States Food and Drug Administration* (FDA) is responsible for developing policy and regulations for dietary supplements; nutrition labelling; development of food standards; and, scientific evaluation to support regulations and policy development (U.S. FDA, 2007b). ONPLDS receives and evaluates health claim petitions.

2.5.2 Relevant Legislation

The *Federal Food, Drug and Cosmetic Act*, the *Food and Drug Administration Modernization Act* (FDAMA) of 1997; the *Code of Federal Regulations* (CFR), and the *Nutrition Labeling and Education Act* (NLEA) of 1990 are relevant food legislation in the United States (U.S. FDA, 2006e).

NLEA was designed to make available scientifically valid information, to consumers, about the foods they eat. Among other provisions, NLEA authorized FDA to allow statements that describe the relationship between a nutrient and a disease or health related condition on foods and dietary supplements – *i.e.*, health claims (U.S. FDA, 1999a).

FDAMA amended the *Federal Food, Drug, and Cosmetic Act* relating to the regulation of food, drugs, devices, and biological products to adapt FDA's operations to the 21st century's advances in technology and trade. FDAMA eliminated the requirement of FDA's pre-market approval for most food packaging and substances that come into contact with food, and expanded procedures for the authorization of health claims and nutrient content claims (U.S. FDA, 1998a).

2.5.3 Profile and Regulation of Health Claims

Health claims refer to an implied or expressed statement on foods that represent a relationship between a substance (*i.e.*, specific food or component of food) and a disease (damage to an organ, part, structure, or system of body) or health-related condition (a state of health that leads to a disease) (U.S. FDA, 2006d). See Table 2.5.3-1.

Foods and dietary supplements that permissibly characterize a relationship of a food to a disease or health-related condition are not regulated as drugs solely because they contain such claims (U.S. FDA, 2004).

Health claims are of two types: qualified (by FDA) or authorized (by FDA, a federal scientific body or the National Academy of Sciences). Structure/function claims and nutrient content

claims are not considered health claims. All claims can be made for foods and dietary supplements (U.S. FDA, 2003b). See Table 2.5.3-2.

Although structure/function claims are not classified as health claims, they can describe a relationship between food and health (e.g., health maintenance, general well-being) or conditions associated with various life stages that naturally occur (e.g., menopause symptoms). Structure/function claims must not express or imply a disease state or conditions/processes/symptoms/signs that lead to or are characteristic of a disease that are not also characteristic of a non-disease state. See Table 2.5.3-3.

Conventional foods differ in their eligibility for structure/function claims compared to dietary supplements in that the subject of the claim for the former must have “nutritive value” (a value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy) - a criterion not required for dietary supplements. Additionally, for conventional foods, FDA does not have to be notified of structure/function claims nor is a disclaimer required; the disclaimer for dietary supplements making structure/function claims must state “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease” (U.S. FDA, 2002a, 2003b). See Table 2.5.3-2.

Prior to FDAMA, companies could not use a health claim or nutrient content claim in food labelling unless FDA published a regulation authorizing such a claim. FDAMA permits distributors and manufacturers to use such claims on foods, without a published regulation, if such claims are based on current, published, authoritative statements from certain federal scientific bodies or the National Academy of Sciences and upon notification to, and without rejection by, the FDA (U.S. FDA, 1998b).

Table 2.5.3-1 Legal Definition of Health Claim in the U.S. and Main Points of Definition (U.S. FDA, 2006d)	
Legal Definition of a Health Claim	Key points from definition
<p>Any claim made on the label or in labelling of a food, including a dietary supplement, that expressly or by implication, including “third party” references, written statements (e.g., a brand name including a term such as “heart”), symbols (e.g., a heart symbol), or vignettes, characterizes the relationship of any substance¹ to a disease² or health-related condition.</p> <p>Implied health claims include those statements, symbols, vignettes, or other forms of communication that suggest, within the context in which they are presented, that a relationship exists between the presence or level of a substance in the food and a disease or health-related condition.³</p>	<p>Applies to conventional foods or dietary supplements</p> <p>Refers to expressed or implied claims in written statements or symbols</p> <p>Represents a relationship between a substance (i.e., specific food or component of food) and a part or system of the body that does not function properly because it is damaged (or state of health that leads to such dysfunctioning)</p>
<p>¹ Substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement that includes vitamins, minerals, herbs, or other similar nutritional substances.</p> <p>² Disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that disease resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition.</p> <p>³ The stated claim or a “reference statement” which states location of full claim on the food package must appear in immediate proximity to graphics that suggest/imply health claim.</p>	

Table 2.5.3-2 A Description of U.S. Claims Classified or Not Classified as Health Claims (U.S. FDA, 2003b)				
	Claims Classified as Health Claims		Claims Not Classified as Health Claims	
Classification	Qualified Health Claims	Authorized Health Claims¹	Structure/Function Claims	Nutrient Content Claims
Applicability	Conventional food/food component Dietary supplement ²	Conventional food/food component Dietary supplement ²	Conventional food/food component ³ Dietary supplement ²	Conventional food/food component Dietary supplement ²
Subject of claim related to health outcome	A disease or health-related condition (see footer 2 in Table 2.5.3-1)	A disease or health-related condition (see footer 2 in Table 2.5.3-1)	Normal structures or functions in humans; general well-being; signs, symptoms that are characteristic of non-disease states; a benefit related to a nutrient deficiency disease as long as statement also describes prevalence of disease in the U.S.	None - states or implies the level of a nutrient outside the Nutrition or Supplement Facts Table ⁴

Table 2.5.3-2 A Description of U.S. Claims Classified or Not Classified as Health Claims (U.S. FDA, 2003b)				
	Claims Classified as Health Claims		Claims Not Classified as Health Claims	
Classification	Qualified Health Claims	Authorized Health Claims¹	Structure/Function Claims	Nutrient Content Claims
Level of scientific support	Moderate, low or extremely low; not based on significant scientific agreement (SSA). See Table 2.5.4-3.	High; based on significant scientific agreement (SSA). See Table 2.5.4-3.	Not prescribed. Food manufacturer should be confident that the claim is based on adequate information	n/a
Level of scientific evidence supporting claim included in claim statement	Yes - e.g., "one small study suggests.... however, this evidence is limited and not conclusive"	No	No	No
FDA approval for claim use	Yes - FDA either rejects the claim or issues "a letter of enforcement discretion" in which FDA indicates it does not object to use of the claim so long as it follows FDA's specifications for claim wording	Yes - FDA publishes an interim or final rule in the regulations (Federal Register)	No	No
Notification to FDA by food manufacturer	No	No	Conventional foods: No Dietary supplements: Yes (no later than 30 days after marketing the dietary supplement; includes text of S/F claim)	No for pre-approved claims Yes for a claim not included in the regulations and based on an authoritative statement by a U.S. government scientific body
Truthful and not misleading	Yes	Yes	Yes	Yes
FDA Disclaimer	No	No	Conventional foods: No Dietary supplements: Yes; disclaimer required that states "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."	No

Table 2.5.3-2 A Description of U.S. Claims Classified or Not Classified as Health Claims (U.S. FDA, 2003b)				
	Claims Classified as Health Claims		Claims Not Classified as Health Claims	
Classification	Qualified Health Claims	Authorized Health Claims¹	Structure/Function Claims	Nutrient Content Claims
Eligibility criteria regarding other nutrients that are not subject of the claim	Yes ⁵	Yes ⁵	No	Yes ⁶
<p>¹ Refers to Nutrition Labeling and Education Act (NLEA) Authorized Health Claims. However, health claims for foods, but not dietary supplements, can also be authorized based on authoritative statements from a scientific body of the U.S. Government or the National Academy of Sciences, as a result of the Food and Drug Administration Modernization Act (FDAMA). FDAMA upholds the “significant scientific agreement” (SSA) standard for health claims and requires notification to FDA of the claim at least 120 days before its use on products. In its review of a health claim based on an authoritative review, FDA intends to determine whether SSA has been achieved and may issue a regulation to prohibit or modify the claim. See Table 2.5.4-3.</p> <p>² "Dietary supplement" means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any aforementioned ingredient.</p> <p>³ Foods/food components must have “nutritive value” - “a value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy”. There is a growing inability on FDA’s part to clearly define “nutritive value” due to the progression and evolution of science and food processing and to new perspectives regarding nutrition. Food components (e.g., bioactive ingredients) must be “generally recognized as safe” (GRAS) and/or have passed a food additive review and the active ingredient and vehicle for the active ingredient must be a “food”. A food is defined as “consumed primarily for taste, aroma, or nutritive value”. The qualification of a food or food component being used “primarily” for taste, aroma, or nutritional value has provided some degree of flexibility in considering appropriate structure and function claims.</p> <p>⁴ A manufacturer may make a statement about a nutrient for which there is no established daily value so long as the claim specifies the amount of the nutrient per serving –e.g., "x grams of omega-3 fatty acids". To use the words "contains" or "provides" for nutrients without DV's, the specific amount of the nutrient must be stated –e.g., "Contains x grams of omega-3 fatty acids per serving" or "Provides x g of omega-3 fatty acids".</p> <p>⁵ Food contains, prior to fortification, 10% or more of the Daily Value (DV) for one of six nutrients - vitamin A, vitamin C, calcium, protein, iron, or fibre; and, food contains less than the specified levels of four nutrients - fat, saturated fat, cholesterol, sodium. Exceptions are if alternative levels provided for in regulations or if FDA approves exception because food will assist consumers in maintaining healthy dietary practices; disclosure statement would be included highlighting nutrient that exceeds disqualifying level e.g., ‘See nutrition information for X content’, where X is nutrient that has exceeded permissible levels.</p> <p>⁶ If food, meal product or main dish product exceed specified levels of fat, saturated fat, cholesterol and sodium, a disclosure statement would need to be included on food –e.g., ‘See nutrition information for X content’, where X is nutrient that has exceeded permissible levels.</p>				

Table 2.5.3-3 Acceptable and Unacceptable Structure/Function Claims for Foods and Dietary Supplements in the U.S. (U.S. FDA, 2002b).			
Acceptable structure/function claims for foods		Unacceptable structure/function claims for foods	
Claim	Rationale for why acceptable	Claim	Rationale for why unacceptable
“A good diet promotes good health and prevents the onset of disease”	Claim infers the effect is not a result of the product itself	“Promotes good health and prevents the onset of disease”	Claim infers the effect is a result of the product itself
“Improves absentmindedness”	Although associated with a disease state (e.g., Alzheimer’s disease), it is also characteristic of a non-disease state		
“Supports the immune system”	Not specific enough to imply prevention of a disease because the immune system has both structure/function and disease-fighting roles	“Supports the body’s ability to resist infection”	Context of claim limited to disease prevention and treatment
“Counterbalances effect of drug X on nutrient Y depletion”	Adverse event (i.e., nutrient depletion) not a disease condition	“To maintain the intestinal flora in people on antibiotics”	Claim implies that product will prevent a pathogenic/disease condition (i.e. bacterial overgrowth)
“Fibre maintains bowel regularity”	Maintenance of normal bowel function		

2.5.4 Guidance Documents for Health Claim Substantiation

The *Code of Federal Regulations* outlines general requirements for health claims – *i.e.*, their definition, eligibility criteria, labelling requirements, prohibited claims (U.S. FDA, 2006d) and, more specifically, requirements for health claim petitions (U.S. FDA, 2006c). Requirements for health claim petitions include information primarily on efficacy with limited data on quality assurance (e.g., to ensure amount of effective substance is present in food; non-clinical studies conducted in compliance with Good Laboratory Practices) and safety provided. Evidence on safety requires demonstration that the substance is an approved food additive or has GRAS status; the level of the substance at which an adverse effect may occur for any segment of the population; specific subgroups of the population that may be at risk with intake of the substance; positive or negative nutritional/health considerations with intake of the substance (e.g., changes in dietary practices and nutrient intakes); and an analysis of current dietary intakes and increased intakes of the substance due to use of the claim (U.S. FDA, 2006c). See Table 2.5.4-1.

For quality assurance, analytical data confirming an amount of the substance in foods that are candidates to bear the claim would be required in addition to data showing compliance with Good Laboratory Practices and ethics approval for clinical trials (U.S. FDA, 2006c).

To help petitioners understand the evidence requirements to support efficacy of a substance (food or component of food) on health/disease, the FDA published a draft guidance document (July 2007) for industry– *Evidence-based review system for the scientific evaluation of health claims* – that explains the approach FDA intends to use to evaluate the validity of health claims (U.S. FDA, 2007a). See Table 2.5.4-2.

The FDA recommends that validation of a health claim require application of a systematic evaluation of the totality of evidence on the claim – favourable and unfavourable evidence - which considers the methodological quality⁴ of studies conducted in humans (intervention and observational); relevance of the health claim to the U.S. population or a subgroup of it; and overall consistency of the evidence (*i.e.*, number of studies that show a statistically significant positive effect of the substance, taking into account the number of study types and sample sizes). Based on the strength of the totality of evidence, FDA determines whether an authorized or qualified health claim is justified or whether there is insufficient evidence to support any claim (U.S. FDA, 2007a).

The primary difference between qualified and authorized health claims relates to the level of scientific support. Qualified health claims are based on weaker science such as observational studies alone, or non-randomized intervention studies. As a result, they require claim language that describes (*i.e.* qualifies) the level of science that supports and/or does not support the claim so consumers are not misled into thinking there is a high level of scientific support for the claim⁵. Authorized claims are supported by stronger science; they require randomized, controlled intervention studies. As such, they do not require a disclaimer that qualifies or states the strength (or lack thereof) of evidence that supports the claim. See Table 2.5.4-3 for a comparison of evidence requirements.

⁴ The methodological quality of studies is evaluated at two steps in the systematic approach. The first step considers quality items that can individually trump the inclusion of a study from further review, whereas the second step grades the quality of the remaining studies as high, moderate or low. Both steps of quality appraisal addressed factors related to study design, conduct and analysis. No system of objectively rating study quality is included and thus no objective guidance is provided on what differentiates a high, moderate, or low quality study; rather, U.S. FDA states that high, moderate, low quality ratings are assigned based on the “extent of the deficiencies or uncertainties in the quality factors”.

⁵ The first Amendment does not permit U.S. FDA to reject health claims that the agency determines to be potentially misleading unless the agency also reasonably determines that a disclaimer would not eliminate the potential deception.

Table 2.5.4-1 Authorized and Qualified Health Claim Petition Requirements (U.S. FDA, 2006c)	
Factor	Details
Substance meets “eligibility criteria” for a health claim (includes safety information)	<p>Substance is associated with a disease/health-related condition of public health importance</p> <p>If substance to be consumed as a component of conventional food at decreased dietary levels, the substance must be a nutrient required to be included in the labelling of the food</p> <p>If substance (food or dietary supplement) not to be consumed at decreased levels, it must contribute taste, aroma, nutritive value¹, or a technical effect and retain that property when consumed at levels to justify claim, and be safe for use at levels necessary to justify use of claim (e.g., an approved food additive or GRAS)</p>
<p>Summary of scientific information, favourable and unfavourable (includes efficacy and safety information)</p> <p>See Table 2.5.4-2 for guidance</p>	<p>Evaluation of the evidence and indication that it supports significant scientific agreement²</p> <p>Substance conforms to definition of term “substance”</p> <p>Public health benefit of claim including, if appropriate, the prevalence of the disease/health-related condition in U.S. population</p> <p>Relevance of the claim in the context of the total daily diet</p> <p>If claim intended for a specific group of the population, a discussion of their dietary practices and nutritional needs and a justification of how the claim will help meet these needs</p> <p>Optimum level of substance to be consumed beyond which no benefit to be expected</p> <p>Level of substance at which an adverse effect occurs for any segment of the population</p> <p>Certain populations that need to receive special consideration</p> <p>Nutritional or health factors (positive or negative) to consider with consumption of substance – <i>i.e.</i>, adverse or beneficial changes in dietary practices and nutrient intakes with an analysis of current intakes plus increased intakes due to claim</p>
Quality assurance	<p>Analytical data to confirm amount of substance in foods that are candidates to bear the claim; if no AOAC method available, petitioner shall submit the assay method used and data establishing its validity</p> <p>Non-clinical laboratory studies conducted in compliance with Good Laboratory Practice Regulations; if not, a brief statement of reason for non-compliance</p> <p>Clinical studies conducted in compliance with requirements for institutional review (e.g., received ethics approval)</p>
Model health claim	<p>Model health claim shall include:</p> <ol style="list-style-type: none"> 1. A brief statement of the relevant conclusions of the scientific summary 2. Statement of how substance helps consumer to attain a total dietary pattern or goal associated with the health benefit

Table 2.5.4-1 Authorized and Qualified Health Claim Petition Requirements (U.S. FDA, 2006c)	
Factor	Details
Copies of information	<p>Copies of computer literature searches</p> <p>All information relied upon for support of claim (e.g., copies of publications or other information cited in review)</p> <p>All information concerning adverse consequences to any segment of population (e.g., sensitivity to substance)</p> <p>All information pertaining to the U.S. population</p>
<p>¹ Nutritive value” is defined in the CFR as “a value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy”.</p> <p>² For qualified health claims, rather than providing support for significant scientific agreement, a summary should explain how credible evidence supports the claim as worded in petition and why petitioner believes that the wording of claim including any disclaimer or other qualification is accurate and not misleading. FDA encourages inclusion of consumer research to document consumer understanding.</p>	

Table 2.5.4-2 FDA’s Systematic Approach for the Evaluation of Health Claims (U.S. FDA, 1999a, 2003c, 2007a)¹	
<p>Step 1. Identify studies that evaluate the substance/disease relationship The substance that is the subject of the claim is specified and measured The disease or health-related condition that is the subject of the claim is specified and measured (measurement of disease incidence, associated mortality, or validated surrogate endpoints that predict risk of a disease)</p>	
<p>Step 2. Categorize studies by type Intervention studies; observational studies (cohort, case-control, case-cohort, cross-sectional, ecological); research synthesis studies; animal and <i>in vitro</i> studies</p>	
<p>Step 3. Evaluate human studies¹⁶ FDA intends to evaluate each individual human study to determine whether any scientific conclusions about the substance/disease relationship can be drawn from the study. Certain critical elements of a study such as design, data collection, and data analysis may be so seriously flawed that they may make it impossible to draw scientific conclusions from study. FDA does not intend to use studies from which it cannot draw any scientific conclusions about the substance/disease relationship and plans <u>to eliminate</u> such studies from further review. Below are <u>examples</u> of questions the agency intends to consider to determine whether scientific conclusions can be drawn from the study.</p>	
<p>Intervention studies</p> <ul style="list-style-type: none"> - Baseline health status of subjects: are subjects healthy or do they have the disease that is the subject of the claim?² - Control group: was it appropriate?³ - Intake of substance: was its independent effect investigated or was it inappropriately co-administered with other components that could have affect health outcome of interest? - Comparability of groups at baseline: were levels of the health endpoint different between groups at baseline?⁴ - Statistical analysis of results: was it appropriate?⁵ - Biomarker: was it appropriate? - Study duration: was it appropriate?⁶ - Compliance to dietary advice: was there proper follow-up? - Study setting: was it relevant to U.S. population?⁷ 	
<p>Observational studies</p> <ul style="list-style-type: none"> - Information collected to measure food exposure: was it appropriate?⁸ 	

Table 2.5.4-2 FDA's Systematic Approach for the Evaluation of Health Claims (U.S. FDA, 1999a, 2003c, 2007a)¹

- Estimate of intake of substance: were validated dietary assessment methods used?⁹
- Relationship between disease and food/food component: Was it evaluated?¹⁰

Step 4. Assess methodological quality of studies (high, moderate, or low)¹⁶

For studies not eliminated in Step 3, their quality is rated as high, moderate or low. FDA intends to base their quality rating on several factors related to study design, data collection, quality of statistical analysis, type of outcome measured, and study population characteristics. If the study adequately addressed all or most of these factors, FDA plans to give it a high methodological quality rating; moderate or low quality ratings would be given based on the extent of deficiencies or uncertainties in quality factors. Examples of factors FDA intends to consider in assessing methodological quality of studies remaining at this point are indicated below.

Intervention studies

- Whether study was randomized, blinded and placebo controlled
- Description of inclusion/exclusion criteria and key information on characteristics of study population
- Assessment, explanation, and reasonability of study attrition

Observational studies

- Adequacy of adjustment for confounders of disease risk¹¹
- Type of dietary assessment method used to estimate dietary intake¹²

Step 5. Evaluate the totality of scientific evidence¹⁷

Based on the totality of evidence of studies from which scientific conclusions can be drawn, FDA determines whether the evidence in support of a substance/disease relationship outweighs the evidence against it and determines whether the evidence supports an authorized health claim, based on significant scientific agreement, or a qualified health claim, or no claim at all.

Within each study type (intervention, prospective cohort, case-control, cross-sectional) studies are reviewed for:

- Quantity: number of studies in the study type category and their sample sizes (e.g., range of sample sizes)
- Methodological quality: Studies with high, moderate, or low quality
- Outcome: Existence of a statistically significant difference between the group receiving the substance and the control group, at $p < 0.05$ ¹³
- Consistency: Consistency in the outcome; consistency among the studies in showing a statistically significant beneficial relationship between the substance and disease outcome¹⁴
- Relevance to the general U.S. population¹⁵

Step 6. Specify the claim language

¹ FDA's systematic approach is not described in such a step-by-step fashion in its guidance document as it is in this table.

² Health claims involve reducing the risk of a disease in people who do not have the disease that is the subject of the claim. However, FDA will consider studies with: 1. subjects at risk of getting the disease that is the subject of the claim – e.g., elevated LDL cholesterol levels; or 2. subjects who have the disease that is the subject of the claim if it is appropriate to extrapolate to individuals who do not have the disease – e.g., the mitigation/treatment effect of food substance in diseased populations is same as mechanism for risk reduction in non-diseased populations and the substance affects these mechanisms in the same way in both diseased and healthy people.

³ If an appropriate control is not included then it is not possible to ascertain whether changes in endpoint of interest were due to substance or due to unrelated and uncontrolled extraneous factors.

⁴ If baseline values for endpoint being measured are significantly different between groups, it is difficult to interpret independent effect of treatment on changes in health endpoint. Providing a "lead-in" or "wash-out" period, prior to randomization, for studies with a crossover design, can help reduce likelihood of different baselines.

⁵ Statistical analysis of the study data is a critical factor because it provides the comparison between subjects consuming the substance and those not consuming the substance to determine whether there is a reduction in risk of disease. For example: when conducting statistical analyses among more than two groups, data should be analyzed by a test designed for multiple comparisons (e.g., Bonferroni, Duncan); differences that are not statistically significant

Table 2.5.4-2 FDA's Systematic Approach for the Evaluation of Health Claims (U.S. FDA, 1999a, 2003c, 2007a)¹

should be described as not demonstrating a difference rather than as showing a trend; relative and absolute effects should be distinguished.

⁶ Studies that use a surrogate endpoint should be conducted long enough to ensure that any change in endpoint is due to intervention and not homeostatic changes to background diet, for example.

⁷ Study population must be relevant to general U.S. population or subgroup of population. Differences in nutrition (presence of malnourishment), diet (inadequate intakes of substance common), and disease risk factors (aetiology of disease different) between the United States and the country where a study was done may mean the study results cannot be extrapolated to U.S. population/subgroup of population.

⁸ Biological samples (e.g., blood, urine, tissue, hair) should be used to establish intake of substance only if a dose-response relationship has been demonstrated between intake of substance and level of substance in biological sample. In case-control studies, biological samples should not be used to measure intake of substance since its metabolism/concentration may be altered with disease (i.e. in subjects who are "cases").

⁹ A single 24-hour recall, dietary history, and food frequency questionnaire all have their limitations. Validation of dietary assessment tools is essential to draw conclusions from data.

¹⁰ Because observational studies estimate intakes of whole foods based on recorded dietary intake methods, it is difficult to ascertain an accurate intake amount of a food component, part of a whole food. Also, because whole foods and products such as multi-nutrient supplements consist of many food components, it is difficult to study the food components in isolation and thus observed effects could be due to the food component alone, or its interactions with other food components, or other food components acting alone or together, or displacement of other foods from the diet with the intake of the food substance. For this reason, scientific conclusions cannot be drawn about a relationship between a food component and a disease. Observational studies, however, can be used to measure associations between a whole food and a disease.

¹¹ There can be multiple non-dietary risk factors for a disease (e.g., smoking, body mass index, age) which should be accounted for in a study design/statistical analysis of results so that observed effects are correctly attributed to substance.

¹² Validated food frequency questionnaires are more reliable in estimating usual intake of foods compared to diet records or 24-hour food recall methods.

¹³ For intervention studies, the intervention group should be statistically significantly different from the control group at $p < 0.05$. For observational studies, confidence intervals for risk are significant when the value "1" is not included. For observational studies, many studies analyze the statistical significance of the linear relationship (trend) between the substance and the disease. Although this trend may be significant ($p < 0.05$), the difference in risk between the various levels of intake (e.g., tertiles, quartiles, quintiles) may not be significant; in that case, the studies show no effect.

FDA does not use magnitude of effect in their evaluation of outcomes between studies due to differences in study design and research conduct that may affect the magnitude of effect. FDA does consider magnitude of effect in their evaluation of outcomes within studies (e.g., when multiple treatments may be compared to a control group) since the same experimental conditions apply to such comparisons.

¹⁴ The greater the consistency among studies in showing a beneficial relationship, the greater the level of confidence that a substance/disease relationship exists. Conflicting results do not disprove an association (because the elements of study design may account for lack of effect) but tend to weaken confidence in the strength of an association.

¹⁵ FDA evaluates whether the totality of evidence supports a claim for the entire U.S. population or just a subgroup. If evidence only supports a claim for a subgroup, that information would be set out in the claim. If the substance is one that must be used for risk reduction at much higher levels than the normal U.S. intake, that information would also be reflected in the claim.

¹⁶ Quality assessment criteria not listed in FDA's "Guidance for Industry Evidence-Based Review System for the Scientific Evaluation of Health Claims" but included in FDA's "Guidance for Industry: Significant Scientific Agreement

Table 2.5.4-2 FDA’s Systematic Approach for the Evaluation of Health Claims (U.S. FDA, 1999a, 2003c, 2007a)¹

in the Review of Health Claims for Conventional Foods and Dietary Supplement”: Intervention studies: Efforts made to detect harmful as well as beneficial effects; appropriate wash-out period for cross-over designs; employment of a lead-in period for dietary interventions; description and measurement of background diets; assessment of dietary intake; research aim described; methodology clearly described; confounding factors identified and controlled for; sample size large enough to detect a significant effect.

¹⁷ Inference of a causal relationship not listed in FDA’s “Guidance for Industry Evidence-Based Review System for the Scientific Evaluation of Health Claims” but included in FDA’s “Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplement”: Causality can be best established by intervention data, particularly from randomized, controlled clinical trials that show altering the intake of a substance results in a change in the health endpoint. In the absence of such data, a causal relationship can be inferred from observational and mechanistic data through strength of association, consistency of association, independence of association, dose-response relationship, temporal relationship, effect of dechallenge, specificity, and biological plausibility.

Table 2.5.4-3 A Comparison of Substantiation Requirements for Authorized Versus Qualified Health Claims (U.S. FDA, 2003c)

	Type of Health Claim			
	Authorized	Qualified		
Level of comfort among qualified scientists that claim is valid ¹	High – Evidence meets SSA standard characterized by features listed in this column	Moderate	Low	Extremely Low
Acceptable quality of studies ²	- High	- High - Moderate	- Moderate - Low	- Moderate - Low
Acceptable study types ³	- Randomized, controlled intervention - Prospective observational cohort	- Randomized, controlled intervention - Prospective observational cohort - Nonrandomized intervention studies - Case control studies	- Nonrandomized intervention studies - Case control studies	- Non-randomized intervention studies - Case control studies
Sufficiency of number of individuals studied	Sufficient	Sufficient	Insufficient	Insufficient
Consistency of Evidence	High - Studies of different design would almost always result in similar findings	Moderate – Studies of similar or different design would generally result in similar findings	Low – Studies of different design would generally result in similar findings but uncertainties would exist	Very low – Studies of different design would generally result in similar findings but uncertainties would exist
Physiological meaningfulness of benefit	Physiologically meaningful	Reasonably considered to be physiologically meaningful	Uncertainties exist as to whether the benefit would be physiologically meaningful	Uncertainties exist as to whether the benefit would be physiologically meaningful

Table 2.5.4-3 A Comparison of Substantiation Requirements for Authorized Versus Qualified Health Claims (U.S. FDA, 2003c)				
	Type of Health Claim			
	Authorized	Qualified		
Benefit achievable under conventional intake and use conditions	Achievable	Reasonably considered to be achievable	Uncertainties exist	Uncertainties exist
¹ Comfort rank determined based on information specified in each column. ² Factors to be considered in evaluating quality are specified; however, no objective system is recommended for deciding between a high, moderate, or low quality study. ³ No claim will be approved if it is only supported by cross-sectional studies, case series, and/or analyses of secondary disease endpoints in intervention trials.				

2.5.5 Health Claim Wording and Eligibility

The FDA specifies maximum levels of total fat, saturated fat, cholesterol, and sodium above which the food will be disqualified from making a health claim unless an exception is provided. See Table 2.5.5-1. FDA may permit a claim despite the fact that a nutrient is present in the food that exceeds the disqualifying level if such a claim will assist consumers in maintaining healthy dietary practices. A disclosure statement must be included on the food in these circumstances that highlights the nutrient that exceeds the disqualifying level – e.g., “See nutrition information for X content”, where X is nutrient that has exceeded permissible levels (U.S. FDA, 2006c).

Except for dietary supplements or where provided for in regulations, the food must also contain 10% or more of the Reference Daily Intake or the Daily Reference Value for vitamin A, vitamin C, iron, calcium, protein or fibre per reference amount customarily consumer prior to any nutrient addition. See Table 2.5.5-2. The purpose of this provision is to prevent the use of health claims on foods of minimal nutritional value (U.S. FDA, 2006c).

If the claim is about a substance to be consumed at low or high levels and a definition for use of the term “low” or “high” has been established for the substance, respectively, the substance must be present at levels that meet those requirements. If no definition for “low” has been established, the level of the substance must meet the level established in the regulation authorizing the claim. If no definition for “high” has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect, as established in the regulation authorizing the claim (U.S. FDA, 2006c).

Claim wording must enable the public to understand the relative significance of the information in the context of a total daily diet. Additionally, where factors other than dietary intake of the substance affect the relationship between the substance and the disease or health-related condition, such factors may require declaration in the health claim; use of the word “may” to

characterize the relationship between the substance and the disease or health-related condition has been used in the past to indicate the disease or health-related condition is caused by many factors (U.S. FDA, 2006c).

For qualified health claims, claim wording must “qualify” the level of science that exists regarding the claim –e.g., “supportive but not conclusive research shows..” (U.S. FDA, 2003d).

	Total fat (g)	Saturated fat (g)	Cholesterol (mg)	Sodium (mg)
Per reference amount customarily consumed (RACC) and per label serving size Per 50 g for foods with RACC of 30 g or less or 2 tablespoons or less	13	4	60	480
Per label serving size for main dish products	19.5	6	90	720
Per label serving size for meal products	26	8	120	960

Nutrient	Reference Value	10% of Reference Value
Vitamin A	5000 I.U.	500 I.U.
Vitamin C	60 mg	6 mg
Iron	18 mg	1.8 mg
Calcium	1000 mg	100 mg
Protein	50 g	5 g
Fibre	25 g	2.5 g

2.5.6 Regulatory Processes Pertaining to Health Claim Approvals

2.5.6.1 Accountability

The FDA has a high level of accountability related to its activities; health claim petitions and their evaluation are no exception. Both the *Federal Food, Drug and Cosmetic Act* and the *Code of Federal Regulations* include timelines for decisions pertaining to food health claims with consequences if timelines for issuing regulations on authorized health claims are not respected – i.e., Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate must be provided with the reasons action on the regulation did not occur within 540 days. Authorization of qualified and authorized health claims can be up to 330 days (~1 year) and 640 days (~2 years), respectively, from the date of receipt of the petition (U.S. FDA, 2006a, 2006c). See Tables 2.5.6.1-1 and 2.5.6.1-2.

When a notification for a health claim or nutrient content claim is received based on an authoritative scientific body (notification of the claim should be received by FDA at least 120 days before the first introduction of the food with the claim in the marketplace), FDA intends to notify the submitter by letter within 120 days after submission when the notification does not comply with FDAMA; use of the claim is not authorized if it does not comply with FDAMA. The submitter may choose to revise the notification and resubmit it, in which case a food could not be marketed with the claim until at least 120 days after resubmission (U.S. FDA, 1998b).

Table 2.5.6.1-1 A Description of the Timelines for the Approval of an Authorized Health Claim in the U.S. (U.S. FDA, 2006c)	
Timeline	Action
Within 15 days of receipt of petition	Petitioner notified, in writing, of the following: <ol style="list-style-type: none"> 1. Date on which petition was received 2. That the petition is undergoing agency review 3. The petitioner will be notified of agency's decision to review or deny the petition
Within 100 days of receipt of petition ¹	Petitioner notified, in writing, of the following: That the petition has either been filed for comprehensive review or denied; reasons for denying the petition will be stated. If filed, the date of the letter becomes the "date of filing".
Within 90 days of date of filing of petition (<i>i.e.</i> , within 190 days of receipt of petition) ²	Petitioner notified, in writing, of the following: That the petition has been denied or that a <u>proposed</u> regulation to provide for the use of the health claim will be published in the Federal Register; reasons for denying the petition will be stated.
If petition not denied, within 90 days of date of filing of petition (<i>i.e.</i> , within 190 days of receipt of petition)	FDA will publish the <u>proposal</u> to amend the regulations to provide for the use of the health claim; the proposal will also announce the availability of the petition for public review.
Within 270 days of date of publication of the proposal (<i>i.e.</i> , within 460 days of receipt of petition). ³ If two extensions granted, timeline can be within 640 days (1 year, 9 months) of receipt of petition.	FDA will publish a final rule that either authorizes the use of the health claim or explains why the agency has decided not to authorize one.
<p>¹ If FDA does not act within 100 days, petition deemed to be denied unless an extension is mutually agreed on by the petitioner and FDA. A petition that is not filed because it is denied or deemed to be denied will not be made available to the public. A filed petition will be made available to the public – <i>i.e.</i>, all data and information in the health claim petition with the deletion of names/information identifying product users or a third party involved with report.</p> <p>² If FDA does not act within 90 days of the date of filing, the petition shall be deemed to be denied unless an extension is mutually agreed on by the petitioner and FDA.</p> <p>³ FDA may extend, no more than twice, the period in which it will publish a final rule; each such extension will be for no more than 90 days. FDA will publish notice of such an extension in the Federal Register and state the basis for extension, length of extension, and date by which final rule will be published.</p>	

Table 2.5.6.1-2 A Description of Actions and Timelines for the Approval of a Qualified Health Claim in the U.S. (U.S. FDA, 2003a, 2006a)	
Action/Timeline	Details
Within 15 days of receipt of petition	FDA acknowledges receipt of petition, in writing
Within 45 days of receipt of petition	FDA plans to determine if petition is complete. If incomplete, the agency plans to inform petitioner of deficiencies and what steps petitioner should take to rectify these deficiencies If petition complete, FDA will “file the petition” and assign it a docket number
Upon filing petition	FDA intends to post petition on its website and request public comment for 60 days; public’s comments to be posted on website or made available for review at Division of Dockets Management
After comment period closes	Scientific data reviewed by FDA internally, or an advisory committee, or a third party (e.g., the Agency for Healthcare Quality and Research which would send the petition to an Evidence-Based Practice Center) ¹
If petition reviewed by a third party, within 120 days after start of petition review ²	FDA would receive a report that includes a description of the evidence reviewed; an analysis of the evidence; a summary of and response to public comments that pertain to the evidence; and its assessment of the scientific certainty of substance/disease relationship.
If petition reviewed by a third party and after third party report received	FDA intends to review and evaluate the third party report; the totality of publicly available evidence; public comments; relevant regulatory considerations; and how claim will affect consumer’s dietary choices in determining whether to consider exercising “enforcement discretion” with respect to claim.
If FDA decides to consider “enforcement discretion”	The agency plans to determine what qualifying statements and other information should accompany the claim to ensure that it is truthful and not misleading.
Within 270 days of receipt of petition ³	FDA plans to notify the petitioner of ⁴ : 1. FDA’s determination and the basis for it 2. The wording of the qualified claim for which the agency intends to consider exercising “enforcement discretion”
¹ FDA intends, as appropriate, to consult with other scientific federal agencies with official responsibility for public health protection or research related to human nutrition and dietary supplements. ² If FDA receives more than one petition for a qualified health claim that describes the same relationship between a substance and a disease/health-related condition, the agency plans to consolidate all the petitions received. ³ Extensions beyond 270 days can be granted upon mutual agreement between the petitioner and FDA ⁴ FDA plans to post this letter and any other third party report on its website.	

2.5.6.2 Transparency

A high level of transparency is maintained and respected by the FDA and a number of accessible mechanisms exist for deriving information: the Federal Register, the FDA website, and the Division of Dockets Management all include current information pertaining to FDA’s activities; the Federal Register includes daily (Monday through Friday) updates on proposed and finalized regulations and the timeframe to comment on proposed regulations.

2.5.6.3 *Prioritization*

To maximize the public health benefit of its claim review process, FDA aims to prioritize petitions. Whether the food/dietary supplement is likely to have a significant impact on a serious life-threatening illness; the strength of the evidence; and whether the substance of the claim has undergone a FDA safety review (*i.e.*, authorized food additive or GRAS) are among the factors considered by FDA in their prioritizing of applications (U.S. FDA, 2006c, 2007a).

2.5.6.4 *Communication*

FDA maintains close communication with health claim petitioners and informs petitioners of deficiencies in their applications (such as for qualified health claim petitions) and what steps the petitioner should take to rectify these deficiencies.

2.5.6.5 *Fees*

No fees are attached to health claim petitions.

2.5.6.6 *Third Party Reviewers*

FDA exercises the option to use third party reviewers of health claim petitions such as the Agency for Healthcare Quality and Research which would send the petition to an Evidence-Based Practice Center. The third party reviewer would analyze the petition and relevant scientific evidence in addition to public comments received during the consultation period and prepare a report to the FDA on their determination of the scientific certainty of substance/disease relationship (U.S. FDA, 2003a).

2.5.7 Functional Foods

Currently, FDA has neither a definition nor a specific regulatory framework for foods marketed as “functional foods”. FDA regulates functional foods under the same regulatory framework as conventional foods.

FDA does not consider dietary supplements to be encompassed by the term functional foods. Dietary supplements have their own definition in the regulatory framework prescribed by Congress in the Dietary Supplement Health and Education Act of 1994 (DSHEA). See Table 2.5.7-1. DSHEA specifically excludes from the definition of dietary supplement any product that is “represented for use as a conventional food or as a sole item of a meal or the diet” (U.S. FDA, 2000)

Although FDA is confident that the existing provisions of the *Federal Food, Drugs and Cosmetic Act* are adequate to ensure that conventional foods being marketed as functional foods are safe and lawful, FDA held a public hearing December 6, 2006 to examine how functional foods fit

into existing regulatory regimes and how FDA should regulate functional foods (U.S. FDA, 2006f). The comment period on this topic was extended to March 5, 2007 (U.S. FDA, 2007c).

The FDA has also discussed and deliberated issues pertaining to structure/function claims given the proliferation of functional foods. In a February 2000 meeting (U.S. FDA, 2000), interested parties met to discuss a conceptual framework for structure/function claims on food, raising lucrative questions outlined in Table 2.5.7-2.

Unlike dietary supplements, conventional foods and functional foods (since they are regulated under the same framework of conventional foods), can include structure/function claims without notifying the FDA and which do not require a FDA disclaimer stating that the product is not intended to diagnose, treat, cure, or prevent any disease, as is required for dietary supplements. Although structure/function claims should be used to describe the role of a nutrient or dietary ingredient intended to affect normal structures or functions in humans or describe general well-being (signs, symptoms that are characteristic of non-disease states) (U.S. FDA, 2003b), their wording can easily be perceived by consumers to imply disease risk reduction or reduction of signs/symptoms associated with disease (U.S. FDA, 2000).

Food	Dietary Supplement	Drug	Comments
Articles used for food or drink for man or other animals, chewing gum, and articles used for components of any such article.	A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described above.	Recognized in the official United States Pharmacopeia or Homeopathic Pharmacopeia or official National Formulary; and, Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and, Articles (other than food) intended to affect the structure or any function of the body of man or other animals; and, Articles intended for use as a component of any articles specified above.	Dietary supplements are a subcategory of foods not drugs (this is unlike Canada where NHPs are a subcategory of drugs). Form/matrix of dietary supplement not defined; can include tablets, capsules, softgels, gelcaps, liquids, powders or food forms such as a bar. Dietary supplements must be labelled as dietary supplements. Dietary supplements must not to be represented for use as a conventional food or as a sole item of a meal or the diet

Table 2.5.7-2 Questions Raised by Interested Parties in the U.S. in a Meeting to Discuss a Conceptual Framework for Structure/Function Claims for Conventional Foods (U.S. FDA, 2000)

<p>Is there need for another category – e.g., functional foods?</p> <p>How can structure/function claims be distinguished from other claims – e.g., drug claims, health claims?</p> <p>Would a requirement of GRAS and/or a food additive status be an appropriate and adequate safety net with or without additional criteria?</p> <p>Is it possible or important to distinguish “naturally occurring” ingredients from “added ingredients”?</p> <p>Is there a distinction between: a) materials derived from plant or animal food sources?; b) materials derived from sources other than plants or animals (e.g., mineral sources, chemical synthesis)?</p> <p>Is the requirement for a food component (<i>i.e.</i>, active ingredient) to have “nutritive value” for structure/function claims an appropriate and adequate anchor for providing guidance and evaluating structure/function claims?</p> <p>How can drugs be kept distinct from foods?</p> <p>Should there be disqualifying nutrients or disqualified vehicles?</p> <p>What is the role of consumer research in evaluating understanding, interpretation, and effectiveness of claims?</p> <p>Should disclaimers be required? Do they have any impact?</p> <p>Should there be pre- and post-market notification requirements?</p> <p>Should positive lists of permitted claims be maintained? Should the requirements for permitted claims be specified?</p> <p>What is a “gold standard” vision for a conceptual framework for structure/function claims on conventional foods?</p>

2.5.8 Highlights of the FDA’s Management of Health Claims and Related Processes

Highlights of FDA’s management of health claims and related processes are outlined in Table 2.5.8-1 and Table 2.5.8-2.

Table 2.5.8-1 Highlights of FDA’s System Pertaining to Evidence Requirements for Health Claim Substantiation

<p>Information pertaining to efficacy primarily required in health claim petition with limited information on safety and quality assurance also required; details of safety and quality assurance provided in GRAS or food additive applications.</p> <p>Evaluation of health claims focuses primarily on human intervention and observational study types. When randomized, controlled intervention studies are consistent in showing or not showing a substance/disease relationship, they trump the findings of any number of observational studies.</p> <p>FDA does not consider the magnitude of a statistically significant effect in their evaluation of consistency of outcomes across studies of a particular type. This is because the magnitude of effect can vary due to experimental conditions</p>
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Table 2.5.8-1 Highlights of FDA’s System Pertaining to Evidence Requirements for Health Claim Substantiation

and as such do not solely reflect the treatment/exposure. FDA reserves its consideration of magnitude of effect for comparing differences in outcomes of multiple treatments/exposures within studies.

Guidance document for health claim substantiation defines study types (e.g. intervention studies; observational studies) in detail and qualitatively ranks their reliability and persuasiveness (e.g., case-control studies less reliable than cohort studies)

Animal and *in vitro* studies considered useful to generate hypotheses or explore a mechanism of action of a food. Lacking any data from human studies, these studies alone would not adequately support a health claim since each suffers from uncertainties of extrapolating to physiological effects in humans.

Research synthesis studies (meta-analyses, systematic reviews) useful as supporting evidence; no health claims have been authorized on the basis of meta-analysis studies alone.

FDA acknowledges that it is not possible to specify the type or number of studies needed to support a health claim. Instead, sound, relevant science in research design and measurement drives the decision to authorize health claims. However, FDA does state that a single, large, well-conducted and controlled clinical trial could provide sufficient evidence to establish a substance-disease relationship, provided there is a supporting body of evidence from observational or mechanistic studies.

Intervention studies with foods may generate data that have less certainty than data from drug intervention studies as a result of the greater likelihood for confounders¹ and bias (e.g., may not be possible to use a placebo control group).

Regarding the standard of “significant scientific agreement”, FDA states that it is necessary to consider both the extent of agreement and the nature of disagreement on a case-by-case basis.

Data and information pertaining to the claim must be available to the scientific community either through publication in peer-reviewed journals or if not published, placed in the public domain.

No guidance is given on literature retrieval for health claim substantiation.

Although study quality factors are outlined, an objective quality appraisal system/tool is not provided.

Guidance documents for health claim substantiation contain non-binding recommendations. FDA states alternative approaches can be used if they satisfy the requirements of the applicable statutes and regulations. FDA also states its willingness to discuss alternative approaches.

FDA encourages potential health claim petitioners to meet with FDA prior to preparing a petition to discuss their plans.

Consumers must understand significance of health claims in the context of a total daily diet

¹ Confounders are factors associated with the disease in question and the intervention and prevent the measured outcome from being attributed unequivocally to the intervention.

Table 2.5.8-2 Highlights of FDA’s System Concerning Its Structure, Operations, and Processes Pertaining to Health Claims

Accountability to timelines for FDA’s review of health claim petitions written in *Federal Food, Drug and Cosmetic Act* and *Code of Federal Regulations*.

Implications if “the Secretary” does not issue a regulation on a health claim within 540 days: Secretary shall provide the Committee on Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate the reasons action on the regulation did not occur within 540 days.

FDA does not have application forms to make/accompany health claim submissions

Transparency of regulatory processes with respect to health claim petitions and FDA’s responses to them as a result of their availability on FDA’s website, in the Federal Register, or through the Division of Dockets Management.

A petitioner may request a reconsideration of a health claim petition if petitioner presents significant new relevant evidence or provides a persuasive analysis that the agency’s interpretation of the original evidence was incorrect. FDA may also on its own initiative decide to reconsider a determination.

FDA contact information – names and telephone numbers – accessible on website

To maximize the public health benefit of its claim review process, FDA intends to prioritize petitions according to: whether food/dietary supplement likely to have a significant impact on a serious life-threatening illness; strength of the evidence; whether consumer research provided to show claim is not misleading; whether substance of claim has undergone a FDA safety review (*i.e.* authorized food additive or GRAS); substance adequately characterized; disease defined; prior review of evidence or claim by a recognized body of qualified experts.

3.0 CRITICAL COMPARISON OF SCIENTIFIC REQUIREMENTS AND REGULATORY PROCESSES FOR HEALTH CLAIM MANAGEMENT

3.1 Scientific Requirements

Tables 3.1-1 through to 3.1-6 compare all 5 jurisdictions' scientific requirements for health claim substantiation, related to efficacy, safety, and quality assurance. The symbol "√" denotes an item is considered by the jurisdiction where as a blank (*i.e.*, "√" not present) indicates an item is not considered by the jurisdiction. The comparisons apply to all health claims in Canada (structure/function, risk reduction, therapeutic claims); high-level health claims in AU/NZ; Article 14 claims in the EU; FOSHU in Japan; and authorized and qualified health claims in the U.S. Japan was not included in some comparisons due to a lack of information provided by this jurisdiction in English; "n/a" denotes its exclusion from comparisons.

As Table 3.1-1 indicates, all jurisdictions require information on efficacy, safety, and quality assurance for health claim substantiation. However, when and where this information is presented differs. Some jurisdictions, like Japan, require all details pertaining to these three areas to be included in one application. Other jurisdictions, like Canada and the U.S., require all three areas to be addressed, but to different degrees, depending on whether a safety assessment has previously been conducted (Canada), whether a food is modified (Canada), or a GRAS assessment or food additive application exists (United States). Moreover, some jurisdictions do not require all 3 areas to be addressed, such as Australia/New Zealand and the European Union, since novel food applications are used to address requirements pertaining to safety (AU/NZ, EU) and quality assurance (AU/NZ).

Efficacy, which allows the assessment on whether food X causes a change in health outcome Y (*i.e.*, causality), is a complex area that can take into consideration a multitude of factors, as Table 3.1-2 demonstrates. Overall, fourteen items were considered for the assessment of efficacy across jurisdictions. Canada scored similarly to AU/NZ, requiring 10 of 14 items to be considered on efficacy, compared to the U.S. which scored 7/14 and the EU which scored 12/14. Five of the 14 items were unanimously required by all jurisdictions: a requirement for human studies (intervention and/or observational studies); evidence on an effective intake of the food or information on dose-response; consistency of findings across studies; relevance of studies' findings/populations/diets to the general population or target group of the claim; and whether effective intakes of the food can be reasonably achieved under conventional use of the food. There was variability among the jurisdictions on the remaining 9 of the 14 items. Canada's requirements on efficacy are adequate and comparable to international standards. They are similar to AU/NZ requirements and are more comprehensive than U.S. requirements and less comprehensive than EU requirements.

Efficacy is a complex area to address and one that warrants the provision of guidance aimed at health claim applicants by a regulatory body. As Table 3.1-3 indicates, not all jurisdictions similarly provide guidance on meeting efficacy requirements related to literature retrieval, evaluation of study quality, tabulation/synopses of individual studies, and evaluation of the totality of evidence. AU/NZ and the EU provide the most guidance on efficacy covering all aforementioned areas and thus scoring 4/4, while Canada and the U.S. provide less guidance, scoring 3/4 and 2/4, respectively.

As Table 3.1-4 indicates, 3 items were considered related to the organization of scientific requirements on efficacy in health claim applications: the expectation of a detailed synopsis/tabulation of individual human studies; categorization of the evidence per study type; and visual plots of the effect of the food intake on the health outcome. The EU required all three areas to be included in a health claim application, scoring 3/3, while Canada and AU/NZ scored 2/3 (not requiring visual plots) and the U.S. scored 1/3 (only requiring categorization of the evidence per study type).

As Table 3.1-5 indicates, 2 items were considered related to the evaluation (either by the applicant or the regulatory body) of the totality of evidence (TOE) on a food/health relationship: whether study quality (based on research design and research methodology) was a consideration in the evaluation of the TOE; and, whether the TOE was ranked for its strength. Not including Japan, all 4 jurisdictions (AU/NZ, EU, U.S., Canada) require the applicant or the regulatory body to give consideration to the quality of studies in drawing conclusions on efficacy using the totality of evidence. Additionally, 3 of the 5 jurisdictions (AU/NZ, Japan, U.S.) rate the TOE for its strength while two jurisdictions do not (EU, Canada).

A comparison of the scientific requirements pertaining to safety is summarized in Table 3.1-6. All 5 jurisdictions have similar requirements on this topic, the major difference being whether those requirements are to be addressed in health claim applications. AU/NZ and the EU almost entirely rely on novel food applications to cover aspects of safety while Japan covers all aspects of safety in health claim applications. Canada's requirements on safety in health claim applications differ depending on whether safety has been previously reviewed by Health Canada while the U.S. balances its requirements on safety between food additive/GRAS assessments and health claim applications.

A comparison of requirements pertaining to quality assurance is outlined in Table 3.1-7. Both Japan and the EU solely rely on health claim applications to cover requirements on this topic while AU/NZ solely relies on novel food applications to cover aspects of quality assurance. The U.S. uses both the GRAS/food additive assessments and health claim applications to address quality assurance while Canada's requirements for health claim applications are contingent on whether a previous safety assessment has been conducted by Health Canada on the food of interest.

Overall, Canada's scientific requirements on efficacy, safety, and quality assurance are comparable to international standards and are reasonable and adequate. The biggest difference between jurisdictions is whether these requirements are addressed in a health claim application or through other applications, such as for novel foods, food additives, or GRAS assessments.

3.2 Regulatory Processes

Six thematic areas pertaining to regulatory processes on health claim management are addressed in Table 3.2-1, related to: regulatory mechanisms for the approval of claims that mention a health effect; efficiency; communication/transparency; accountability; market advantage; and prioritization.

Similar to the comparison on scientific requirements, the symbol "√" denotes an item is considered by the jurisdiction where as a blank (*i.e.*, "√" not present) indicates an item is not considered by the jurisdiction.

Apart from the first item related to regulatory mechanisms, the remaining thematic areas apply to all health claims in Canada (structure/function, risk reduction, therapeutic claims); high-level health claims in AU/NZ; Article 13 and 14 claims in the EU; FOSHU in Japan; and authorized and qualified health claims in the U.S. The first item applies to all claims that can mention a health effect, which may include claims that are not classified as health claims. Thus this first item applies to all health claims in Canada (structure/function, risk reduction, therapeutic claims) in addition to biological role claims; general and high-level health claims in AU/NZ; Article 13 and 14 claims in the EU; FOSHU and FNFC in Japan; and authorized and qualified health claims and structure/function claims in the U.S. Japan was not included in some comparisons due to a lack of information provided by this jurisdiction in English; "n/a" denotes its exclusion from comparisons.

Similar to Japan and the EU, Canada requires its regulatory body to approve all claims that are not part of an existing positive list of claims and that mention a health effect. AU/NZ and the U.S., on the other hand, have routes with less oversight by a regulatory body and for general level health claims in AU/NZ and structure/function claims (not classified as health claims) in the U.S., both categories of claims that can mention a health effect, no approval is required from a regulatory body for their use.

Related to efficiency, three (AU/NZ, U.S., Canada) of 4 jurisdictions conduct a preliminary screening of applications to ensure their completeness; the EU does not. Not including AU/NZ and the EU, which use independent scientific bodies to conduct health claim application reviews, Japan and the U.S. outsource expertise, when necessary, to assist in health claim application reviews; Canada does not outsource expertise for this purpose.

For the thematic area on communication/transparency, all 4 jurisdictions (AU/NZ, EU, U.S., Canada) provide some information related to health claim applications in the public domain although the depth and breadth of information provided varies between jurisdictions. Among the same four jurisdictions (AU/NZ, EU, U.S., Canada), three (AU/NZ, EU, U.S.) ensure communication with the health claim applicant throughout the review process and provide easy access to contact information in the public domain; Canada falls short on both these initiatives.

Four (AU/NZ, Japan, EU, U.S.) of 5 jurisdictions have target timelines for the review and approval of health claim applications that range from 9 months to close to 2 years. Canada does not have a commitment to timelines for this purpose.

AU/NZ, EU, and Canada offer market advantages to health claim applicants by allowing applicants exclusive rights to a health claim in specific situations (EU, Canada) and/or options to expedite the health claim application review (AU/NZ, EU). The U.S. does not provide for market advantages.

Two jurisdictions (AU/NZ, U.S.) use a system to prioritize health claim applications which the EU and Canada do not do. The U.S. prioritizes applications based on whether the health claim can have an impact on a serious life-threatening disease, the strength of the evidence and whether the substance has undergone a safety review.

Overall, Canada’s regulatory processes pertaining to health claim management are not comparable to international standards; there is room for improvement.

Table 3.1-1 Scientific Requirements in Health Claim Applications					
Item	Regulatory Body / Country				
	Food Standards Australia New Zealand (FSANZ) / Australia and New Zealand	Ministry of Health Labour and Welfare (MHLW) / Japan	European Food Safety Authority (EFSA) / European Union	Food and Drug Administration (FDA) / United States of America	Health Canada / Canada
Efficacy	√	√	√	√	√
Safety	*	√	*	√ ¹	√ ^{2, 3}
Quality Assurance	*	√	√	√ ¹	√ ²
TOTAL	1/3	3/3	2/3	3/3	3/3
¹ Not comprehensive assessments; information on these areas addressed in generally recognized as safe (GRAS) or food additive applications. ² Requirements differ depending on whether the food is modified or unmodified. ³ Requirements differ depending on whether a review of the food’s safety has already been conducted by Health Canada. *Addressed in novel food applications. The symbol “√” denotes an item <u>is considered</u> by the jurisdiction where as a blank (<i>i.e.</i> , “√” not present) indicates an item is <u>not considered</u> by the jurisdiction.					

Table 3.1-2 Scientific Requirements on Efficacy in Health Claim Applications					
Item	Regulatory Body / Country				
	Food Standards Australia New Zealand (FSANZ) / Australia and New Zealand	Ministry of Health Labour and Welfare (MHLW) / Japan	European Food Safety Authority (EFSA) / European Union	Food and Drug Administration (FDA) / United States of America	Health Canada / Canada
Human studies (intervention and/or observational)	√	n/a	√	√	√
Effective Intake/Dose-Response	√	n/a	√	√	√
Consistency of findings across studies	√	n/a	√	√	√
Relevance of studies' findings/populations/diets to general population/target group of claim	√	n/a	√	√	√
Whether effective intake can reasonably be achieved under conventional use	√	n/a	√	√	√
Alternative explanations/Independence of association	√	n/a	√	√	√ - not essential
Magnitude of outcome	√	n/a	√		√
Physiological relevance of magnitude of effect	√	n/a	√		√
Statistical significance of outcome		n/a	√	√	√
Sustainability of effect	√	n/a	√		√
Specificity of effect	√ - secondary focus	n/a	√		√ - not essential
Biological plausibility	√ - secondary focus	n/a	√		√ - not essential
Reversal of effect	√ - secondary focus	n/a			√ - not essential
Temporal relationship	√ - secondary focus	n/a			√
TOTAL (# essential items in health claim applications/14)	10/14	n/a	12/14	7/14	10/14
The symbol "√" denotes an item <u>is considered</u> by the jurisdiction where as a blank (i.e., "√" not present) indicates an item is <u>not considered</u> by the jurisdiction.					

Table 3.1-3 Provision of Guidance to Address Efficacy					
Item	Regulatory Body / Country				
	Food Standards Australia New Zealand (FSANZ) / Australia and New Zealand	Ministry of Health Labour and Welfare (MHLW) / Japan	European Food Safety Authority (EFSA) / European Union	Food and Drug Administration (FDA) / United States of America	Health Canada / Canada
On Literature Retrieval	√ - example provided	n/a	√ - brief		
On Study Quality Appraisal	√ - not presented as a checklist	n/a	√ - presented as a checklist but items not scored	√ - not presented as a checklist	√ - brief; not presented as a checklist
On Tabulation/ Synopses of Individual Studies	√	n/a	√		√
On Evaluation of Totality of Evidence	√	n/a	√	√	√
TOTAL	4/4	n/a	4/4	2/4	3/4

The symbol “√” denotes an item is considered by the jurisdiction where as a blank (*i.e.*, “√” not present) indicates an item is not considered by the jurisdiction.

Table 3.1-4 Organization of Scientific Requirements on Efficacy in Health Claim Applications					
Item	Regulatory Body / Country				
	Food Standards Australia New Zealand (FSANZ) / Australia and New Zealand	Ministry of Health Labour and Welfare (MHLW) / Japan	European Food Safety Authority (EFSA) / European Union	Food and Drug Administration (FDA) / United States of America	Health Canada / Canada
Detailed synopses/tabulation of individual human studies expected	√	n/a	√		√
Categorization of evidence per study type (<i>e.g.</i> , intervention, observational, systematic reviews) recommended	√	n/a	√	√	√
Visual plots of effect of food intake recommended		n/a	√		
TOTAL	2/3	n/a	3/3	1/3	2/3

The symbol “√” denotes an item is considered by the jurisdiction where as a blank (*i.e.*, “√” not present) indicates an item is not considered by the jurisdiction.

Table 3.1-5 Evaluation of Totality of Evidence to Assess Efficacy in Health Claim Applications					
Item	Regulatory Body / Country				
	Food Standards Australia New Zealand (FSANZ) / Australia and New Zealand	Ministry of Health Labour and Welfare (MHLW) / Japan	European Food Safety Authority (EFSA) / European Union	Food and Drug Administration (FDA) / United States of America	Health Canada / Canada
Consideration of study quality in evaluation of totality of evidence (TOE)	√ – greater weight placed on higher quality studies	n/a	√ - weighing the evidence is a component in EFSA's evaluation of health claim applications	√ – studies excluded if scientific conclusions cannot be drawn from study due to methodological flaws	√ – studies must be of acceptable quality and design
Strength of totality of evidence ranked	√ – convincing, probable, possible, insufficient	√ – A, B, C ¹		√ – high, moderate, low, extremely low	
TOTAL	2/2	1/1	1/2	2/2	½
The symbol “√” denotes an item <u>is considered</u> by the jurisdiction where as a blank (<i>i.e.</i> , “√” not present) indicates an item is <u>not considered</u> by the jurisdiction.					

Table 3.1-6 Scientific Requirements on Safety in Health Claim Applications					
Item	Regulatory Body / Country				
	Food Standards Australia New Zealand (FSANZ) / Australia and New Zealand	Ministry of Health Labour and Welfare (MHLW) / Japan	European Food Safety Authority (EFSA) / European Union	Food and Drug Administration (FDA) / United States of America	Health Canada / Canada
History of safe use	*	√	*	*	√ ¹
Dietary exposure (current and increased due to claim)	*		*	√	√
Dietary/nutritional impacts	*	√	*	√	√
Adverse effects from human studies	*	√	√	√	√ ¹
Toxicological data from animal studies	*	√	*	*	√ ¹
TOTAL (# required in health claim applications/5)	0/5	4/5	1/5	3/5	2/5 to 5/5 depending on whether safety previously approved
¹ Not required for inclusion in health claim application if the food's safety has been previously reviewed by Health Canada. *Addressed in novel food applications (Australia/New Zealand, European Union) or GRAS/food additive applications (for United States). The symbol "√" denotes an item <u>is considered</u> by the jurisdiction where as a blank (<i>i.e.</i> , "√" not present) indicates an item is <u>not considered</u> by the jurisdiction.					

Table 3.1-7 Scientific Requirements on Quality Assurance in Health Claim Applications					
Item	Regulatory Body / Country				
	Food Standards Australia New Zealand (FSANZ) / Australia and New Zealand	Ministry of Health Labour and Welfare (MHLW) / Japan	European Food Safety Authority (EFSA) / European Union	Food and Drug Administration (FDA) / United States of America	Health Canada / Canada
Characterization of food (compositional analysis; physical/chemical characteristics; impurity profile)	*	√	√	√	√
Manufacturing Process	*	√	√	*	√ ¹
Stability/shelf-life		√	√	*	√ ¹
Compliance with specifications	*	√	√	*	√ ¹
Quality systems in place (Good clinical/laboratory/manufacturing practices)		√	√	√	√ ¹
TOTAL (# required in health claim applications/5)	0/5	5/5	5/5	2/5	1/5 to 5/5 depending on whether food is modified
<p>¹ Only required for modified foods (<i>i.e.</i>, a food that has undergone changes during its manufacturing to enhance the food's functionality such as the addition of a bioactive ingredient or modification of the levels or bioactivity of a naturally occurring component of the food). *Addressed in novel food applications (for Australia/New Zealand) or GRAS/food additive applications (for United States) The symbol "√" denotes an item <u>is considered</u> by the jurisdiction where as a blank (<i>i.e.</i>, "√" not present) indicates an item is <u>not considered</u> by the jurisdiction.</p>					

Table 3.2-1 Comparison of Regulatory Processes Pertaining to Health Claim Application Reviews and Approvals					
Item	Regulatory Body / Country				
	Food Standards Australia New Zealand (FSANZ) / Australia and New Zealand	Ministry of Health Labour and Welfare (MHLW) / Japan	European Food Safety Authority (EFSA) / European Union	Food and Drug Administration (FDA) / United States of America	Health Canada / Canada
Regulatory Mechanisms for Approval of Claims that Mention a Health Effect					
Approval required by regulatory body for all claims that are <u>not</u> part of a positive list of claims <u>and</u> that mention a health effect		√	√		√
Efficiency					
Preliminary screening of applications to ensure completeness before assessment proceeds	√	n/a		√	√
Outsourcing of expertise to help with health claim application evaluations	n/a – FSANZ is an independent scientific body	√ – local authorities	n/a – EFSA is an independent scientific body	√ – Agency for Healthcare Quality and Research	
Communication / Transparency					
Health claim application information available in public domain	√ - all information pertaining to applications except that which is confidential available on FSANZ's website or Public Register	n/a	√ – EFSA will make public a “summary” of all applications received and its scientific opinion on approved claims	√ - all information pertaining to approved or rejected applications, except confidential information, available on FDA's website, Federal Register or Division of Dockets Management	√ - decision summaries of approved claims on website
Communication with applicant throughout review process	√ - formally obliged to notify applicants in writing at specific points during the assessment process which can be up to 7 times	n/a	√ – minimal (e.g., to confirm receipt of application)	√ - formally obliged to notify applicants in writing at 3 specific points during the review process	
Easy accessibility of contact person/telephone number for help	√		√	√	

Table 3.2-1 Comparison of Regulatory Processes Pertaining to Health Claim Application Reviews and Approvals					
Item	Regulatory Body / Country				
	Food Standards Australia New Zealand (FSANZ) / Australia and New Zealand	Ministry of Health Labour and Welfare (MHLW) / Japan	European Food Safety Authority (EFSA) / European Union	Food and Drug Administration (FDA) / United States of America	Health Canada / Canada
Accountability					
Accountability to timelines for review and approval or rejection of health claim application	√ - timelines for applications to vary the Code range from 3 to 18 months; timelines for high level health claim reviews not yet established	√ - ~1 year	√ - 9 to 10 months	√ - 9 months (qualified claims) to 1 year, 9 months (authorized claims); extensions permitted with mutual agreement by FDA and applicant	
Market Advantage					
Applicant has exclusive rights to health claim			√ - for claims approved based on proprietary data		√ - for product-specific claims (generally based on proprietary data)
Options available to expedite review process	√ - application fee can be paid	n/a	√ - EFSA will expedite review of health claims based on newly developed science to stimulate product innovation		
Prioritization					
System used to prioritize applications	√	n/a		√ - based on impact on a serious life-threatening disease, strength of evidence, whether substance has undergone a safety review	
The symbol "√" denotes an item <u>is considered</u> by the jurisdiction where as a blank (<i>i.e.</i> , "√" not present) indicates an item is <u>not considered</u> by the jurisdiction.					

3.3 Implications on Trade

As mentioned earlier, the management of health claims reflects a country's level of interest in various factors including health promotion (a reflection of culture); facilitation of trade; economics; enabling food research, innovation and development; enabling industry competitiveness; public health; consumer choice; consumer protection; and civil rights (e.g., freedom of speech). Health claim management is also influenced by the organizational structure and operations of regulatory bodies, which are directly affected by their capacity (human resources) and level of commitment to efficiency and effectiveness of work outputs; accountability to stakeholders and the public; and interest in ensuring transparency of decision-making processes and work outputs. Jurisdictions prioritize these factors differently and as such their frameworks for managing health claims differ.

Canada places a high priority on consumer protection (*i.e.*, injury prevention and avoidance of misleading claims) more than some other jurisdictions, such as the U.S.; the U.S. values freedom of speech. A country's values influence the development and framework of policy and legislation. Canada's interest in protecting consumers translates to a high level of oversight (*i.e.*, supervision) on health claims, whereas, there is more flexibility in the management of claims in the U.S. due to a greater interest in the freedom of speech: qualified claims based on weak science are permitted and structure/function claims do not require approval by the FDA.

Canada's food legislation is such that it requires claims that mention a disease or modification of an organic structure beyond what is considered physiologically normal to be exempted from the provisions in the Act pertaining to drugs and Schedule A. This requires extensive legal drafting (*i.e.*, writing) and is unlike the requirements in other jurisdictions, such as the U.S.

Overall, Canada's value system and food legislation increase the time-to-market for health claims; this can impact trade.

3.4 Recommendations

Related to the scientific requirements on health claim substantiation, Canada is primarily lacking in the clear communication of these requirements and the provision of guidance to meet these requirements. Applicants of health claims could benefit from a user-friendly guidance document/handbook that not only outlines what the requirements are but how to achieve them – *i.e.*, a systematic, step-by-step approach.

Related to regulatory processes for health claim application reviews, Canada is primarily lacking in the efficiency of claim reviews; communication/transparency with health claim applicants; and accountability to timelines for health claim reviews.

Recommendations outlined in Table 3.4-1 are likely to increase the efficiency of completing a health claim application; efficiency in reviewing a health claim application; and effectiveness of the application process.

Some recommendations are clear inferences from the comparative analyses in Sections 3.1 and 3.2 while others are drawn from a consideration of items not necessarily reviewed across jurisdictions but summarized for specific jurisdictions and deemed useful.

Table 3.4-1 Recommendations for Canada	
Factor	Recommendation
Consultation	Make public consultations an essential part of decision-making processes and ensure sufficient time is provided for comment submission. When appropriate, contact specific stakeholder groups to inform them of a consultation.
Substantiation Criteria/Approval Process	Consider a “step-up” or “tiered” process for the approval of different types of claims (nutrient content claims vs. function claims vs. disease risk reduction claims) related to the breadth and depth of criteria to support/substantiate the claims and the claim approval process.
Prioritizing	Consider a mechanism of prioritizing health claim submission reviews based on impacts on consumers, the food industry, and government.
Guidance Document Revision	Revise Canada’s Interim Guidance Document for health claim submissions so that it: <ul style="list-style-type: none"> a) Clearly articulates what the requirements on efficacy, safety, and quality assurance are and <u>how</u> to meet these requirements (e.g., a step-by-step approach). b) Provides a systematic, actionable tool for study quality appraisal that facilitates differentiation of “good” from “poor” quality studies – e.g., a checklist that scores a study for quality. c) Clarifies criteria that differentiate claim categories (e.g., product-specific vs. generic claims). d) Facilitates the comparability of research findings to evaluate efficacy. e) Includes a workable application template.
Document/Handbook Development	Develop a handbook for applicants describing the process and requirements for approval of novel foods, functional foods, health claims, etc. Ensure guidance documents for industry are clear, concise and understandable.
Impact Assessment	Require health claim applicants to discuss impacts (costs and benefits) of a health claim – on government, the food industry, and consumers (understanding and behaviour).
Authoritative Reviews	Simplify application process for health claim substantiation if critical reviews by credible, authoritative bodies (national or international governments; international agencies; internationally recognized scientific bodies) exist.
Nutrient Profiling	Implement a nutrient profiling criterion for foods eligible to carry health claims, with consideration to exemptions, to ensure foods carrying health claims are consistent with national dietary guidelines and to decrease consumer judgement on the overall healthiness of a food.
Fees	Consider implementing an application fee, at the least as an option for applicants that would like to have the review of their application expedited.
Accountability to Timelines	Set targets for timelines related to the review of health claim applications and make these timelines available in the public domain.
Market Advantage	Consider a first-to-market advantage for health claim applicants.
Communication	Mandate communication with applicants at specific points during the health claim review process.
Contact Information	Make available an organizational chart that describes names, contact information, and

Table 3.4-1 Recommendations for Canada	
Factor	Recommendation
	roles of Health Canada employees involved with pertinent processes to health claim application reviews.
Website	Create a more user-friendly and organized website; see FSANZ's website.
Outsource	Outsource expertise, when necessary, to help review health claim applications.
Differentiation of Claim Categories	Clarify criteria that differentiate product-specific from generic health claims for the current system or function claims from disease risk-reduction claims for the new proposed system.
Transparency	Make accessible all information pertaining to health claim applications in the public domain, except for confidential/proprietary data. Public notification of an application's receipt should be carried out as soon as it is received to avoid duplication of an application. Information pertaining to approved and rejected claims with reasons for rejection should also be publicly available. Consider using Health Canada's website that lists all health claim applications received and their status in the review process.
Research	Execute research, where appropriate and necessary, to resolve uncertainties or gaps in the understanding of consumer perceptions (e.g. research to understand consumer perceptions of claims; whether consumers distinguish between claims on health promotion <i>versus</i> disease risk-reduction).
Biomarkers	Provide a non-static publicly available list of acceptable surrogate biomarkers of disease risk.

4.0 REVIEW OF EXISTING CANADIAN AND INTERNATIONAL REGULATIONS PERTAINING TO NOVEL FOODS

4.1 Introduction

This review is intended to familiarize the reader with the requirements for attaining novel food approval in Canada and internationally. As described in Section 2, all health claim applications require a scientific demonstration of efficacy. In Canada and Japan, health claim applications in which the subject of the claim is a novel food, also are required to demonstrate product safety and quality, while in Australia/New Zealand, the EU, and the U.S., product safety and quality of novel foods are considered under separate submissions and require separate regulatory approval. Thus, when functional foods or food ingredients are “novel”, safety and quality can be assessed independent of or prior to submission of health claim applications. In the following section, novel food regulations in Australia/New Zealand, Canada, the EU, Japan, the U.S., and the Codex Alimentarius Commission are reviewed. A summary of the regulatory processes for novel foods in each jurisdiction is presented in Table 4.7-1.

4.2 Australia and New Zealand

4.2.1 Relevant Regulatory Bodies

Novel foods proposed for sale in Australia and New Zealand are regulated through a bi-national agency called Food Standards Australia New Zealand (FSANZ). FSANZ came into effect on July 01, 1996, and is a joint partnership between Australia and New Zealand that was created with the goal of improving productivity and economic efficiency by reducing trade barriers between the countries. The agency is responsible for developing and reviewing food standards with the aim of producing a single set of standards between the two countries.

4.2.2 Relevant Legislation and Definition of Novel Foods

Under FSANZ, foods are regulated by the Australia New Zealand Food Standards Code (the Code). Standard 1.5.1 (Novel Foods) of the Code contains definitions of novel foods, as well as regulations pertaining to the sale of novel foods and food ingredients (ANZFA, 2007). Standard 1.5.1 was incorporated into the Code in December 1999, and clause 2 of the Standard, which prohibits the sale of a novel food (either by way of retail as food or for use as a food ingredient) unless included in the Table to that clause, came into full effect in June 2001. "Novel food" is defined in clause 1 of Standard 1.5.1 of the Code as "a non-traditional food for which there is insufficient knowledge in the broad community to enable safe use in the form or context in which it is presented, taking into account:

- (a) the composition or structure of the product; or
- (b) levels of undesirable substances in the product; or
- (c) known potential for adverse effects in humans; or
- (d) traditional preparation and cooking methods; or
- (e) patterns and levels of consumption of the product."

A "non-traditional food" is defined in clause 1 of Standard 1.5.1 of the Code as "a food which does not have a history of significant human consumption by the broad community in Australia or New Zealand". It is noteworthy that under clause 1 of Standard 1.5.1, novel food includes novel foods used as ingredients in another food.

Under Standard 1.5.1, foods are prohibited for sale unless they are listed in the Table to clause 2, for which specific conditions of use apply and are listed. The regulations pertaining to GM foods are beyond the scope of this report and will not be reviewed. As seen in Table 4.2.2-1, the number of foods listed in the Table to clause 2 of standard 1.5.1 is limited to 11 compounds.

Table 4.2.2-1	List of Novel Foods and Novel Food Ingredients Permitted for Sale in Australia and New Zealand Without the Requirement for Pre-Market Clearance*
	α-cyclodextrin
	γ-cyclodextrin
	Diacylglycerol oil (DAG-Oil)
	Docosahexaenoic acid – rich dried marine micro-algae (<i>Schizochytrium</i> sp.)
	Docosahexaenoic acid – rich oil derived from marine micro-algae (<i>Schizochytrium</i> sp.)
	Docosahexaenoic acid – rich oil derived from marine micro-algae (<i>Ulkenia</i> sp.)
	Isomaltulose
	Phytosterol esters
	D-Tagatose
	Tall oil phytosterols
	Trehalose

* Note that many of these foods also contain specific conditions of use.

Novel foods are required to undergo pre-market safety evaluation and amendments to the Code are required once a novel food is approved. Provisions for amending the Code are prescribed in the Food Standards Australia New Zealand Act 1991.

4.2.3 Regulatory Processes Pertaining to Novel Food Approvals

Foods that are not listed under clause 2 of Standard 1.5.1 require an amendment of the Code to include a new set of standards specific to the novel food. If a company is unclear whether or not their food or food ingredient is novel, the applicant is advised to approach the FSANZ for a review of the “novelty” of the product. The food or food ingredient is then reviewed by the Novel Foods Reference Group (NFRG), which is internal to FSANZ, to determine whether in fact the food is novel based on the following considerations:

1. whether or not the food or food ingredient appears to be traditional or non-traditional according the definitions laid out in clause 1 of Standard 1.5.1 of the Code; and
2. if the food or food ingredient is non-traditional, whether or not it is also novel according to the definitions laid out in clause 1 of Standard 1.5.1 of the Code. In some cases, this may require additional information to be sought from the inquirer or from other sources.

The NFRG makes an initial determination regarding the novelty of a food; however, the determination is made in collaboration with the Senior Food Officers (SFOs) in Australian State and Territory jurisdictions and in New Zealand, and the Australian Quarantine and Inspection Service (AQIS). The level of involvement of the SFOs and AQIS with the NFRG depends largely on the complexity of the novel food. If a novel food is determined to comply with Standard 1.5.1 regarding the definition of the novel food, the novel food must undergo pre-

market safety assessment prior to sale in Australia or New Zealand. This pre-market safety assessment requires that an application containing all supporting safety data for the novel food under its proposed uses be sent to the FSANZ to amend the Code.

In October 2007, FSANZ published a guidance document for applicants interested in varying the Code – *Food Standards Australia New Zealand – Application Handbook* (Commonwealth of Australia, 2007). The process to amend to Code permits 3 different procedures (Minor, General, and Major Procedures) for applications, based on each application's level of complexity. A detailed comparison of these procedures is provided in Table 2.1.6.1-1 of Section 2. Each procedure is described briefly:

Minor Procedure – applies to applications for insignificant variations to the Code (such as a typographical error or minor editorial change). Assessment takes approximately 3 months and involves only 1 round of consultation with government and, if necessary, affected parties.

General Procedure – applies to applications requesting alterations to a food regulation; also is the default procedure, requiring 9 months for assessment.

Major Procedure – applies to applications requesting the development of a new food standard or a major variation to a food regulation that is scientifically or technically complex; it involves two rounds of public consultation and takes 12 months to complete the assessment; however, time can be extended by up to 6 months.

Although all 3 procedures vary with respect to assessment times and number of public consultations, all procedures are preceded by an administrative assessment. The administrative assessment is conducted within 15 business days following receipt of an application to vary the Code. The administrative assessment is conducted to determine: whether the application meets the application requirements; the procedure (minor, general, or major) under which the application will be assessed; whether fees will be applied (in the event that the applicant wishes to expedite the review or the applicant is found to have exclusive capturable commercial benefit); and, if the application is acceptable, when assessment of the application will commence (Work Plan). The final stage for all three procedures is a review by the Ministerial Council. Following the review, the Ministerial Council must decide to 1) Inform FSANZ that it does not intend to amend or reject the draft; 2) amend the draft; or 3) Reject the draft.

4.2.4 Requirements for Safety Assessments of Novel Foods and Guidance Documents

The FSANZ has published an Application Handbook that was approved by the FSANZ Board in March 2007 and that was registered as a Legislative Instrument in July 2007. Thus, the guidelines published in the Application Handbook are mandatory. If guidelines on Novel Foods (Section 3.5.2 of the Application Handbook) are not followed by the applicant, then FSANZ is

able to reject the application. The requirements to support an application for a novel food are listed in Table 4.2.4-1.

Table 4.2.4-1 Safety Assessment of Novel Foods – Requirements as per the FSANZ Application Handbook	
Part	Contents
Part A – General Information on the Applicant	<ol style="list-style-type: none"> 1) Purpose of the application 2) Justification for the application 3) Support for the application
Part B – Technical Information on the Novel Food	<ol style="list-style-type: none"> 1) Information on the type of novel food 2) Information on the physical and chemical properties 3) Information on the impurity profile for a typical preparation 4) Manufacturing process 5) Specification for identity and purity 6) Analytical method for detection
Part C – Information on the Safety of the Novel Food ¹	<p><u>General</u></p> <ol style="list-style-type: none"> a) The history of use as food in other countries b) The composition of the novel food, particularly the levels of anti-nutrients and naturally-occurring toxins c) The method of preparation and specifications d) Potential for allergenicity e) Metabolism/toxicokinetic studies f) Animal toxicity studies g) Human toleration studies <p><u>I Plant or animals (or their components)</u></p> <ol style="list-style-type: none"> 1) Information on the composition 2) Information on the effects of food processing or preparation 3) Information on use in population subgroups or in other countries 4) Information regarding potential adverse effects <p><u>II Plant or animal extracts</u></p> <ol style="list-style-type: none"> 1) Information on the method of extraction and the composition of the concentrated extract 2) Information on the use of this plant or animal extract as a food in other countries 3) Information on the toxicity of the extract obtained from studies conducted in humans or animals <p><u>III Herbs (both culinary and non-culinary) including extracts</u></p> <ol style="list-style-type: none"> 1) Information on the history of use of the herb 2) Information on the composition of the herb 3) For a herbal extract, information on the method of extraction and the composition of the concentrated extract 4) Information on the use of this herb or herbal extract as a food in other countries 5) Information regarding the potential allergenicity of the herb or herbal extract 6) Information on the toxicity of the herb, herbal extract, or any key constituents obtained from studies conducted in animals or humans 7) Safety assessment reports by international agencies or other national government agencies <p><u>IV & V Single Chemical Entities and Dietary Macro-components</u></p> <ol style="list-style-type: none"> 1) Information on the toxicokinetics and metabolism of the single chemical entity and, where appropriate, its degradation products and major metabolites 2) Information from studies in animals or humans that is relevant to the toxicity of the single chemical entity and, where appropriate, its degradation products and major metabolites.² 3) Safety assessment reports prepared by international agencies or other national government agencies <p><u>VI Micro-organisms (Including Probiotics)</u></p> <ol style="list-style-type: none"> 1) Information on potential pathogenicity 2) Information on the effects of the micro-organism on gut microflora

Table 4.2.4-1 Safety Assessment of Novel Foods – Requirements as per the FSANZ Application Handbook	
Part	Contents
	3) Information on the use of this micro-organism as a food in other countries 4) Information on human toleration studies <u>VII Food Ingredients Derived from a New Source</u> 1) Information on the safety of the source organism 2) Information on the composition of the novel food ingredient derived from a new source 3) Information on the toxicity of the novel food ingredient derived from the new source 4) Safety assessment reports prepared by international agencies or other national government agencies <u>Food Produced by a Process not Previously Applied to a Food</u> 1) Details of the process not previously applied to food 2) Information on the toxicity of the novel food produced by a process not previously applied to food 3) Safety assessment reports prepared by international agencies or other national government agencies.
Part D – Information on Dietary Exposure to the Novel Food ³	<u>Information on dietary exposure to the novel food</u> 1) A list of the foods or food groups proposed to contain the novel food ingredient 2) The proposed level of the novel food ingredient for each food or food group 3) The percentage of the food group in which the novel food ingredient is proposed to be used or the percentage of the market likely to use the novel food ingredient 4) Data to show whether the food, or the food in which the novel food ingredient is used, is likely to replace another food from the diet, if applicable 5) Details of target group and at risk groups in the population 6) Information relating to the use of the novel food or novel food ingredient in other countries, if applicable
Part E – Information on the Nutritional Impact of the Food	<u>Information to demonstrate that the use of the novel food or novel food ingredient will not cause a nutritional imbalance in the diet</u> 1) Information to demonstrate consumer awareness and understanding of the novel food or novel food ingredient
Part F – Information Related to Potential Impact on Consumer Understanding and Behaviour	1) Information to demonstrate consumer awareness and understanding of the novel food or novel food ingredient 2) Information on the actual and/or potential behaviour of consumers in response to the novel food or novel food ingredient 3) Information to demonstrate that the food(s) containing the novel food ingredient will not adversely affect any population groups (e.g. particular age or cultural groups)
Part G – Information Related to Impact on the Food Industry (Industry Applicants Only)	1) Data on the projected impact on the food industry of the proposed novel food or novel food ingredient 2) Impact on international trade.
¹ Section 3.5.2 of the Application Handbook states that the data required for a safety assessment will vary depending on the nature of the novel food. ² The Application Handbook advises that the following categories of animal studies be addressed in the toxicity assessment of a single chemical entity: Acute toxicity studies, short-term toxicity studies; long-term toxicity studies and carcinogenicity studies, reproductive toxicity studies, developmental toxicity studies, genotoxicity studies, special studies such as neurotoxicity or immunotoxicity. ³ FSANZ will conduct dietary exposure assessments for all novel food applications. For novel foods which are either the final food or a major component of the final food, the dietary exposure assessment may be based on the projected market share data, or data from markets in other countries. For novel foods which are minor components of the final food, a custom-made computer program (DIAMOND) will be used (this program combines food consumption data from the latest Australian and New Zealand National Nutrition Surveys with data provided by the applicant on intended food uses and proposed levels of use.	

The purpose of the safety evaluation of a novel food is to establish a “reasonable certainty of no harm” that will result from the intended use of the food. Several factors are evaluated during a novel food safety assessment, including:

- The source and process by which the food has been prepared;
- The composition of a novel food, or the structure and specifications of a novel ingredient;
- The history of use (whether in a particular population group or as a component of traditional foods);
- The level of consumption or extent of use (current and proposed);
- Data on the metabolism of novel ingredients;
- Data from toxicity studies in animals;
- The toxicity of any related substances or foods; and
- Any known cases of adverse effects on humans.

4.2.5 Highlights

Highlights of the management of novel foods in Australia/New Zealand are summarized in Table 4.2.5-1.

Table 4.2.5-1 Highlights of the Management of Novel Foods in Australia/New Zealand	
Feature	Description
Confidentiality	FSANZ can be requested to treat parts of the application as confidential; if request is denied, applicant has the ability to withdraw the application in full or in parts.
Work Plan	Following the Scoping Stage, applications are put on a Work Plan, which dictates when formal assessment of the application will begin.
Costs	Fees are charged if the applicant wishes to have an expedited review or if FSANZ determines that the applicant would have an “exclusive capturable commercial benefit”.
Website	The FSANZ website is well-organized and easy to navigate.
Electronic Applications	The FSANZ website permits applications to be submitted electronically.
Communication	FSANZ keeps applicants informed about the progress of their application.
Provision of Guidance Documents	The Application Handbook provides guidance on several other regulatory processes relating to food.
Market Advantage	In September 2007, the FSANZ Board approved an amendment to the Novel Food Standard to allow for 15 months exclusive use for the maker/brand of a novel food. If no review is requested by the Ministerial Council, the amendment is expected to be gazetted before the end of the year.
Advice Line	To communicate to interested parties information about the Code and individual Standards.

Table 4.2.5-1 Highlights of the Management of Novel Foods in Australia/New Zealand	
Feature	Description
Urgency Provisions	To amend the Code (for instance, where not doing so immediately may have a negative impact on trade).
Transparency	A "Record of Views Formed in Response to Inquiries" is publicly available on the FSANZ website; details regarding NFRG decisions regarding the classification of foods as "non-traditional/traditional" and or "novel/not novel" are provided; All applications and decisions are posted on the FSANZ website; Work Plan is posted on FSANZ website.

4.3 Canada

4.3.1 Relevant Regulatory Bodies

Novel food safety assessments are conducted by the Food Directorate, Health Products and Food Branch of Health Canada. The Food Directorate is the federal health authority responsible for establishing policies, setting standards, and evaluating the safety and nutritional value of food (Health Canada, 2006).

4.3.2 Relevant Legislation and Definition of Novel Foods

Division 28 of Part B of the Food and Drug Regulations sets out the definition of novel foods (B.28.001) as well as the procedures for pre-market notification (B.28.002) and the responsibilities of the Director in responding to a pre-market notification (B.28.003).

Pursuant to Division 28.001 of Part B of the Canadian *Food and Drugs Act and Regulations* (Health Canada, 2006), a novel food is defined as follows:

- (a) a substance, including a micro-organism, that does not have a safe history of use as a food;
- (b) a food that has been manufactured, prepared, preserved or packaged by a process that:
 - (i) has not been previously applied to that food, and
 - (ii) causes the food to undergo a major change; and
- (c) a food that is derived from a plant, animal or micro-organism that has been genetically modified such that:
 - (i) the plant, animal or micro-organism exhibits characteristics that were not previously observed in that plant, animal or micro-organism,
 - (ii) the plant, animal or micro-organism no longer exhibits characteristics that were previously observed in that plant, animal or micro-organism, or
 - (iii) one or more characteristics of the plant, animal or micro-organism no longer fall within the anticipated range for that plant, animal or micro-organism.

The definition of “major change” is a change in the food that, based on the manufacturer’s experience or generally accepted nutritional or food science theory, places the modified food outside of the accepted limits of natural variations for that food with regard to:

- (a) the composition, structure or nutritional quality of the food or its generally recognized physiological effects, or
- (b) the manner in which the food is metabolized in the body, or
- (c) the microbiological safety, the chemical safety, or the safe use of the food.

4.3.3 Regulatory Processes Pertaining to Novel Food Approvals

Applicants wishing to sell a novel food meeting the definitions outlined above must submit a Pre-Market Notification to the Food Directorate of the Health Products and Food Branch of Health Canada. Under regulation B.28.002 (1), No person shall sell or advertise for sale a novel food unless the manufacturer or importer of the novel food (a) has notified the Director in writing of their intention to sell or advertise for sale the novel food; and (b) has received a written notice from the Director. Under B.28.002 (2), the following information should be contained within the notification:

- (a) the common name under which the novel food will be sold;
- (b) the name and address of the principal place of business of the manufacturer and, if the address is outside Canada, the name and address of the principal place of business of the importer;
- (c) a description of the novel food, together with
 - i) information respecting its development;
 - ii) details of the method by which it is manufactured, prepared, preserved, packaged and stored;
 - iii) details of the major change, if any;
 - iv) information respecting its intended use and directions for its preparation;
 - v) information respecting its history of use in a country other than Canada, if applicable; and
 - vi) information relied on to establish that the novel food is safe for consumption;
- (d) information respecting the estimated levels of consumption by consumers of the novel food;
- (e) the text of all labels to be used in connection with the novel food; and
- (f) the name and title of the person who signed the notification and the date of signing.

Following submission of a Notification, the Novel Foods Section of the Food Directorate distributes relevant material of the Pre-Market Notification to specialized bureaux within the Food Directorate, including the Bureau of Nutritional Safety, the Bureau of Chemical Safety, the Bureau of Microbial Hazards, and in certain cases, the Environmental Assessment Unit, Healthy Environments and Consumer Branch of Health Canada. Each of these specialized bureaux prepares a scientific review. If, following the safety assessments, the food is determined to be safe, the Food Directorate drafts a proposal, which contains a summary of the scientific reviews

conducted by each of the relevant Bureaux of the Food Directorate. The proposal is presented to the Food Rulings Committee for consideration, and if there is agreement that the food be permitted for sale in Canada, the applicant is notified, in writing. The review process is supposed to take approximately 45 days following receipt of the Pre-Market Notification; however, review times are generally longer. As per [B.28.003 (1)(a)(b)], the Food Directorate notifies the applicant, in writing, that the information supporting the safety of the novel food is sufficient or that additional information to support safety is necessary. If additional information to support the safety of the novel food is submitted, review of the additional information is then conducted within 90 days of receiving the new information, at which point the Director will make a final decision on whether or not the scientific and technical information support the safety of the novel food for consumption. Once the applicant has received written notification from the Director, the product is permitted to enter the Canadian market. Submissions remain confidential; however, the Food Directorate prepares Novel Food Decision Documents for each novel food pre-market notification, which is a summary document of the information supporting the safety of the novel food. Novel Food Decision Documents are posted on the Novel Foods page of the Health Canada website (<http://www.novelfoods.gc.ca>) for all novel foods determined to be safe.

4.3.4 Requirements for Safety Assessments of Novel Foods and Guidance Documents for Novel Food Submissions

In regards to part B.28.002(c)(vi), *information relied on to establish that the novel food is safe for consumption*, The Food Directorate of the Health Products and Food Branch of Health Canada has issued guidelines for the safety assessment of novel foods that can be used to address part (f) of the novel food petition called “Guidelines for the Safety Assessment of Novel Foods” (Health Canada, 2006). The Food Directorate has acknowledged that due to the inherent diversity that exists among novel foods and novel food ingredients, that special considerations will be required for each heading. To facilitate the applicant in addressing these concerns in a manner that is specific to their novel food, the Food Directorate has categorized novel foods and novel food ingredients into 3 classes: substances with no history of use; substances produced using novel processes, and substances produced using genetic modification. The guidelines contain safety considerations specific to each category that should be considered when preparing the notification, not all of which will be relevant in each circumstance. In general the starting point for review of the safety of a novel food is to determine the degree of similarity between the novel food and its conventional counterpart with the intention of identifying new or altered hazards relative to the conventional counterpart. If a significant change is found that may be of nutritional or toxicological concern, the hazard will be assessed for potential impact on human health and if insufficient information exists to derive a conclusion, additional animal studies may be warranted. In cases where no conventional counterpart exists (e.g., botanical extract or small molecule) safety will be based on evidence of historical human exposure and/or experimental studies, the specific nature of which will be determined on a case-by-case basis.

4.3.5 Highlights

Highlights of the management of novel foods in Canada are summarized in Table 4.3.5-1.

Table 4.3.5-1 Highlights of the Management of Novel Foods in Canada	
Standard Operating Procedures	Standard Operating Procedures regarding the processing of a novel food notification/submission in the Food Directorate are posted on the Health Canada website.
Transparency	While a listing of Novel Food Decisions Documents is posted on the Food Directorate's web-site for foods issued a letter of no objection, it appears that the list is not all-inclusive and that rejections are not posted; original notifications are not in the public domain; however, synopses of the application and review process are provided by the Food Directorate; evaluation times are not posted on the listing of novel food decisions.
Website	Contains easily accessible fact sheets and frequently asked questions, guidelines, policies.
Communication	A contact address for novel food pre-market notifications/submissions is provided; however, contact names, numbers, and e-mail addresses are not provided.
Costs	There are no fees associated with assessments of novel food pre-market notifications.
Market Advantage	Approvals are company specific; thus, all companies must submit Pre-market Novel Food Notifications, even if the same novel food has already undergone review

4.4 European Union

4.4.1 Relevant Regulatory Bodies

In the EU, authorisation of novel foods and novel food ingredients is harmonized. Several regulatory bodies are involved in the novel food application process including the Member State competent food safety authority body where the novel food or novel food ingredient is intended to be first marketed, the food safety authority bodies of all other Member States, and the European Commission (the Commission). In certain circumstances (discussed in Section 4.3.2), the Commission may seek the assistance of the European Food Safety Authority Standing Committee for Foodstuffs and the Council.

4.4.2 Relevant Legislation and Definition of Novel Foods

Novel foods are defined in the EU as foods and food ingredients that have not been used for human consumption to a significant degree within the Community before 15 May 1997. Foods commercialised in at least 1 Member State prior to the entry into force of the Regulation on Novel Foods on 15 May 1997 are permitted for sale in the EU market under the “principle of mutual recognition”. The placement of novel foods and novel food ingredients on the market in the EU is regulated according to Regulation (EC) No 258/97 of the European Parliament and the Council of 27 January 1997 concerning novel foods and novel food ingredients (European Union, 1997). Under Article 1(2) of Regulation (EC) No 258/97, novel foods or food ingredients are defined as substances that fall under 1 of the 6 following categories:

- (a) foods and food ingredients containing or consisting of genetically modified organisms within the meaning of Directive 90/220/EEC;
- (b) foods and food ingredients produced from, but not containing, genetically modified organisms;
- (c) foods and food ingredients with a new or intentionally modified primary molecular structure;
- (d) foods and food ingredients consisting of or isolated from micro-organisms, fungi or algae;
- (e) foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and which have a history of safe use;
- (f) foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the

composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances.

In addition to specifying what a novel food or novel food ingredient *is*, Regulation (EC) No 258/97, under Article 3(1), specifies that a novel food or novel food ingredient must not:

- present a danger for the consumer,
- mislead the consumer,
- differ from food or food ingredients which they are intended to replace to such an extent that their normal consumption would be nutritionally disadvantageous for the consumer.

4.4.3 Regulatory Processes Pertaining to Novel Food Approvals

Regulation (EC) 258/97 lays out 2 regulatory procedures for assessment of novel food and novel food ingredient applications. The first procedure (which will be referred to as a full assessment), is described in Articles 4, 6, 7, and 8 and pertains to novel foods and novel food ingredients that fall under categories 2(a), (c), and (f) of Article 1. The second procedure (which will be referred to as a simplified procedure), is described in Article 5 and pertains to novel foods and novel food ingredients that fall under categories 2(b), (d), and (e) of Article 1. The simplified procedure is applied to novel foods and novel food ingredients that are substantially equivalent to existing foods or food ingredients as regards to their composition, nutritional value, metabolism, intended use, and the level of undesirable substances contained therein. The full assessment is applied to novel foods and novel food ingredients for which substantial equivalence to an existing food or food ingredient cannot be demonstrated.

For the simplified procedure, the applicant must simply notify the Commission that the novel food or food ingredient has been placed on the market; the notification must include the basis on which substantial equivalence was made (composition, nutritional value, metabolism, intended use, levels of undesirable substances). This Notification is circulated to Member States by the Commission within 60 days of receipt.

For novel foods and food ingredients requiring full assessment, the applicant must submit a Request to the Member State to which the applicant intends to market the product for the first time. Applications submitted to the Member State are reviewed by their respective competent food assessment body and an Initial Assessment report must be drawn up within 3 months. The report of the Initial Assessment is then circulated to the other Member States whose respective competent authorities have a period of 60 days to circulate comments or concerns regarding the conclusions of the initial assessment. If objections are raised by a Member State, final authorization must then be decided by The European Food Safety Authority Standing Committee for Foodstuffs or, if further assistance is required, the Council.

The regulatory processes for the full assessment and the simplified procedure are summarized in Table 4.4.3-1.

Table 4.4.3-1 Comparison of Simplified and Full Assessment Procedures for Novel Foods and Food Ingredients in the EU		
Criterion	Simplified Procedure	Full Assessment
Scope	Novel foods and novel food ingredients which are substantially equivalent ¹ to existing foods or food ingredients.	Novel foods and novel food ingredients which are not substantially equivalent ¹ to existing foods or food ingredients.
Relevant categories of novel foods and food ingredients	Article 1(2): (b) foods and food ingredients produced from, but not containing, genetically modified organisms; (d) foods and food ingredients consisting of or isolated from micro-organisms, fungi, or algae; (e) foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe food use.	Article 1(2): (a) foods and food ingredients containing or consisting of genetically modified organisms within the meaning of Directive 90/220/EEC; (c) foods and food ingredients with a new or intentionally modified primary molecular structure; (f) foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances.
Articles in which relevant regulatory procedures are described	Article 5	Articles 4, 6, 7 and 8
Notification sufficient	Yes – Applicant may notify the Commission directly once product is placed on market.	No
Request to market product in Member State required	No.	Yes – the applicant is required to submit a Request ² to the Member State in which the product is to be placed on the market for the first time. At the same time, the applicant must forward a copy of the Request ² to the Commission.
Role of Member State where product is to be placed on the market for the first time	Active – The competent food assessment body of the Member State typically determines whether the novel food or novel food ingredient is substantially equivalent to an existing food or food ingredient.	Active – The Member State commissions its competent food assessment body (or asks the Commission to coordinate this with another Member State) to conduct an Initial Assessment ³ of the request.
Role of other Member States	None – Member States simply receive a copy of the Notification ⁶ from the Commission within 60 days of Notification receipt.	Active – The Commission circulates to the Member States a copy of the summary provided by the applicant, the name of the competent body responsible for carrying out the Initial Assessment ³ , and the report of the Initial Assessment ³ . Member States then have a period of 60 days to send comments/objections to the Commission, which then circulates these to all Member States. ⁴

Table 4.4.3-1 Comparison of Simplified and Full Assessment Procedures for Novel Foods and Food Ingredients in the EU		
Criterion	Simplified Procedure	Full Assessment
Conflict Resolution	Not applicable	Yes – If it is determined in the Initial Assessment ³ that an Authorization Decision ⁵ is required or an objection is raised by a Member State, the Commission seeks the assistance of the European Food Safety Authority Standing Committee for Foodstuffs; if a decision still cannot be reached, the Commission seeks the assistance of the Council.
Time from receipt of application/notification to marketing of product	Immediate	5 months – if it is determined from the Initial Assessment ³ that an Authorization Decision ⁵ is not required and no concerns are expressed by other Member States. > 5 months if it is determined from the Initial Assessment that an Authorization Decision ⁵ is required and/or concerns are expressed by other Member States.
Confidential information protected	Yes	Yes
Reversal of decision based on new information or reassessment of existing information	Yes – Member State with objection may temporarily restrict or suspend the trade or use of the novel food or novel food ingredient; Member State notifies Commission, which then seeks the assistance of the European Food Safety Authority Standing Committee for Foodstuffs	Yes – Member State with objection may temporarily restrict or suspend the trade or use of the novel food or novel food ingredient; Member State notifies Commission, which then seeks the assistance of the European Food Safety Authority Standing Committee for Foodstuffs
Publication of Notification/Decision	Yes – A summary of Notifications is published in the “C” series of the Official Journal of the European Communities	Yes – Decisions are published in the Official Journal of the European Communities
<p>Note: All Articles references are those contained within Regulation (EC) No. 258/97.</p> <p>¹ Substantial equivalence to existing foods or food ingredients is described in Article 3(4) as regards to their composition, nutritional value, metabolism, intended use, and the level of undesirable substances contained therein.</p> <p>² The Request must include a copy of the studies which have been carried out as well as any other data available to demonstrate the safety of the novel food or novel food ingredient; an example of the presentation and labelling of the food, in accordance with Article 8 of Regulation (EC) No. 258/97; and a summary of the dossier.</p> <p>³ The Initial Assessment must be carried out within 3 months, and the report of the Initial Assessment should indicate 1 of 2 decisions: (1) that the applicant may place the food or food ingredient on the market; or (2) that an Authorization Decision is required. The report of the Initial Assessment is sent to the applicant, as well as to the Commission (the latter which must also be notified of the name and address of the food assessment body responsible for preparing the report).</p> <p>⁴ If a Member State requests more information, the applicant may provide this; again, the level of transparency is high, as new information is circulated to all Member States.</p> <p>⁵ The Authorization Decision defines the scope of the authorization and takes into account 3 factors: (1) the conditions of use of the food or food ingredient; (2) the designation of the food or food ingredient, and its specification; and (3) the specific labelling requirements, as referred to in Article 8 of Regulation (EC) No. 258/97.</p> <p>⁶ The Notification must demonstrate that a national food assessment body has determined that the novel food or food ingredient is substantially equivalent to an existing food or food ingredient (see table note 1); alternatively, applications undergoing an Initial Assessment by a food assessment body of a Member State may be found to be “substantially equivalent” to an existing food or food ingredient.</p>		

4.4.4 Requirements for Safety Assessments of Novel Foods and Guidance Documents

Recommendations regarding scientific aspects and the presentation of information required to support the safety of placing a novel food or food ingredient on the European market are presented in 97/618/EC (European Parliament and the Council of the European Union, 1997).

Based on the classification system of novel foods and novel food ingredients [Regulation (EC) No 258/97] reviewed above in Section 4.4.2, it is clear that foods or food ingredients falling into one or more of these categories will display very broad characteristics such that the complexity of scientific information to establish toxicological and nutritional safety can be quite varied. Thus, to facilitate the scientific evaluation of novel foods or food ingredients, 6 classes of novel foods are identified in the recommendations, and some elements of the safety evaluation may be specific to a given class of food. The 6 classes of novel foods are presented in Table 4.4.4-1.

Table 4.4.4-1		Classes of Novel Foods, as Defined in 97/618/EC: Commission Recommendations	
Class	Description		
Class 1*	Pure chemicals or simple mixtures from non-Genetically Modified (GM) sources		
Class 2*	Complex novel foods from non-GM sources		
Class 3*	Genetically modified plants and their products		
Class 4*	Genetically modified animals and their products		
Class 5*	Genetically modified micro-organisms and their products		
Class 6	Novel foods and food ingredients produced using a novel process that results in changes in the chemical composition or structure of the food or food ingredient affecting its nutritional value, metabolism, or the level of undesirable substances		
*Classes 1 through 5 are sub-divided into one of two sub-classes that are further defined on the basis of history of use in the community.			

The recommendations (97/618/EC) further set out the headings required for the application dossier pertaining to non-genetically modified foods as follows (Commission of the European Communities, 1997):

- I. Specification of the novel food
- II. Effect of the production process applied to the novel food
- III. History of the organism used as the source of the novel food
- IX. Anticipated intake/extent of use of the novel food
- X. Information from previous human exposure to the novel food or its source
- XI. Nutritional information on the novel food

XII. Microbiological information on the novel food

XIII. Toxicological information on the novel food.

Sections IV through VIII have been excluded as they pertain to GM foods, a discussion of which is beyond the scope of this review. For each category (I through XIII), structured schemes have been developed by the Scientific Committee on Food (SCF), which consist of a decision-tree-like set of questions designed to elicit sufficient data for a comprehensive safety and nutritional evaluation of the novel food. As outlined below in Table 4.4.4-2 (for Sections I through XIII), the required questions are identified and subsequently addressed with the appropriate data.

Table 4.4.4-2 Questions to be Addressed in the Safety Evaluation of Novel Foods and Novel Food Ingredients	
Section	Questions to be Addressed
Section I – Specifications of the Novel Food	<ul style="list-style-type: none"> • “...is appropriate analytical information available on potentially toxic inherent constituents, external contaminants and nutrients?” • “Is the information representative of the novel food when produced on a commercial scale?” • “Is there an appropriate specification (including species, taxonomy <i>etc.</i> for living organisms) to ensure that the novel food marketed is the same as that evaluated?”
Section II – Effect of the Production Process Applied to the Novel Food ¹	<ul style="list-style-type: none"> • “Does the novel food undergo a production process?” • “Is there a history of use of the production process for the food?” • “Does the process result in a significant change in the composition or structure of the NF compared to its traditional counterpart?” • “Is information available to enable identification of the possible toxicological, nutritional and microbiological hazards arising from use of the process?” • “Has the process the potential to alter the levels in the NF of substances with an adverse effect on public health?” • “After processing is the NF likely to contain micro-organisms of adverse public health significance?”
Section III - History of the Organism Used as the Source of the Novel Food	<ul style="list-style-type: none"> • “Is the novel food obtained from a biological source, <i>i.e.</i>, a plant, animal or micro-organism?” • “Has the organism used as the source of the novel food been derived using GM?” • “Is the source organism characterized?” • “Is there information to show that the source organism and/or foods obtained from it are not detrimental to human health?”
Sections IV – VIII – Only Apply to Genetically Modified Foods	<ul style="list-style-type: none"> • Beyond the scope of this review.
Section IX – Anticipated Intake/Extent of Use of the Novel Food	<ul style="list-style-type: none"> • “Is there information on the anticipated uses of the novel food based on its properties?” • “Is there information to show anticipated intakes for groups predicted to be at risk?” • “Will introduction of the novel food be restricted geographically?” • “Will the novel food replace other foods in the diet?”

Table 4.4.4-2 Questions to be Addressed in the Safety Evaluation of Novel Foods and Novel Food Ingredients	
Section	Questions to be Addressed
Section X – Information from Previous Human Exposure to the Novel Food or Its Source	<ul style="list-style-type: none"> • Is there information from previous direct, indirect, intended or unintended human exposure to the novel food or its source which is relevant to the EU situation with respect to production, preparation, population, lifestyles and intakes?” • “Is there information to demonstrate that exposure to the novel food is unlikely to give rise to mitochondrial, toxicological and/or allergenicity problems?”
Section XI – Nutritional Information on the Novel Food	<ul style="list-style-type: none"> • Is the novel food expected to have an important role in the diet, whereby its consumption may be expected to replace existing foods in the diet? • Under specific circumstances, the authority may consider if the novel food will affect physiological and/or metabolic requirements in populations who may display sensitive dietary requirements (<i>i.e.</i>, infants, children, pregnant and lactating women, the elderly, diabetics...) • What are the long-term and short-term nutritional impacts of consuming the novel food?
Section XII – Microbiological Information on the Novel Food	<ul style="list-style-type: none"> • “Is the presence of any microorganisms or their metabolites due to the novelty of the product/process?” • “Is there information to show that the NF is unlikely to contain microorganisms and/or their metabolites of adverse public health significance?” • “Are the procedures for handling, cooking or processing the existing food adequate to ensure safety if applied to the NF?”
Section XIII – Toxicological Information on the Novel Food	<ul style="list-style-type: none"> • Consideration of the possible toxicity of the analytically identified individual chemical components. • <i>In vitro</i> and <i>in vivo</i> toxicity studies, including mutagenicity studies, reproduction and teratogenicity studies, and long-term feeding studies. • Studies on potential allergenicity.
<p>¹ Following recommendations from the SCF, information must be available to enable the identification of the possible toxicological, nutritional, and microbiological hazards arising from the production process and means must be identified for controlling the process to ensure that the novel food complies with its specification. It also will be considered important to show that a Hazard Analysis and Critical Control Point (HACCP) plan is in place with the appropriate analysis for contaminants conducted.</p>	

In addition to the recommendations detailed in 97/618/EC and reviewed above, the Institute for Life Science Research (ILSI) has published a set of guidelines that allows an applicant to take a case-by-case approach to ensure that adequate scientific information has been collected when seeking approval for a novel food product, and uses a concept called Safety Assessment of Food by Equivalence and Similarity Targeting (SAFEST) (ILSI Europe Novel Food Task Force, 1995). The ILSI guidelines were not intended to replace recommendations in 97/618/EC or present a step-by-step list of tasks that must be adhered to in order for approval to be granted, but were designed to aid Industry and governing bodies on what information is reasonably expected to substantiate that the use of a novel food or novel food ingredient is safe.

4.4.5 Highlights

Highlights of the management of novel food and novel food ingredients in Europe are summarized in Table 4.4.5-1.

Table 4.4.5-1 Highlights of the Management of Novel Foods and Novel Food Ingredients in Europe	
Confidentiality	Regulation (EC) No 259/97 (Article 10) provides for the protection of confidential information in an application.
Communication	Names, titles, and contact information for key contacts are readily available.
Timelines	Regulation (EC) No 259/97 defines clear timelines regarding when the applicant should be communicated with.
Transparency	Summaries of Notifications and Decisions regarding novel food and novel food ingredient applications are published in the Official Journal of the European Communities; applicant's dossier, as well as reports of Member States' Initial Assessments are made available to all Member States; likewise, concerns/objections raised by a Member State are made available to all other Member States.
Website	Very comprehensive and user-friendly.
Provision of Guidance Documents	Very detailed recommendations on data required for the substantiation of safety are provided in 97/618/EC.
Costs	May be incurred, depending on the Member State; fees are variable.
Efficiency	Simplified procedures for novel foods and novel food ingredients that are substantially equivalent to existing foods and food ingredients (notification as opposed to authorisation).
Safety Monitoring	Regulation (EC) No 259/97 provides for the reversal of positive decisions regarding novel foods and novel food ingredients should new information or a reassessment of existing information bring into question the safety of these novel foods and novel food ingredients.

4.5 United States

4.5.1 Relevant Regulatory Bodies

Within the FDA, the Center for Food Safety and Applied Nutrition's (CFSAN) Office of Food Additive Safety is responsible for reviewing safety information for food ingredients and food packaging.

4.5.2 Relevant Legislation and Definitions

Food additives are regulated under Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act (the Act). These sections were enacted in 1958 as part of the Food Additives Amendment to the Act. A food additive is any substance that is intentionally added to food; legally, the definition of a food additive is "any substance the intended use which results or may reasonably be expected to result-directly or indirectly-in its becoming a component or otherwise affecting the characteristics of any food" [21 CFR 170.3(e)(1)]. This definition includes any substance used in the production, processing, treatment, packaging, transportation or storage of food. The Food Additives Amendment to the Act requires pre-market review and approval by the FDA of all food additives, unless the food additive meets 1 of the following 2 conditions:

1. The substance is demonstrated, under the conditions of its intended use, to be Generally Recognized as Safe (GRAS) among qualified experts ["safe" is defined in 21 CFR 170.3(i) as "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use"]; or
2. The substance is excluded from the definition of a food additive (e.g., pesticides, a dietary ingredients of a dietary supplements, a color additives, new animal drugs, or substances approved for such use prior to September 6, 1958 are excluded from the definition of food additive).

21 CFR 170.30(f) defines substances on the basis of their GRAS eligibility. These include the following:

- 1) Any substance of natural biological origin that has been widely consumed for its nutrient properties prior to January 1, 1958, without known detrimental effect, for which no health hazard is known, and which has been modified by processes first introduced into commercial use after January 1, 1958, which may reasonably be expected significantly to alter the composition of the substance.
- 2) Any substance of natural biological origin that has been widely consumed for its nutrient properties prior to January 1, 1958, without known detrimental effect, for which no health hazard is known, that has had a significant alteration of composition by breeding or

selection after January 1, 1958, where the change may reasonably be expected to alter the nutritive value or concentration of its constituents.

- 3) Distillates, isolates, extracts and concentration of extracts of GRAS substances.
- 4) Reaction products of GRAS substances.
- 5) Substances not of a natural biological origin including those for which evidence is offered that they are identical to a GRAS counterpart of natural biological origin.
- 6) Substances of natural biological origin intended for consumption for other than their nutrient properties.

In general, materials of natural biological origin that have no significant detrimental effect and no known health hazard are eligible for GRAS determination.

4.5.3 Regulatory Processes Pertaining to GRAS Substances and Food Additives

4.5.3.1 GRAS Substances

There are 2 ways in which a substance can be demonstrated to be GRAS. Provisions for these GRAS determinations are provided under Sections 201(s) and 409 of the Act and in regulations 21 CFR 170.3 and 21 CFR 170.30.

1. A GRAS determination may be made through scientific procedures, whereby pivotal data and information corroborating the safety of the substance are widely known (*i.e.*, the essential information is published in peer-reviewed journals and may be corroborated by additional unpublished data and information), and there is consensus among experts qualified by scientific training and expertise, that the totality of evidence establishes that the substance is safe under the conditions of its intended use [21 CFR 170.30(b)]; or
2. For a substance used in food prior to 1958, a GRAS determination may be made through experience based on common use in food; a substantial history of consumption in food (either in or outside the U.S.) by a significant number of consumers is required [(21 CFR 170.30(c) and 170.3(f)].

Once a substance has been established to be GRAS under either 1 of the 2 methods outlined above, a company may inform FDA of the GRAS determination through the GRAS Notification Program. The GRAS Notification Program is a voluntary procedure that is operating under a proposed rule issued in 1997 (62 Federal Register, 18938; April 17, 1997). The GRAS Notification Program was created in order to replace the GRAS Affirmation Process, a process developed by the FDA in the 1970s that permitted any individual to petition the FDA to review and “affirm” the GRAS status of any substance. In the 1997 proposed ruling, FDA explained that the Agency could no longer devote time and resources to the voluntary GRAS affirmation

petition process described in 21 CFR 170.35(c), and proposed to replace the GRAS Affirmation Process with the voluntary GRAS Notification Program. Although notification is not required to market a product, it is useful under specific conditions, and many food manufactures have adopted policies where all new food ingredients must receive a positive GRAS notification letter from the FDA before they will consider using it in their food products. Pre-Notification meetings with the FDA can be arranged to discuss a GRAS determination and to indicate to the FDA the intent to file a Notice. The Notice typically includes the following information (62 Federal Register, 18938; April 17, 1997):

- A GRAS exemption claim, that provides specific information about a GRAS determination in a consistent format [*i.e.*, a succinct description of the "notified substance" (*i.e.*, the substance that is the subject of the notice), the applicable conditions of use, and the basis for the GRAS determination (*i.e.*, through scientific procedures or through experience based on common use in food) and would be dated and signed by the notifier], as well as a statement that the information supporting the GRAS determination was available for FDA review and copying or would be sent to FDA upon request; and
- Detailed information about the identity and properties of the notified substance and a detailed discussion of the basis for the notifier's GRAS determination.

The FDA determines whether the data and information contained within the Notice are sufficient for a GRAS determination and whether there are any issues, either within the Notice or otherwise available to FDA, which bring into question the safety of the substance under its intended conditions of use. Despite the GRAS Notification Program being in a proposed rule, FDA has received and evaluated several hundred GRAS Notices. The proposed rule states that FDA will respond to a Notice within 30 days of its receipt; nevertheless, FDA typically responds to a notification within 180 days. The response takes the form of 1 of 3 formats:

1. The Agency does not question the basis for the notifier's GRAS determination;
2. The Agency concludes that the Notice does not provide a sufficient basis for a GRAS determination (*e.g.*, data and information are lacking or safety concerns have been raised by the available data and information); or
3. The Agency has, at the notifier's request, ceased to evaluate the GRAS Notice.

Once a substance is determined to be GRAS under the specified conditions of use, it can be marketed in the U.S. immediately, even if a response from the FDA to a Notice is pending, and even if FDA responds negatively to a Notice. The Office of Food Additive Safety maintains a

website entitled “A Summary of All GRAS Notices”; copies of the Agency’s response to each Notice can be located here.

4.5.3.2 *Food Additive Petitions*

The regulatory processes involved in the review, by the Office of Food Additive Safety, of a food additive petition are detailed in 21 CFR 171 and are summarized in Table 4.5.3.2-1.

While the safety and technical requirements for food additives and substances under GRAS evaluation are the same (Section 4.5.4), there are 3 major distinctions in the way each are regulated:

- Food additives require pre-market review and approval by the FDA to ensure safety under the intended conditions of use, whereas substances under GRAS evaluation do not require FDA pre-market review and approval (instead, consensus by qualified experts that the substance is safe under the conditions of its intended use is required);
- For food additives, pivotal supporting data and information may be proprietary or unpublished, whereas for substances under GRAS evaluation, data and information supporting safety must be generally available (published in peer-reviewed journals), and unpublished data and information may be used only as corroborating evidence of safety. (A time-gap between the public availability of the data and time to disseminate the information is required. Although not specifically defined in the CFR, it is generally accepted that this period be 6 months.)
- If a food additive is approved, a final regulation is required to be published in the Federal Register (not so for GRAS substances); because the statute requires that a food additive cannot be used until a regulation permitting its use is published in the Federal Register, time-to-market a food additive (from submission of the food additive petition to publication of the final regulation) is generally ≥ 2 years. During this time, objections, hearings, and court challenges may take place.

Table 4.5.3.2-1 Regulatory Processes in the Evaluation of Food Additive Petitions	
Process	Description
Submission of a Food Additive Petition to the Office of Food Additive Safety	<ul style="list-style-type: none"> • A Consumer Safety Officer is appointed to the Food Additive Petition and serves as the petitioner’s primary point of contact, as the primary point of contact with FDA technical experts, and to arrange meetings and provide updates on the status/progress of the review • The petition is evaluated for completeness and, if found to be adequate, a filing notice is published in the Federal Register • The need for review by FDA technical experts outside of the Center for Food Safety and Applied Nutrition is evaluated
Distribution of the Different Sections of the Petition to Relevant Experts for Evaluation by the Consumer Safety Officer	<ul style="list-style-type: none"> • Chemistry Review – review of analytical methods, specifications, method of manufacture, use, functionality, and exposure estimates; probable exposure level is calculated • Toxicology Review – review of safety studies; acceptable exposure level is determined • Environmental Review – review of environmental studies and assessment of environmental impact; an environmental memo is prepared • Evaluation by Other Government Experts – if necessary; a report is prepared • Evaluation by Non-government Experts – if necessary; a report is prepared
Formulation of Decisions	<ul style="list-style-type: none"> • The final safety evaluation is made, with input from an advisory committee, if necessary • The Administrative Record¹ is compiled • A Final Rule is drafted for the Federal Register
Publications	<ul style="list-style-type: none"> • Final Regulation is published in the Federal Register • Regulation appears in the Code of Federal Regulations
¹ The Administrative Record consists of several components, including data submitted by the petitioner, records of communication between FDA and the petitioner, memoranda regarding clarifications in data submitted, and the final regulation.	

4.5.4 Requirements for Safety Assessments of Novel Foods and Guidance Documents

21 CFR 170.30 outlines the scientific requirements to establish that a substance is GRAS based on history of use. Such a GRAS determination requires the collection of generally available published evidence, obtained from the scientific literature, documenting that the food or food ingredient has been widely consumed in the general population prior to January 1, 1958. Documented histories of use where exposures are limited to small niche populations are not considered sufficient for the purposes of GRAS by history of use. In instances where documentation of significant history of use prior to January 1, 1958 occurs outside the U.S., this evidence must be supported by a second independent reference, and this reference must be generally available in the U.S.; furthermore, the FDA also recommends that it be notified prior to sale on the market so that the information supporting GRAS can be reviewed by the Agency.

According to 21 CFR 170.30(b), “General recognition of safety based on scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient.” Thus, the standards for the demonstration of safety of a food additive apply equally to substances that are the subject of a

GRAS determination. 21 CFR 171.1 outlines the elements required in a food additive petition (Table 4.5.4-1). 21 CFR 570.35(c)(1)(i-iv) outlines the elements required in a GRAS evaluation (Table 4.5.4-2). There is considerable overlap in the scientific and technical requirements for a food additive and for a substance that is the subject of a GRAS evaluation.

Table 4.5.4-1	Elements of a Food Additive Petition (21 CFR 171.1)
	Applicant's information
	Chemical identity and composition of the food additive; analytical methods
	Method of manufacture
	Proposed use and use level
	Functionality
	Estimated exposure from proposed use
	Full reports of all safety studies
	Proposed tolerances
	Environmental information (in accordance with the National Environmental Policy Act; July 29, 1997)

Table 4.5.4-2	Elements of a GRAS Evaluation [21 CFR 570.35(c)(1)(i-iv)]
	(i) Description of the substance, including: <ul style="list-style-type: none"> (a) Common or usual name (b) Chemical name (c) Chemical Abstract Service (CAS) registry number (d) Empirical formula (e) Structural formula (f) Specifications for food-grade material, including arsenic and heavy metals (g) Quantitative compositions (h) Manufacturing process (excluding trade secrets)
	(ii) Use of the substance, including: <ul style="list-style-type: none"> (a) Data when use began (b) Information and reports or other data on past uses in food (c) Foods in which used, and levels of use in such foods, and for what purposes
	(iii) Methods for detecting the substance in food, including: <ul style="list-style-type: none"> (a) References to qualitative and quantitative methods for determining the substance(s) in food, including the type of analytical procedures used (b) Sensitivity and reproducibility of such methods
	(iv) Information to establish the safety and functionality of the substance in food. Published scientific literature, evidence that the substance is identical to a GRAS counterpart of natural biological origin, and other data may be submitted to support safety. Any adverse information or consumer complaints shall be included. Complete bibliographic references shall be provided where a copy of the article is not provided.

The FDA has not enforced, in regulations, the precise technical and safety information required to support the safety of a food additive or a substance subject to a GRAS evaluation based on scientific procedures; however, the Agency has several guidance documents to which readers are referred for further information. All of these are accessible from the following website: <http://www.cfsan.fda.gov/~dms/opa-guid.html#tg>.

4.5.5 Highlights

Highlights regarding the management of food additive petitions and GRAS substances in the U.S. are summarized in Table 4.5.5-1.

Table 4.5.5-1 Highlights of the U.S. Management of Food Additive Petitions and GRAS Substances	
Website	Website is very comprehensive and very user-friendly.
Communication	The FDA provides contact names, titles, and numbers for several key individuals; for Food Additive Petitions, a Consumer Safety Officer is appointed to an applicant and serves as the primary point of contact; FDA is open to pre-petition and pre-notification meetings.
Costs	Incurred only for the review of color additive petitions.
Transparency	FDA is extremely transparent with respect to written communications with applicants and with respect to placing notifications/food additive petition reviews in the public domain.
Confidentiality	Provisions are made to keep trade-secret data confidential.
Provision of Guidance Documents	FDA has a very comprehensive inventory of guidance documents, which are easily accessible by interested parties. Many are very basic, easy-to-read question and answer documents. There is also provision of national guidance documents (OECD, ICH).
Market Advantage	While, for a GRAS determination, data supporting safety must be in the public domain, the Food Additive Petition process permits manufacturers to develop new food additives and keep the data proprietary.
Urgency Provisions	Provisions exist for expedited review of food additive petitions if it is determined that such an approval would be beneficial to the population at large (e.g., antimicrobial agents in poultry).
Efficiency	GRAS determinations by scientific procedures using an Expert Panel free up resources within the FDA.
Safety Monitoring	The FDA set up, in 1985, an Adverse Reaction Monitoring System (ARMS), which is a passive, postmarketing surveillance program designed to collect and analyze reports of adverse events allegedly due to food additives and other food ingredients. This information is used to assess whether positive associations exist between a food ingredient and an adverse effect.
Reversal of GRAS Self-affirmation	21 CFR 170.3(l) provides for the reconsideration of the GRAS status of a food ingredient with the development of new information that brings into question the safety of the food ingredient.

4.6 Novel Foods Japan

The general requirements and standards for the safety evaluation of food are governed by the Japanese Ministry of Health, Labour, and Welfare (MHLW). Currently, specific regulations for the evaluation of novel foods do not exist. Although there are regulations for food additives, “substances that are both generally provided for eating or drinking as foods and used as food additives” are exempt from the regulations for food additives. Examples of such substances include konjac extract, and lactic acid bacteria concentrates. The list of substances that are both generally provided for eating or drinking as foods and used as food additives was published by the Ministry of Health and Welfare in May 1996 (MHW, 1996), and guidelines for modification of this list do not exist. A food for which a health claim is being proposed must be demonstrated to be safe in the health claim submission, and discussion of safety requirements is reviewed in Section 2, Table 2.4.4-1.

4.7 Codex

“The Codex Alimentarius Commission was created in 1963 by FAO and WHO to develop food standards, guidelines, and related texts such as codes of practice under the Joint FAO/WHO Food Standards Programme. The main purposes of this Programme are protecting the health of consumers, ensuring fair trade practices in the food trade, and promoting coordination of all food standards work undertaken by international governmental and non-governmental organizations” (Codex, 2006).

Currently there are no specific guidelines published by Codex pertaining to the safety assessment of novel foods, and a novel food would be treated as a food additive in regards to the issuance of standards pertaining to its safe use in food. Standards for the safe use of food additives are issued by the joint FAO/WHO Expert Committee on Food Additives (JECFA). JECFA is an international scientific expert committee that is jointly governed by the FAO of the United Nations and the WHO. The safety evaluation process is in many ways streamlined to the evaluation of food additives, and an extensive review of the process and existing guidelines will not be reviewed in this report. However, it should be known that there is no formal petition process whereby any novel food can be submitted for evaluation by the Committee. The Committee meets twice a year and a number of additives/foods/food ingredients are chosen by expert scientists of various disciplines for evaluation. In general, the foods chosen are often selected based on considerations that the evaluation and setting of international standards for a novel food or food additive occurs for products where it is considered that access to these products will improve the health and well-being of developing nations, and to ensure that fair practices in the trade of safe food exist for these products.

4.8 Summary

The types of novel foods and the inherent risks associated with the use of novel foods can vary substantially. For example, novel foods can be defined as foods without any history of human use; foods with limited human use; foods which are intended to be used in a manner that differs from traditional uses; or foods that are manufactured using techniques which have not been used historically for the manufacture of the food. Broad physico-chemical differences can also be found for the types of novel foods (*i.e.*, small molecule *vs.* whole food), as well as the intended use-levels and anticipated exposures ($\mu\text{g}/\text{kg}$ *vs.* g/kg). Therefore, the regulatory process by which these compounds/complex mixtures are evaluated, to ensure they are safe, must be highly flexible. As a result, regulatory authorities are unable to provide inflexible checklists or guidelines by which they consider a novel food must be evaluated to ensure its safety for a given use, and most countries state that the level of information required to establish that a novel food is safe will be evaluated on a case-by-case basis. Most countries, with the exception of the U.S., have attempted to categorize novel foods into specific groups to differentiate the types of nutritional and toxicological concerns requiring consideration in an

effort to bring some level of order to the process; however, it is unclear if this has achieved its desired effect, and most guidelines remain rather vague, providing guidance documentation (which in many cases can be quite extensive in length) for a multitude of toxicological and nutritional safety aspects that may require consideration, but provide no definitive or minimum standard by which these considerations must be assessed. Only the Application Handbook, which was registered in Australia/New Zealand as a Legislative Instrument, has guidelines for safety assessments that are mandatory; all other jurisdictions studied offer guidance documents on how to establish safety of a novel food.

The EU has adopted simplified procedures for the evaluation of novel foods or food ingredients that are found to be substantially equivalent (with respect to composition, nutritional value, metabolism, intended use, and levels of undesirable substances). The substantial equivalence approach was originally designed with the specific aim of evaluating genetically modified foods; however, in some cases, it is relevant also to novel foods, particularly for whole novel foods or novel foods for which a new manufacturing process has been applied. The EU has embraced this approach for novel food assessment, requiring only that an applicant simply notify the Commission directly once the product is on the market. In addition, an initial determination of substantial equivalence is used as a starting point in most novel food evaluations in the EU while substantial equivalence simplifies safety determinations of novel foods and food ingredients and eases the burden on regulatory bodies, a downfall is that it prevents market advantage; that is, once the first novel food is approved, all manufacturers making variations of that food can simply “tag along”. In the U.S., the food additive petition process permits market advantage, since pivotal data supporting the food additive are subject to FDA review and may be proprietary. FSANZ has recently recommended, in a proposed rule, that companies be permitted market advantage of a branded novel food or food ingredient for 15 months following approval – this is expected to be gazetted by the end of this year (2007). Canada has no provision for market advantage.

In general, the process by which most novel foods are regulated, although very different with regards to the logistical process by which the foods/ingredients are evaluated, are in many ways very similar with respect to the depth and quality of safety information that is required to establish that a novel food or food ingredient is safe, such as manufacturing details, dietary intake estimates, toxicological information, and nutritional implications. Without question the most unique process by which the safety of novel foods is assessed is the GRAS process of the U.S., and the process of self-affirmed GRAS status for a new food ingredient is probably the most cost-effective and efficient process in comparison to all other countries. An overview of management of Novel Foods in Canada, U.S., EU, and Australia/New Zealand is presented in Table 4.7-1. Japan has been excluded from this comparison due to lack of regulation of novel foods and food ingredients.

	Australia/New Zealand	Canada	EU	U.S.
Relevant Regulatory Body	Food Standards Australia New Zealand	Food Directorate of the Health Products and Food Branch, Health Canada	The European Commission, Member States' Competent Authority on Food Safety, and the European Food Safety Authority Standing Committee for Foodstuffs	Center for Food Safety and Applied Nutrition, Office of Food Additive Safety, Food and Drug Administration
Relevant Legislation	Standard 1.5.1 of the Australia New Zealand Food Standard Code Application Handbook ¹	Division 28 of Part B of the Canadian Food and Drugs Act and Regulations (B.28.001, B.28.002, B.28.003)	Regulation (EC) No 258/97	Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act (the Act) 21 CFR 170.3 21 CFR 170.30 21 CFR 171
Requirements for Demonstration of Safety Included as Legislature (must be adhered to)	Yes – in Application Handbook ¹	No – guidance documents provide recommendations only	No – guidance documents provide recommendations only	No – guidance documents provide recommendations only
Pre-market Review and Review by Authoritative Body Required	Yes	Yes	Yes – for novel foods that are not substantially equivalent ² to an existing food. No – for novel foods that are substantially equivalent ² to an existing food.	Yes – for food additive petitions No – for substances determined to be GRAS (voluntary notification procedure exists)
Simplified Procedures for Novel Foods that are Substantially Equivalent to Existing Foods	No	No	Yes	No
Regulatory Amendments Required Following Approval of the Novel Food	Yes – the Australia New Zealand Food Standard Code must be amended	No	No	Yes – for food additives, a final regulation is published in the Code of Federal Regulations No – for substances determined to be GRAS (voluntary Notification Program exists)

	Australia/New Zealand	Canada	EU	U.S.
Time-to-Market (from submission of application to sale of novel food/ingredient)	12 months for review of a novel food or food ingredient application; time can be extended by 6 months	45 days – if additional information to assess safety is not requested. 90 days – if additional information to assess safety is requested. Timelines are typically much longer	Immediate – for novel food demonstrating substantial equivalence to existing foods 5 months – if input for the European Food Safety Authority Standing Committee for Foodstuffs is not required > 5 months if input from the European Food Safety Authority Standing Committee for Foodstuffs or the Council is required	Immediate – for substances determined to be GRAS After ≥2 years – for food additive petitions
Fees Charged	Yes, if the applicant wishes to expedite the review or the applicant is found to have exclusive capturable commercial benefit	No	Fees for Initial Assessments by member State competent food safety authority may or may not be charged (depending on the Member State), and are variable.	Yes, for color additive petitions, which are beyond the scope of this review.
Confidential (Trade-Secret) Information Kept Confidential	Yes	Yes	Yes	Yes
Work Plan	Yes	No	No	No
Website	Exemplary	Good	Exemplary	Exemplary
Market Advantage	Yes – an amendment to the Novel Food Standard to allow 15 months exclusive use for a maker/brand of a novel food is expected to come into force by the end of the year.	Yes – approvals are company specific; all companies must submit Pre-market Novel Food Notifications, even if the novel food has already undergone review	No	No – for substances determined to be GRAS (information to establish safety must be in public domain) Yes – for food additive petitions (safety assessment by FDA can be done on unpublished proprietary data)
Urgency Provisions to Amend Regulations	Yes	Not applicable	Not applicable	Yes

Table 4.7-1 Comparison of Canadian and International Regulations Pertaining to Novel Foods				
	Australia/New Zealand	Canada	EU	U.S.
Transparency	Yes – the FSANZ website maintains publicly available records of work plan, all applications, and all decisions.	No – Regulatory decisions as well as Health Canada’s summary of the data, are often (but not always) published on the web-site	Yes – Notifications and Decisions are published in the Official Journal of the European Communities	Yes – Notifications and Food Additive Petition reviews are placed in the public domain
Contacts	Names, titles, and phone numbers are readily accessible	Names, titles, and phone numbers are not easily accessible	Names, titles, and phone numbers are readily accessible	Names, titles, and phone numbers are readily accessible
Safety Monitoring	No	No	No	Yes – Since 1985, the FDA has managed a passive post-marketing surveillance program (the Adverse Reaction Monitoring System) to collect and analyze reports of adverse events related to food additives
<p>¹ The Application Handbook contains guidelines on the safety evaluation of novel foods; it was registered by Food Standards Australia New Zealand as a Legislative instrument in July 2007; thus, guidelines must be followed; otherwise, the application may be rejected.</p> <p>² The demonstration of substantial equivalence requires that the novel food be demonstrated to be similar to an existing food with respect to composition, nutritional value, metabolism, intended use, and the level of undesirable substances contained therein.</p>				

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Appendix A

APPENDIX A

Table A-1 Approved Diet and Disease Claims in Five Jurisdictions	
Jurisdiction	Substantiated Health Claims
Australia/New Zealand	<p>Currently available for use Folic acid and neural tube defects</p> <p>High-level health claims that will be available for use once Standard 1.2.7 comes into effect</p> <ul style="list-style-type: none"> - Calcium (with or without vitamin D) and osteoporosis - Sodium (with or without potassium) and hypertension - Saturated fat and/or trans fat and elevated serum cholesterol or heart disease - Fruit and vegetables and coronary heart disease
Canada	<p>Approved</p> <ul style="list-style-type: none"> - Sodium and high blood pressure, a risk factor for stroke and heart disease - Calcium and vitamin D, and regular physical activity, and osteoporosis - Saturated and trans fats and heart disease - Vegetables and fruit and some types of cancer - Fermentable carbohydrates and dental caries <p>Under Review</p> <ul style="list-style-type: none"> - Soluble fibre from certain foods (oats, psyllium, barley) and risk of coronary heart disease - Soy protein and risk of coronary heart disease - Plant sterols/stanols and risk of coronary heart disease
European Union	<ul style="list-style-type: none"> - Each member state has its own health claim provisions. A unified list of claims not yet available since EU regulation came into force January 19, 2007. A confirmed list of Article 13 claims expected by January 31, 2010. Timelines for approval of Article 14 claims not clear.
Japan	<ul style="list-style-type: none"> - Calcium and osteoporosis - Folic acid and neural tube defects
United States	<p>Authorized Claims</p> <ul style="list-style-type: none"> - Calcium and osteoporosis - Sodium and hypertension - Dietary fat and cancer - Dietary Saturated Fat and Cholesterol and Risk of Coronary Heart Disease - Fibre-Containing Grain Products, Fruits, and Vegetables and Cancer - Fruits, Vegetables and Grain Products that contain Fibre, particularly Soluble Fibre, and Risk of Coronary Heart Disease - Fruits and Vegetables and Cancer - Folate and Neural Tube Defects - Dietary Sugar Alcohol and Dental Caries - Soluble Fibre from Certain Foods and Risk of Coronary Heart Disease - Soy Protein and Risk of Coronary Heart Disease - Plant Sterol/stanol esters and Risk of Coronary Heart Disease - Whole Grain Foods and Risk of Heart Disease and Certain Cancers* - Potassium and the Risk of High Blood Pressure and Stroke* - Fluoride and risk of dental caries* - Saturated fat, cholesterol, and trans fat and risk of heart disease* - Substitution of saturated fat with unsaturated fatty acids and risk of heart disease* <p>*Authorization based on authoritative statements by federal scientific bodies</p> <p>Qualified Claims</p> <ul style="list-style-type: none"> - Specific foods approved for 6 health categories: cancer, cardiovascular disease, cognitive function, diabetes, hypertension, neural tube defects

Table A-2 Standards and Specifications for Food with Nutrient Function Claims (FNFC) in Japan			
Nutritional Ingredient	Specified Range of nutritional ingredient of the advisable daily intake	Function Claims	Warning Indication
Niacin	3.3 ~ 60 mg	Helps to maintain skin and mucosa healthy.	Increased intake of this product will not result in curing diseases nor promoting health. Please comply with the advisable daily intake.
Pantothenic acid	1.65 ~ 30 mg	Helps to maintain skin and mucosa healthy.	
Biotin	14 ~ 500 µg	Helps to maintain skin and mucosa healthy.	
Vitamin A	135 ~ 600 µg	Helps to maintain vision in the dark, and helps to maintain skin and mucosa healthy.	Increased intake of this product will not result in curing diseases nor promoting health. Please comply with the advisable daily intake. Women within the third months of pregnancy or women considering to be pregnant should be careful of over consumption.
Vitamin B1	0.30 ~ 25 mg	Helps to produce the energy from carbohydrate and to maintain skin and mucosa healthy.	Increased intake of this product will not result in curing diseases nor promoting health. Please comply with the advisable daily intake.
Vitamin B2	0.33 ~ 12 mg	Helps to maintain skin and mucosa healthy.	
Vitamin B6	0.3 ~ 25 mg	Helps to produce the energy from protein and to maintain skin and mucosa healthy.	
Vitamin B12	0.60 ~ 60 µg	Aids in the red blood cell formation.	
Vitamin C	24 ~ 1000 mg	Helps to maintain skin and mucosa healthy and has anti-oxidizing effect.	
Vitamin D	1.5 ~ 5.0 µg	Promotes to absorb calcium in gut intestine and aids in the growth of bone.	
Vitamin E	2.4 ~ 150 mg	Helps to protect fat in the body from being oxidized and to maintain the cell health.	
Folic acid	60 ~ 200 µg	Aids in the red blood cell formation, and contributes the normal growth of the foetus.	
Zinc	2.1 ~ 25 mg	Necessary nutrient to maintain normal taste and helps to maintain healthy skin and mucous membranes. It is involved in the metabolism of protein and nucleic	Increased intake of this product will not result in curing diseases nor promoting health. Too much intake of zinc might inhibit absorption of copper. Please comply with the advisable daily

Table A-2 Standards and Specifications for Food with Nutrient Function Claims (FNFC) in Japan			
Nutritional Ingredient	Specified Range of nutritional ingredient of the advisable daily intake	Function Claims	Warning Indication
		acids and is helpful in maintaining health.	intake. Infants and young children should avoid use of this product.
Calcium	210 ~ 600 mg	Necessary in the development of bone and teeth.	Increased intake of this product will not result in curing diseases nor promoting health. Please comply with the advisable daily intake.
Iron	2.25 ~ 10 mg	Necessary in the red blood cell formation.	
Copper	0.18 ~ 6 mg	Helps to form red blood cells and helps proper function of many body enzymes and bone formation.	Increased intake of this product will not result in curing diseases nor promoting health. Please comply with the advisable daily intake. Infants and young children should avoid use of this product.
Magnesium	75 ~ 300 mg	Necessary in the development of bone and teeth, maintain proper blood circulation, and helps proper function of many body enzymes and energy generation.	Increased intake of this product will not result in curing diseases nor promoting health. Increased intake might cause diarrhoea. Please comply with the advisable daily intake. Infants and young children should avoid use of this product.

Table A-3 Biological Role Claims in Canada		
Nutrient	Biological Role	Specifications
Energy Any nutrient	<ul style="list-style-type: none"> - is a factor in the maintenance of good health - is a factor in normal growth and development 	<p>Nutrient value and percentage of daily value must be declared in the Nutrition Facts table on the label of the food, as appropriate.</p> <p>If concerns a nutrient not listed in the Nutrition Facts table, a quantitative statement of the nutrient(s) in grams per serving must appear on the label.</p>
Protein	<ul style="list-style-type: none"> - helps build and repair body tissues - helps build antibodies 	The food must meet the requirements for "source of protein" (The food has a protein rating of 20 or more, as determined by official method FO-1, <i>Determination of Protein Rating</i> , October 15, 1981).
Fat	<ul style="list-style-type: none"> - supplies energy - aids in the absorption of fat-soluble vitamins 	Nutrient value and percentage of daily value must be declared in the Nutrition Facts table on the label of the food.
DHA	<ul style="list-style-type: none"> - DHA, an omega-3 fatty acid, supports the normal development of the brain, eyes and nerves 	A quantitative statement of the nutrient(s) in grams per serving must appear on the label
Carbohydrate	<ul style="list-style-type: none"> - supplies energy - assists in the utilization of fats 	Nutrient value and percentage of daily value must be declared in the Nutrition Facts table on the label of the food.

Table A-3 Biological Role Claims in Canada		
Nutrient	Biological Role	Specifications
Vitamin A	<ul style="list-style-type: none"> - aids normal bone and tooth development - aids in the development and maintenance of night vision - aids in maintaining the health of the skin and membranes 	<p>Nutrient value and percentage of daily value must be declared in the Nutrition Facts table on the label of the food.</p> <p>The food must contain a minimum of 5% of the Recommended Daily Intake.</p>
Vitamin D	<ul style="list-style-type: none"> - factor in the formation and maintenance of bones and teeth - enhances calcium and phosphorus absorption and utilization 	
Vitamin E	<ul style="list-style-type: none"> - protects the fat in body tissues from oxidation 	
Vitamin C	<ul style="list-style-type: none"> - factor in the development and maintenance of bones, cartilage, teeth and gums 	
Thiamine (Vitamin B ₁)	<ul style="list-style-type: none"> - releases energy from carbohydrate - aids normal growth 	
Riboflavin (Vitamin B ₂)	<ul style="list-style-type: none"> - factor in energy metabolism and tissue formation 	
Niacin	<ul style="list-style-type: none"> - aids in normal growth and development - factor in energy metabolism and tissue formation 	
Vitamin B ₆	<ul style="list-style-type: none"> - factor in energy metabolism and tissue formation 	
Folate	<ul style="list-style-type: none"> - aids in red blood cell formation 	
Vitamin B ₁₂	<ul style="list-style-type: none"> - aids in red blood cell formation 	
Pantothenic Acid	<ul style="list-style-type: none"> - factor in energy metabolism and tissue formation 	
Calcium	<ul style="list-style-type: none"> - aids in the formation and maintenance of bones and teeth 	
Phosphorus	<ul style="list-style-type: none"> - factor in the formation and maintenance of bones and teeth 	
Magnesium	<ul style="list-style-type: none"> - factor in energy metabolism, tissue formation and bone development 	
Iron	<ul style="list-style-type: none"> - factor in red blood cell formation 	
Zinc	<ul style="list-style-type: none"> - factor in energy metabolism and tissue formation 	
Iodine	<ul style="list-style-type: none"> - factor in the normal function of the thyroid gland 	
<p>Claims may not be made for other components of food, such as lycopene, lutein, anthocyanins, <i>etc.</i> A quantitative statement would be permitted for these other components (e.g., "14 mg of lycopene per 50 g serving."). Other biological role claims for nutrients may also be acceptable and will be evaluated on a case-by-case basis.</p>		

Table A-4 List of Schedule A Diseases in Canada's Food and Drugs Act¹

Alcoholism
Alopecia (except hereditary androgenetic alopecia)
Anxiety state
Appendicitis
Arteriosclerosis²
Arthritis
Asthma
Bladder disease
Cancer²
Convulsions
Depression
Diabetes²
Disease of the prostate
Disorder of menstrual flow
Dysentery
Edematous state
Epilepsy
Gall bladder disease
Gangrene
Glaucoma
Gout
Heart disease²
Hernia
Hypertension²
Hypotension
Impetigo
Kidney disease
Leukemia
Liver disease (except hepatitis)
Nausea and vomiting of pregnancy
Obesity²
Pleurisy
Rheumatic fever
Septicemia
Sexual impotence
Thrombotic and embolic disorders
Thyroid disease
Tumour
Ulcer of the gastro-intestinal tract
Venereal disease

¹ Enacted to prevent claims directed at the general public concerning serious health problems, which should be diagnosed and treated by a medical practitioner.

² Common diet-related chronic diseases