Current Legislation of Probiotic Products

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Outline

- A little history – the scientific foundations for probiotics
- The Japanese Functional Foods Model – a success story?
- International efforts to elaborate a common and sound scientific basis
- The United States – a major challenge
- The Canadian approach to probiotics and health claims
- China – an opportunity but also a challenge
- Some Conclusions and Future Prospects
The Father of (Western) Medicine

**Hippocrates of Kos (c. 460 – c. 377 BC)**

“Let food be thy medicine and medicine be thy food”
Probiotics from traditional to modern

- Fermented Milks have been consumed from the earliest days of dairy farming – c. 6,000 B.C.
  - Traditional fermented milks come in many forms
    - e.g. in the Mediterranean Basin, Near East and Asia (Ayran (TK), Laban/Labneh, Doogh (IR), Lassi (IN) etc.
    - In Europe Kefir, Kumys/Koumiss, Bulgarian milk, Stragisto, Sour buttermilk etc.

- Modern times
  - Yogurt (plain and flavoured), Yogurt with added probiotic cultures, Acidophilus milk, Probiotic drinks (not all milk based)

- Probiotic supplements
  - as tablets, capsules, sachets etc.
The founding father of probiotics

**Ilya (Élie) Mechnikoff (1845 – 1916)**

- Born near Kharkov, Ukraine
- He became interested in the study of microorganisms and especially their roles in the immune system
- 1888 – joined the Instuit Pasteur in Paris
- 1908 – shared the Nobel Prize for Physiology Medicine with Paul Erlich for their work in the field of immunology
- 1908 - The Prolongation of Life: Optimistic Studies which proposed that the longevity of Bulgarian peasant farmers was related to their ingestion of fermented milk products.
- 2007 – the IDF instituted the Élie Metchnikoff Prize in three categories: Microbiology, Biotechnology and Nutrition and Health.

**Stamen Grigorov (1878 – 1945)**

- Born in the village of Studen Izvor, Tran Region, Bulgaria
- 1905, aged 27, working in the laboratory of Professor Masole in Geneva, he identified the microorganism in yogurt, which he called *Bacterium bulgaricum*
- Prof. Masole wrote to Mechnikoff telling him of his assistants findings.
- Metchnikoff invited Grigorov to visit the Institut Pasteur where he read a paper on the lactobacillus he discovered.
- Soon after Coendi and Mikelson, assistants to Mechnikoff, named the microorganism *Bacillus bulgaricus (Grigoroff)* in his honour.
- This is the microorganism is now called *Lactobacillus delbrueckii subsp. bulgaricus*
- 1906 - Gigorov published a scientific report “The Anti-tuberculosis vaccine”, which detailed his application of Penicillium fungi for the treatment of tuberculosis
Alfred Nissle (1874 – 1965)

• Born in Köpenick district in the south-east of Berlin.
• 1912 – joined the Institute of Hygiene of the University of Freiburg.
• From 1915 to 1938 - he was head of the Institute for Infectious Diseases in Freiburg.
• 1917 – he isolated a strain of non-pathogenic E. coli (E. coli Nissle 1917) from the faeces of a WW1 soldier who did not develop enterocolitis during a severe outbreak of shigellosis.
• He used the strain to treat intestinal diseases such as shigellosis and salmonellosis with a considerable amount of success.
• E. coli strain Nissle 1917 (EcN) has many features in common with the probiotic lactic acid bacteria but was the first non-LAB probiotic identified.

Henry Tissier

• A French-born paediatrician, he was contemporary of Mechnikoff at the Institut Pasteur.
• 1899 – he observed that the stools of breast fed children contained Y- or bifid-shaped rods – these became known as the genus *Bifidobacterium*.
• 1906 – he published a paper where he reported the stools of young children with diarrhoea were characterised by low numbers of these bifid-shaped bacteria, while those of healthy children had high numbers of such organisms. He suggested the possibility of administering such bacteria to ill children.
Leo Rettger (1874 – 1954)
- Born in Huntington, Indiana on 17 March 1874
- Taught at Yale University from 1902-1942.
- Was Professor of Bacteriology there and became the first US proponent of probiotics.
- 1920 – he showed *Lactobacillus bulgaricus* could not survive in the human intestine - this seemed to contradict Metchinikoff’s theory and the idea of the benefits of fermented food waned.
- 1935 - Rettger published a paper that identified that certain strains of *Lactobacillus acidophilus* were very active, when introduced to the human digestive tract.
- Tests were carried out and it was found to be helpful in relieving chronic constipation

Minoru Shirota (1899 – 1982)
- Born in Inadani, a village in Western Nagano, Japan
- 1921 - He chose to study medicine in Kyoto Univ. when a number of children died in his village due to infectious diseases and malnutrition.
- Inspired by Mechnikoff, he sought to develop a stronger strain of lactic acid bacteria which would help destroy the harmful bacteria living in the intestines, and thus improve and maintain human health.
- 1930 - he succeed in culturing a strain of lactic acid bacteria, *Lactobacillus casei* strain *shirota*
- 1935 – he succeeded in incorporating this strain into a drink he called Yakult.
- 1964 - Yakult expanded to markets outside Japan and is now sold in 35 countries worldwide
The history of the term **Probiotic**

- There seems to be general agreement that the term **Probiotic** was first used in a 1965 paper entitled: Probiotics: Growth-Promoting Factors Produced by Microorganisms *Daniel M. Lilly and Rosalie H. Stillwell* of the Department of Biology, St. John's University, Jamaica, NY in Science (1965), 147, Issue 3659, pp. 747-748
  - However, in this paper the term was used, in a different context, to describe substances secreted by one organism which stimulate the growth of another (symbiotic?)

- The term probiotic was used as it conveyed the opposite intent of the term antibiotic.

- It was not until 1974 that the term probiotic was actually used to describe a feed or food supplement by R.B. Parker, who defined it as “organisms and substances which contribute to intestinal microbial balance” – but this includes what we now call prebiotics.

- In 1989, Roy Fuller, an expert in gut microecology at the AFRC (Agriculture and Food Research Council), which was then based here in Reading University, modified Parker’s definition to: “live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance”

- In 2002 a Working Group of an FAO/WHO Expert Consultation proposed the following definition: - *Live micro-organisms that when administered in adequate amounts confer a health benefit on the host* This though now widely accepted, at least in the scientific community, has not been adopted into any international standard (at least to date).

- In 2014 a similar panel of scientific experts organised by the International Scientific Association for Probiotics and Prebiotics (ISAPP) agreed that the 2002 FAO/WHO definition for probiotics was still relevant, but advised a minor grammatical correction as follows “*Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host*”
The Japanese Functional Foods Model – a success story?

WHY?

- Post WW2 severe malnutrition among certain groups led to
  - Introduction of schools lunch programmes
  - Allowing the addition of certain nutrients to staple foods e.g. bread and rice

- Concerns arose about an aging population and the consequential burden on state finances in the future
Chronology of Legislation and Structures
Japan

- 1952 – Nutrition Improvement Law created a category of foods for special dietary uses

- 1984 – From analysis of food nutrition surveys by the Ministry of Education, Science and Culture, 3 main functions of food were identified:
  - Nutritive value;
  - Organoleptic appeal;
  - Physiological features; e.g.
    - Regulation of bodily function
    - Disease prevention
    - Recovery promotion
    - Good health
    - Out of the latter grew the concept of functional food and led to the setting up of a Functional Foods Forum

- The Ministry of Health and Welfare promoted functional food and the food industry was keen to make such products that could make health claims
1989 – More comprehensive guidelines were established for the appropriate labelling on health food; this allowed manufacturers of functional foods to make health claims.

1991 – the Nutrition Improvement Law was further amended and the term functional food was replaced by foods for specific health uses (FOSHU); it listed 5 categories:
- Milk Powder for pregnant and lactating women
- Infant Formula
- Food for dysphagia patients (those difficulty in chewing and swallowing, usually the elderly)
- Food for medical patients; and
- Foods for special dietary uses (FOSHU)

2001 - A new regulation system for food with nutrient function claims (FNFC) was introduced.

2005 - Standardised FOSHU, Qualified FOSHU and Disease Reduction Risk FOSHU were also added.

2009 – The Consumer Affairs Agency (CAA) was established and given responsibility for the Japanese food labelling system, including those provisions covering FOSHU.

2015 – A new category of Foods with Function Claims was introduced in order to make more products available, clearly labelled with certain nutritional or health functions, and to enable consumers to make more informed choices.
The Health Food Market in Japan

So-called “Health Foods”
- Dietary supplements
- Other health related products etc
- Prohibited to indicate Health Claims or Function Claims

Food for Specified Health Uses (FOSHU)
- Dietary fibers
- Oligosaccharides
- Isoflavones etc
- Allowed to indicate Claims for Specified Dietary Uses

Food for Special Dietary Uses (FOSDU)
- For patients
- For pregnant and lactating women
- For infants
- For dysphagia patients
- Low protein food
- Lactose-free food
- Infant formula etc
- Allowed to indicate Claims for Special Dietary Uses

Foods with Function Claims (FFC)
- Allowed to indicate Claims for Nutrient Function

VITAMINS & MINERALS

CAА, 2011, 2015
Categories of foods with health claims

Japan

Foods with Nutrient Function Claims (FNFC)

Requires detailed review process with scientific validation

Regular FOSHU

For products with ingredients showing certain health effects but not reaching the established standards for FOSHU approval

New types of FOSHU (introduced in 2005)

Standardised FOSHU

Qualified FOSHU

Reduction of Disease Risk FOSHU

No requirement of detailed review process for food products meeting the established standards and specifications; i.e. a short process for products already approved

Permitted for products whose ingredients are established to reduce a risk of certain disease(s)
Structure following the 2015 change

- Foods in General
  - Cannot make a function claim
  - Foods for Specified Health Uses
    - Foods with Nutrient Function Claims
      - Foods with Function Claims
- Foods with Health Claims
  - Can make a function claim
- Pharmaceutical products
- Quasi-pharmaceutical products

CAA Japan 2015
Features of the (new) category of Foods with Function Claims

- There is no safety assessment or evaluation of functionality by government.
- The food operators can use functional claims on their own responsibility.
- Prior notification must be given to the Consumer Affairs Agency (60 days before launch).
- The notification number appears on the packaging.
- Information of each product (scientific data etc.) can be seen on the website of the CAA. (any revisions/modifications of the text are also clearly shown).
- According to the website of the CAA, there are 225 notifications up to late March 2016.
- Some claims made are quite strong.
FOSHU Approval Process Flow Chart

Applicant → Consumer Affairs Agency (Food Labelling Division)

- Consumer Commission: Assessment and Evaluation Group for Novel Food
  - Reviews efficacy

- Food Safety Commission: Expert Assessment Group for Novel Food
  - Reviews safety

- Consumer Commission: Assessment Committee for Novel Food
  - Reviews efficacy and safety comprehensively

- Ministry of Health, Labour and Welfare: Checks whether the labelling violates Pharmaceutical Affairs Act

Consumer Affairs Agency (Approval)

Source: CAA Japan 2011
FOSHU products by health use category

Probiotics are included in this category

Source: CAA Japan 2011
Growth of FOSHU Approvals

Cumulative total FOSHU Approvals
1993 - 2016

Compiled from data obtained from the site of the CAA Japan to 3 March 2016
Some probiotic products
Japan

Morinaga Milk
Bifidus BB536 Yogurt

Due to the effects of the Yakult strain (Lactobacillus casei strain Shirota), which can reach the intestine alive. Yakult maintains the intestine in good health by increasing beneficial bacteria, decreasing harmful bacteria and by improving the intestinal environment.

Yakult Pretio

Due to the effects of *Bifidobacterium longum* BB536 which reach the intestine alive, the bifido bacteria in the intestines increase and it improves the intestinal environment and regulates the intestinal/tummy (ONAKA) conditions.

Morinaga Caldus Milk

Due to the effects of *Bifidobacterium longum* BB536 which reach the intestine alive, the bifido bacteria in the intestines increase and it improves the intestinal environment and regulates the intestinal/tummy (ONAKA) conditions.

This product contains GABA and is suitable for those who with slightly elevated blood pressure.
Due to the effects of Lactobacillus GG, which can reach the intestine alive, this product increases beneficial bacteria and decreases harmful bacteria. It improves the intestinal environment and regulates the tummy (ONAKA) conditions.

This product contains Bifidobacteria BB 536. It has been reported that Bifido acteria BB 536 improves the intestinal environment and regulate the intestinal/tummy (ONAKA) condition.
Megumi Gasseri strain SP yoghurt

On the Label
- Gasseri strain SP yoghurt which decreases visceral fat.
- A 46 /Food with a function claim: notification number A48
  This product contains Gasseri strain SP and therefore it has the function of decreasing visceral fat.
- This product is notified to the Secretary General of the Consumer Affairs Agency that the food business operation will mention on its own responsibility on the label that special functional effect can be expected. However, unlike FOSHU, the product was not individually assessed by the Secretary General of the CAA
- No Fat (0), No sugars used

Notification of Food with Function Claim (FCC)
This product contains Lactobacillus gasseri strain SP. It has been reported that Gasseri strain SP has the function of decreasing visceral fat.

Yakult Sofhul
Smooth texture yogurt

Due to the effects of the Yakult strain (*Lactobacillus casei* strain Shirota), which can reach the intestine alive. Yakult maintains the intestine in good health by increasing beneficial bacteria, decreasing harmful bacteria and by improving the intestinal environment.
Share of the Japanese Health Food Market

FOSHU v non-FOSHU

Source: CAA Japan 2011
Features of the Japanese Model

For FOSHU

- A proactive approach based on perceived need
- Government endorsed and supported
- A Voluntary system
- Approval given for individual products
- Health claim wording is approved
- Approval based on demonstrated and documented scientific safety and efficacy
- Approved products can use the FOSHU logo on label
Japanese Model – is it a success?

- Given the number approved, and the value of the market for FOSHU – probably a qualified YES

- However:-
  - It is expensive to obtain approval both in terms of cost and time especially for SME’s
    - Some companies estimated to have spent more that £750K and waited more than 3 years for approval (USDA Gain Report 8/3/2015)
  - There remains a large market for “So-called” Health Foods outside the system
  - It is not known how many approved FOSHU products are still on the market.
  - It remains to be seen what the effect of the new Foods with Function Claims (FFC) category will have on approved foods
    - The market size for financial year 2015 (Apr 2015 - Mar 2016) was ¥30.3bn.
    - Estimates for financial year 2016 (Apr 2016 - Mar 2017) is ~¥70bn
    - Estimates for FOSHU market for financial year 2016 predict a decline of ~¥3bn as companies switch priorities from FOSHU to FFC foods
International efforts to elaborate a common and sound scientific basis

- 2001 (Cordoba, AR) – An FAO/WHO Expert Consultation on:- Probiotics in food Health and nutritional properties and guidelines for evaluation
Outcomes of the Expert Group

- Drafted Guidelines for the evaluation of probiotics in food
- 11 experts from 10 countries attended
- They evaluated the latest information on
  - Scientific evidence available on probiotics as functional foods;
  - Food safety aspects of probiotics;
  - Methodologies to assess such aspects.

- In addition to scientific recommendations they made recommendations pertaining to regulatory matters including
  - That to be termed a probiotic, the M/O must be able to confer defined health benefits to consumers in the product as marketed;
  - That GMP must be applied in manufacture and labelling;
  - That the regulatory status should be established at international level;
  - That a regulatory framework be established to include efficacy, safety, food labelling, claims and to prevent fraud;
  - That qualifying probiotics should be allowed to describe properly validated benefits (health claims);
  - That surveillance systems should be established to identify any adverse effects and monitor the long-term health benefits of their consumption.
1992 (London, ON, CA) – A Working Group of the FAO/WHO Expert Consultation established to draft Guidelines for the Evaluation of Probiotics in Food:

- Concluded probiotic effects are strain-specific;
- Elaborated the definition of probiotics as outlined earlier;
- Recommended that adoption of their Guidelines, as contained in their report, should be a pre-requisite for calling a strain a probiotic.

The conclusions and recommendations of these groups are those of the participants and do not imply any opinion on them by the organisers of the Expert Consultation (FAO & WHO).

It is also recognised that the participants were all scientists and not legislators.

Nonetheless, the conclusions appear to have been well received generally – their subsequent adoption is another matter.
CODEX Standards and Guidelines

- **1971 (Rev. 1991)** – Codex General Guidelines on the Use of Claims

- **2007** - Codex Guidelines on the Use of Nutrition and Health Claims

- **2009** – Recommendations on the Use and Substantiation of Health Claims adopted and now included in the 2007 Guidelines

**NOTE:** Codex does not evaluate health claims – the guidelines are intended for individual governments to facilitate their evaluation of health claims made by industry. They also should provide a reference in preparing dossiers aimed at substantiating such claims.
Codex General Guidelines on the Use of Claims

Prohibit

Claims as to the suitability of a food for use in the prevention, alleviation, treatment or cure of a disease, disorder, or particular physiological condition unless they are:
(a) in accordance with the provisions of Codex standards or guidelines for foods as developed by the Committee on Nutrition and Foods for Special Dietary Uses and follow the principles set forth in these guidelines.
or,
(b) in the absence of an applicable Codex standard or guideline, permitted under the laws of the country in which the food is distributed.
Codex Guidelines on the Use of Nutrition and Health Claims

Defines

**Health claim** means any representation that states, suggests, or implies that a relationship exists between a food or a constituent of that food and health. Health claims include the following:

**Reduction of disease risk claims** – Claims relating the consumption of a food or food constituent, in the context of the total diet, to the reduced risk of developing a disease or health-related condition.

Risk reduction means significantly altering a major risk factor(s) for a disease or health-related condition. Diseases have multiple risk factors and altering one of these risk factors may or may not have a beneficial effect. The presentation of risk reduction claims must ensure, for example, by use of appropriate language and reference to other risk factors, that consumers do not interpret them as prevention claims.

**Examples:**

“A healthful diet low in nutrient or substance A may reduce the risk of disease D.
Food X is low in nutrient or substance A.”

“A healthful diet rich in nutrient or substance A may reduce the risk of disease D.
Food X is high in nutrient or substance A.”
Codex Guidelines on the Use of Nutrition and Health Claims

Focus on criteria to be used for substantiation and for systematic review of relevant scientific evidence such as:

- Health claims should primarily be based on evidence provided by well-designed human intervention studies.
- Recognise that human observational studies per se are not necessarily sufficient alone but they may contribute to the totality of the evidence.
- Data from *ex vivo* or *in vitro* animal model studies are not regarded as sufficient but may be used to provide additional supportive information.
- The totality of the evidence should be identified and reviewed.
- Evidence based on human studies should demonstrate a consistent association between the food or food constituent and the claimed health effect.
- Substantiation can take into account specific situations or alternate processes.
- Some health claims, e.g. those involving a relationship between a food category and a health effect, may be substantially based on observational studies.
- Evidence-based dietary guidelines and authoritative statements prepared or endorsed by a competent authoritative body and meeting the same high scientific standards may also be used.
Codex Standard for Fermented Milks

- Adopted in **2003** – replacing 2 earlier yogurt standards
  - Revised **2008** – to include *Drinks based on Fermented Milk*
- Specified min. level of starter cultures = $1 \times 10^7$ cfu/g (or ml)
- Allowed the use of other safe and suitable M/Os
- Allowed the labelling of the presence of specific M/Os, but specified a min. level for such cultures = $1 \times 10^6$ cfu/g (or ml)
- Did not use or reference the term probiotic
- Regional standards for certain fermented milks being considered (doogh, labneh) and others may follow.
  - The current draft of the standard for doogh does include “probiotic provisions”
US Regulatory Implications

- Probiotics are regulated differently depending on the intended use
- Regulations for claims are dictated differently for:
  - Conventional Foods
  - Dietary Supplements
  - Medical Foods
  - Drugs
  - Animal Feed Additives
US Regulatory Implications

- Intended Use
  - Nature of claims made
- Formulation
  - Capsules and pills
- Route of administration
  - Orally for foods & supplements
- Target Consumers
  - Foods intended for general public
- Safety
  - Food - GRAS or approved food additive
  - DS - NDI New dietary Ingredient notification (1994)
## US Types of Food Labelling Claims

<table>
<thead>
<tr>
<th>Type of Claim</th>
<th>FDA standard</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrient Content</td>
<td>FDA Clearance</td>
<td>&quot;&quot;Contains calcium&quot; &quot;Good source of calcium&quot;</td>
</tr>
<tr>
<td>Health Claims</td>
<td>FDA Clearance</td>
<td>&quot;May reduce the risk of osteoporosis&quot;</td>
</tr>
<tr>
<td>Structure/function</td>
<td>Accurate &amp; Substantiated</td>
<td>“Helps build strong bones and teeth”</td>
</tr>
<tr>
<td>Dietary Guidance</td>
<td>Accurate &amp; Substantiated</td>
<td>“Diets rich in dairy foods, fruits and vegetables reduce the risk of some chronic diseases”</td>
</tr>
</tbody>
</table>
Health Claims in US

- Reduction of risk of disease claims
- Statements that describe the relationship between a substance and a disease in the labelling of foods, including dietary supplements
  - Reviewed and authorized by FDA based of "significant scientific agreement" or
  - Appropriately qualified - where quality and strength of scientific evidence is inconclusive
  - Authoritative government body
  - No authorizations for probiotics

*3g of soluble fiber daily from oatmeal, in a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.
Structure/ Function, Health, and Disease Claim Distinction

Describes the role of a substance in maintaining or supporting normal structures of functions of the body?

YES → Structure Function Claim

Substantiation

NO → Claim to Reduce the risk of disease?

YES → Seek FDA Health Claim Authorization or Qualified Health Claim

YES → Approved Health Claim

NO → Product is intended to be used in the diagnosis, cure, mitigation, treatment, or prevent of disease?

YES → “Drug”

YES → Drug Approval

NO → "Drug"
US Regulatory Challenge for Probiotics

Conveying the benefits of a food or dietary supplement containing probiotic organisms to avoid wording claims in a manner that would be viewed by FDA as unauthorized health or drug claim.
Legal Challenges to probiotic claims in US

The Complaints were
1. Dannon’s advertisements for DanActive conveyed to consumers that drinking the product reduces the likelihood of getting a cold or flu

2. In a TV for Activia yogurt, an actress lounging on a couch tells viewers that many people suffer from irregularity, and that “our busy lives sometimes force us to eat the wrong things at the wrong time.” She reassures viewers that Activia can help.

OUTCOME
Dannon had to cease using these health claims
Yet another Class Action in the US

Torrent v. Yakult U.S.A., Inc.

Plaintiff, Nate Torrent, alleged that Yakult violated California’s Unfair Competition Law (UCL) by deceptively claiming that its probiotic beverages containing the Lactobacillus casei Shirota microorganism help balance the digestive system and maintain overall health.
But all challenges **do not** result in a loss

**Stand Down! Court Rejects Yakult Yogurt False Advertising Class for Lack of Standing**

**Morrison & Foerster LLP**

USA | January 19 2016

**Outcome:**
The Court found that the sole named plaintiff lacked Article III standing to seek injunctive relief on behalf of the putative class because he failed to allege or offer evidence of a sufficient likelihood of future harm.

Even on a second challenge

**Class Cert Denial Redux: Plaintiff’s “Manufactured” Standing Falls Short in Yakult Yogurt Action**

**Morrison & Foerster LLP**

USA | April 1 2016

**Outcome:**
The same Judge ruling that his newly alleged intent to buy Yakult in the future was nothing more than a barely disguised attempt to manufacture standing
Claims of products on US Market

Enrich your day with a delicious, creamy Activia lowfat yogurt. Rich in flavor and made with our exclusive probiotic yogurt culture, Bifidus Regularis® (Bifidobacterium lactis DN-173 010), Activia will please your taste buds and your tummy.* Available in seven great flavors.

DanActive helps support your immune system when consumed regularly as part of a balanced diet and healthy lifestyle.
Yakult is a probiotic drink. It contains billions of live and active "good bacteria." Your digestive system naturally contains trillions of bacteria -- some are helpful, some are harmful. When you drink Yakult daily, it makes it difficult for the bad bacteria to take over. Yakult also gives you more of the good bacteria that may help balance your digestive system.

Probiotics

Probiotics support digestive health and immunity so that your body is strong on its own and can proactively fight off infection and help prevent disease.

Bifidobacterium BB12

There is a unique strain of the probiotic Bifidobacterium BB-12® in every cup of La Yogurt Probiotic. This special strain works with the rest of your body to help maintain balanced microflora, support immunity and support digestive health.
So What is the future for Probiotics in US?

Probiotic Foods

or

Probiotics as Supplements (in tablets, sachets, capsules)
Mary Ellen Sanders – a leading US Food Microbiologist and proponent of probiotics

A non-profit public research management corporation whose mission is to lead and deliver best research and science-based educational programs towards innovative and sustainable California and U.S. dairy industry

How FDA’s Actions Are Guaranteeing Research on Probiotic Foods is Not Conducted in the USA

October 13, 2012
By Mary Ellen Sanders, Dairy & Food Culture Technologies

“Probiotics: Achieving a Better Regulatory Fit”

July 24, 2014
By Mary Ellen Sanders, Dairy & Food Culture Technologies

Definition of Probiotics: 12 Years Later

June 10, 2014
By Mary Ellen Sanders, Dairy & Food Culture Technologies
The Canadian approach to probiotics and health claims

- **1998** - HC published a *Policy Paper on Nutraceuticals /Functional Foods and Health Claims on Foods*
- **2002** – HC produced an *Interim Guidance* document that outlined standards of evidence for evaluating foods with health claims
- **2003** – The *Canadian Food and Drug Regulations* were amended to introduce the first series of authorised health claims
- **2009** – HC updated the Interim Guidance replacing it with a *Guidance Document for Preparing a Submission for Food Health Claims*
  - HC posted a guidance document *The Use of Probiotic Microorganisms in Food*
  - HC published a new guidance document *Classification of Products at the Food-Natural Health Product Interface: Products in Food Format*
Categories of Food Claims - Canada

**Nutrition Claims**

- **Nutrient Content Claims**
  Describe the quantity of energy or nutrient e.g. “low”, “high”, “light”, “source”, etc.

- **Nutrient Function Claims**
  "Calcium aids in the formation and maintenance of bones and teeth."

**Health Claims**

- **General Health Claims**
  "Canada’s Food Guide recommends eating at least one dark green and one orange vegetable each day."

- **Function Claims**
  "Consumption of 1 cup of green tea helps to protect blood lipids from oxidation."

**Disease Reduction and Therapeutic Claims**

- **Disease Reduction Claims**

**Probiotic Claims**

- **Non-Strain Specific Probiotic Claims?**
  No strain Specific Claims approved to date

- **Strain Specific Probiotic Claims?**
  No strain Specific Claims approved to date
Health Canada recognizes that the foods we eat can affect our health in different ways. Some food labels contain statements about the beneficial effects of certain foods on a person's health, such as "a healthy diet low in saturated and trans fat may reduce the risk of heart disease". This type of statement is an example of a health claim.

A health claim is any representation in labelling or advertising that states, suggests, or implies that a relationship exists between consumption of a food or an ingredient in the food and a person's health.

**Function claims** are health claims that describe the physiological effects of foods or food constituents on normal functions or biological activities of the body associated with health or performance.

**Therapeutic claims** are claims that would bring a food into the definition of a drug or a natural health product (drug claims). These are claims about the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans, or restoring or correcting organic functions in humans, or modifying organic functions in humans. Products that carry such claims are considered to be represented for "therapeutic use".
Probiotic Health Claims in Canada

• A probiotic health claim can consist of one of the following examples:
  – Use of the term "probiotics" and similar terms or representations;
  – Use of words such as "with beneficial probiotic cultures"; or
  – "contains bacteria that are essential to a healthy system"; and
  – Use of the Latin name of a microbial species modified to suggest a health benefit.

• A probiotic health claim can be presented in either text or graphic, on food labels or in advertisements to suggest that a food confers a health benefit.

• **Non-strain specific probiotic claims** are allowed

• **Strain specific probiotic claims** are allowed – **but none have been approved to date**
Canada - Eligible Genus/Species to make a non-species specific health claim

<table>
<thead>
<tr>
<th>Eligible bacterial species</th>
<th>Acceptable Non-Strain-Specific Probiotic Claims for Food</th>
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</thead>
<tbody>
<tr>
<td><em>Bifidobacterium adolescentis</em></td>
<td>1. Probiotic that naturally forms part of the gut flora.</td>
</tr>
<tr>
<td><em>Bifidobacterium animalis</em> subsp. <em>animalis</em></td>
<td>2. Provides live microorganisms that naturally form part of the gut flora.</td>
</tr>
<tr>
<td><em>Bifidobacterium animalis</em> subsp. <em>lactis</em> -synonym: <em>B. lactis</em></td>
<td>3. Probiotic that contributes to healthy gut flora.</td>
</tr>
<tr>
<td><em>Bifidobacterium bifidum</em></td>
<td>4. Provides live microorganisms that contribute to healthy gut flora.</td>
</tr>
<tr>
<td><em>Bifidobacterium breve</em></td>
<td></td>
</tr>
<tr>
<td><em>Bifidobacterium longum</em> subsp. <em>infantis</em> comb. nov.</td>
<td></td>
</tr>
<tr>
<td><em>Bifidobacterium longum</em> subsp. <em>longum</em> subsp. nov.</td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus acidophilus</em></td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus casei</em></td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus fermentum</em></td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus gasseri</em></td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus johnsonii</em></td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus paracasei</em></td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus plantarum</em></td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus rhamnosus</em></td>
<td></td>
</tr>
<tr>
<td><em>Lactobacillus salivarius</em></td>
<td></td>
</tr>
</tbody>
</table>

- In product labelling, *Bifidobacterium longum* subsp. *infantis* and *Bifidobacterium longum* subsp. *longum* would be considered acceptable nomenclature.
- The word “gut” may be replaced by the expression “digestive tract” in these claims.

A serving of stated size of a product should contain a minimum level of $1.0 \times 10^9$ cfu of one of the eligible microorganism(s) that is(are) the subject of the claim.
### Summary of Canadian Health Claim Requirements

<table>
<thead>
<tr>
<th>Type of Claim</th>
<th>Pre-Market Approval</th>
<th>Scientific Substantiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Health Claims</td>
<td>Follow the Canadian Food Health Claim Roadmap for a logical approach to regulatory considerations en route to using claims</td>
<td>All claims must be supported by scientific evidence in a systematic, comprehensive, and transparent manner</td>
</tr>
<tr>
<td>Nutrient Function Claims</td>
<td>Pre-market notification is not required for accepted nutrient function claims listed in GFLA* Chapter 8 (section 8.6)</td>
<td>New nutrient function claims will be considered only for nutrients with established recommended intakes if the function reflects consensus among authoritative scientific bodies</td>
</tr>
<tr>
<td>General Health Claims</td>
<td>Pre-market notification is not normally required</td>
<td>Consult GFLA* Chapter 8 (sections 8.8–8.15)</td>
</tr>
<tr>
<td>Function Claims</td>
<td>A list of acceptable function claims and conditions for use is maintained in GFLA* Chapter 8 (section 8.5)</td>
<td>Claims must be supported by acceptable standards of evidence</td>
</tr>
<tr>
<td></td>
<td>Pre-market notification is recommended for new function claims</td>
<td>Claims should clearly state a specific and scientifically supported physiological effect associated with good health or performance</td>
</tr>
<tr>
<td></td>
<td>Evidence should be available upon request</td>
<td>Consult Guidance Documents for Preparing Health Claim Submissions</td>
</tr>
<tr>
<td>Disease Risk Reduction and Therapeutic Claims</td>
<td>A list of claims reviewed by Health Canada for scientific validity is published on Health Canada’s Health Claim Assessments web page.</td>
<td>Consult Guidance Documents for Preparing Health Claim Submissions</td>
</tr>
<tr>
<td></td>
<td>Conditions of use and prescribed wording apply</td>
<td>Submissions for new claims must characterize the food and the health effect, substantiate claim validity, demonstrate feasibility of consumption of effective dose, and propose claim wording</td>
</tr>
<tr>
<td></td>
<td>If a claim associates a food as a treatment, preventative or cure for any of the diseases referred to in Schedule A of the FVM, then a regulatory amendment is needed prior to use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If the claim is not subject to Schedule A, then a regulatory amendment may not be required before the claim can be used</td>
<td></td>
</tr>
</tbody>
</table>

*GFLA = CFA’s Guide to Food Labelling and Advertising

Source: Health Canada (2012)
Examples from the Canadian Market

Find out how Activia can help you

**ACTIVIA**

**MAY REDUCE THE FREQUENCY**

of minor digestive issues

**WHEN CONSUMED TWICE**

**PER DAY**

**FOR**

2 weeks

**AS A PART OF A**

balanced diet and healthy lifestyle

Find out how Activia can help you.

Every bite of food you eat has an impact on your digestive system. Activia’s exclusive probiotic BL Regularis culture survives gastric acids and enzymes. It reaches your intestinal tract alive, active and in great numbers. Friendly bacteria present in the large intestine, contained in Activia, help digest our food and produce certain vitamins, help to make conditions unfavourable for some harmful bacteria.

**Friendly bacteria**

DanActive contains 3 different cultures: Streptococcus thermophilus, Lactobacillus bulgaricus, and Lactobacillus casei, a probiotic culture that contributes to healthy gut flora.

**Vitamin D**

Vitamin D helps build strong bones. By choosing a yogurt made with vitamin D fortified milk, you can contribute to your daily intake of this vitamin. Not a bad way to start the day!

**Calcium**

Whatever your age, calcium aids in the formation and maintenance of bones. DanActive is a source of calcium.
China – an opportunity but also a challenge

- Traditional Chinese Medicine (TCM) has a long-documented history – back to the Western Zhou Dynasty => 1046 - 771 BC.

- The term Medicinal Food is first found in the literature of the Han Dynasty => 206 BC - 220 AD

- Early 1980’s – saw the development of Healthy (Functional) Foods, some of which claimed to improve health and remedy certain diseases or conditions

- By 1991 the China Market estimated as £3bn – but there were concerns as regards
  - Identity
  - Efficacy
  - Possibly Food Safety
  This led to the necessity to establish evaluation and assessment procedures and for regulatory control and monitoring

- 1995 - Food Hygiene Law of the P. R. China – the basic food law legislation

- 1996 – Ministry of Health Regulation set Administrative Provisions for Health Foods
- **2005** – Interim Regulations for the Control of Health Foods

- **From 2008 onwards** – Regulation(s) on the Inspection and Administration of Health Food

- **2009** – The Food Hygiene Law was replaced by **Food Safety Law**

  revisions of this law are ongoing

- **2009** - Regulation on the Implementation for the Food Safety Law

- **2012** – The CFDA issued **Requirements on and a Guide to the Naming of Health Foods**

- **2016** – CFDA issued provisions for **Health Food Registration and Filing**
CFDA (sometimes the abbreviation SFDA is used) got its current name in 2003 with added supervision and administration functions in food and cosmetics.

In 2008, its responsibilities underwent 2 major changes.
- Its responsibility of coordinating food safety and investigating major food safety incidents was transferred to the MOH.
- It took over MOH’s responsibility of supervising food safety e.g. food hygiene licensing, the catering sector etc., as well as overseeing health food and cosmetics.

It is now responsible for protecting public health by assuring the safety, efficacy, and security of drugs, biological products, medical devices, food supply (including Health Foods) and cosmetics.

As a direct part of the State Council, CFDA has regulatory and legal enforcement functions in the supervision the above fields.
Main Provisions for Administration of Health Food

- **Definition of Health Foods**
  Food products that claim specific health functions and have been approved according to Regulations

- **Scope:**
  The product is suitable for a specific population to consume, assists with regulating different body functions, and is not intended to cure disease

- Nutrient supplements, specifically including vitamins and minerals designed to supplement people’s diet, are regulated by the health food regulations
<table>
<thead>
<tr>
<th>Health Food Categories in China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhancing immunity</td>
</tr>
<tr>
<td>Accelerating lactating</td>
</tr>
<tr>
<td>Assisting blood sugar reduction</td>
</tr>
<tr>
<td>Assisting blood lipids reduction</td>
</tr>
<tr>
<td>Improvement of growth and development</td>
</tr>
<tr>
<td>Enhancing anoxia tolerance</td>
</tr>
<tr>
<td>Assisting irradiation hazard protection</td>
</tr>
<tr>
<td>Increasing bone density</td>
</tr>
<tr>
<td>Eliminating acne</td>
</tr>
<tr>
<td>Improving skin moisture (water content)</td>
</tr>
<tr>
<td>Anti-oxidation</td>
</tr>
<tr>
<td>Improving nutritional anaemia</td>
</tr>
<tr>
<td>Facilitating digestion</td>
</tr>
<tr>
<td>Co-protection of chemical liver damage</td>
</tr>
</tbody>
</table>
Approval Process - China

Testing

Application

Technical Review

Approval

CFDA Approved Testing Body

Provincial FDA (CDFA for Imports)

Evaluation Agency

CFDA

6 – 12 months

3 months

Total Costs of approval estimated as between £10,500 and £25,000 in 2008
Main Tests and Evaluations

- Toxicological, physical and chemical, microbiological and quality stability

- Functional evaluation - Scientific substantiation is the key for efficacy claims
  - Depending on the category the type of trials required may be
    - Animal (n = 7) e.g. increasing bone density, or enhancement of the immune system:
    - Human (n = 4) e.g. eliminating skin cloasma (melasma); or
    - Both Animal and Human trials (n=15) e.g. adjusting intestinal bacterial flora

- Quantitative test of level of active/marker ingredients

- Tests of nutrient content
Technical Review - Key issues

- **Safety**: focusing on novel ingredients/raw materials and formula

- **Efficacy confirmation**: scientific substantiation, including functional tests.

- **Quality control**: contents of active/marker ingredients and product standards - challenges of complex and diverse factors affecting stability and consistency.

- **Quantitative assessment**: safety usage/relationship between dosage and efficacy.

- **Assessment of formulation/combination**: challenges of scientific evidence, interaction, etc.
Market size 2007 to 2014 (£bn.)
Market size 2007 to 2014
Product approval numbers and top categories

- Between **1996 and mid-2007**, approx. **8,200** health food products were approved by the Ministry of Health and the CFDA – at the end of that period it was estimated only about **30%** of the approved products were still on the market.
  
  Source: Hong Kong Trade Development Council (HKTDC), 2015

- As of **mid-July 2015**, the CFDA had approved a total of **15,802** health food products.
  - Of these **95%** (n=15,063) were **made in China** and **5%** (n=739) were **imported**.
  - It is estimated that functional foods account for **about 65%**, with nutritional supplements accounting for the remaining **35%**.
  - No figures are available for the number of these products that are still on the market there.

- Top Categories were regulating the immune system, alleviating physical fatigue, anti-ageing (likely involving multiple categories) and assisting blood lipids reduction.

  Source: Hong Kong Trade Development Council (HKTDC), 2015
Some Conclusions and Future Prospects

• The scientific basis for the benefits of probiotics have been recognised for over 100 years but the regulatory status has not evolved at the same rate as the science.

• Though all regulatory systems we have looked at use scientific validation for health claims the outcomes differ.
  – This is likely due to different levels or standards for approval being applied.

• Probiotic related claims fare better in Japan and China than in the US and the EU - well they could hardly fare worse!

• Canada recognises 17 probiotic species; permits specified non-strain health claims; and allow strain specific claims – though none of the latter are approved – at least as yet.

• Will the future for probiotics be in foods or sold as supplements – this is likely to be decided for individual markets.

• In the markets of developed countries, leading probiotic brands may continue to grow.

• What will happen in developing markets? How will new products be promoted?

• In countries where regulatory challenges are greatest, will the use of scientific conferences aimed at health professionals substitute/replace claims in labelling and advertising?
Acknowledgements

In conclusion I should like to express my sincere thanks to two valued IDF colleagues and good friends for their most generous help and assistance in preparing this presentation.

- Yuki Morita, Director Regulations and Public Affairs, Yakult Europe

While I have used information and material supplied by these colleagues, the opinions, views and conclusions expressed are mine alone and do not purport to be theirs.
Thank you for your kind attention

Any Questions?

But not too difficult please!