The importance of balance: Matching science with advocacy to encourage enlightened regulation

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Presentation Overview

I. Introduction

II. Safety Standards & Regulatory Trends

III. Advances in Genomics

IV. Advocacy Strategies
I. Introduction
History of Probiotics: Traditional Uses

Examples of sources from traditional foods
- Japan- natto \(^{58,61,69}\) (Bacillus)
- China- douchi \(^{69}\) (Bacillus), kurut \(^{27}\) (Enterococcus, Streptococcus)
- Mongolia- fermented yak milk \(^{66}\) (Enterococcus, Lactobacillus, Streptococcus), koumiss \(^{80}\) (Lactobacillus)
- India- kinema \(^{69,70}\) (Bacillus)
- Kenya- maasai \(^{79}\) (Lactobacillus)
- Spain- kefir \(^{78}\) (Lactobacillus, Streptococcus)
- Thailand- thua-nao \(^{69}\) (Bacillus)
- African countries- ogiri \(^{61}\) (Bacillus), fermented locust bean \(^{62}\) (Bacillus), soumbala \(^{69}\) (Bacillus)
- Italy- cheese \(^{81}\) (Lactobacillus)
- Argentina- cheese \(^{81}\) (Lactobacillus)
- Korea- kimchi \(^{84,85}\) (Bacillus, Lactobacillus)
- Malaysia- tempeh \(^{86}\) (Lactobacillus)

Other natural sources
- Breastmilk \(^{81,82,83}\) (Bifidobacterium, Enterococcus, Lactobacillus)
- Soil \(^{69}\) (Bacillus)
- Seawater \(^{72}\) (Bacillus)
Probiotic Effects on Human Gut Health

Probiotics support **overall gut health** by:

- Reducing inflammation\(^\text{10}\)
- Enhancing digestive health and nutrient absorption\(^\text{13, 47}\)
- Decreasing bloating, gas, and diarrhea\(^\text{16, 21}\)
- Aiding in appetite control and satiation\(^\text{46}\)

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Probiotics inhibit **pathogenic bacteria** by:

- Competitive adhesion\(^\text{23}\)
- Decreasing intestinal permeability\(^\text{23}\)
- Producing lactic acid (**Lactobacillus** spp, **Lactococcus** spp, **Bacillus** spp)\(^\text{24}\)
- Boosting immune system activity\(^\text{10}\)
II. Safety Standards & Regulatory Trends
## Safety aspects of potential probiotic candidates

<table>
<thead>
<tr>
<th>Safety Standards</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>World Health Organization (WHO)</td>
<td>Antibiotic resistance patterns</td>
</tr>
<tr>
<td></td>
<td>Metabolic activity assessment</td>
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<td></td>
<td>Side-effects assessment during human studies</td>
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<td>Toxicity tests</td>
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<td>Hemolytic activity assessment</td>
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<td>Surveillance of adverse effects (post-market)</td>
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<td></td>
<td>Optional: testing on immunocompromised animals</td>
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<tr>
<td>European Food Safety Authority (EFSA)</td>
<td>Toxicity tests including genotoxicity, sub-chronic, chronic, carcinogenicity,</td>
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<tr>
<td></td>
<td>reproductive and developmental toxicity</td>
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<tr>
<td>Norwegian Scientific Committee for Food Safety</td>
<td>Antibiotic resistance profile</td>
</tr>
<tr>
<td></td>
<td>Certain metabolic activities</td>
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<tr>
<td></td>
<td>Side-effects assessment on systemic infections, deleterious, excessive immune</td>
</tr>
<tr>
<td></td>
<td>stimulation in susceptible individuals, gene transfer to other bacteria</td>
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<tr>
<td></td>
<td>Pathogenic activity in clinical trials</td>
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<tr>
<td></td>
<td>Proper identification, isolation, and maintenance of probiotic strain (i.e. PCR,</td>
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<td></td>
<td>RNA sequencing)</td>
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<td></td>
<td>Antagonistic or synergistic interactions with other foodstuffs, as well as</td>
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<td></td>
<td>therapeutic agents</td>
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</tbody>
</table>
# Regulatory trends for potential probiotic candidates

<table>
<thead>
<tr>
<th>Regulatory Standards</th>
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</table>
| World Health Organization (WHO) (Reference 90) | - Strain identification  
- Animal, *in vitro* tests OR human clinical trials  
- 1 clinical trial plus 2nd clinical trial OR effectiveness trial OR probiotic food with proper labelling |
| European Food Safety Authority (EFSA) (Reference 92) | - Identification at genus, species, strain levels  
- Product composition and stability  
- Toxicology and allergenicity  
- Production process  
- History of use and source  
- Target population and anticipated intake  
- Estimated exposure to undesirable substances  
- Precautions and restrictions of use  
- Nutritional information |

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</table>
| Health Canada (Reference 95) | - Must be subjected for approval if strain specific  
- Unless the product contains at least $10^9$ CFU of eligible microorganisms from the *Bifidobacterium* or *Lactobacillus* genus |
| Japan Ministry of Health, Labour and Welfare (Reference 100) | - Scientific evidence required to show effectiveness in the human body  
- Use of nutritionally appropriate ingredients  
- Compatibility with product specifications by the time of consumption  
- Established quality control methods, such as specifications of products and ingredients, processes, and methods of analysis |
**Other desirable attributes of probiotic candidates**

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerance to gut conditions</td>
<td>Gastric juice (pH 1 -2)</td>
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<tr>
<td></td>
<td>Bile salts (pH 8 - 9)</td>
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<tr>
<td></td>
<td>Osmotic stress (salts, chemicals)</td>
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<td></td>
<td>Oxidative ($O_2$, $CO_2$, $H_2S$)</td>
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<tr>
<td>Compete &amp; protect itself against other microbes</td>
<td>Producing antimicrobial substances (e.g. acids, short-chain fatty acids, bacteriocins, etc)</td>
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<td></td>
<td>Fast growth rate and establishment within the gut</td>
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</table>

<table>
<thead>
<tr>
<th>Attributes</th>
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</tr>
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<tbody>
<tr>
<td>Tolerance to processing conditions</td>
<td>Fermentation (e.g. bench top, pilot and scale up production)</td>
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<td>Heat (e.g. sterilizing, mixing, blending, discharging)</td>
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<tr>
<td></td>
<td>Drying (e.g. extraction, spray or freeze-drying)</td>
</tr>
<tr>
<td></td>
<td>Pressure (e.g. spray drying, tableting)</td>
</tr>
<tr>
<td></td>
<td>Chemicals (e.g. sanitizers, processing aids, ingredients)</td>
</tr>
<tr>
<td>Tolerance to storage &amp; transportation conditions</td>
<td>Storage &amp; shipping (e.g. exposure to various temperatures)</td>
</tr>
</tbody>
</table>
Summary of regulatory trends - APAC

• Most APAC countries classify probiotics as health functional foods or dietary supplements (Japan\textsuperscript{104}, Korea\textsuperscript{93}, Taiwan\textsuperscript{105}, Singapore\textsuperscript{103}, Malaysia\textsuperscript{96}, Philippines)
  
  — Exception: Australia New Zealand\textsuperscript{102} (complementary medicine)

• Claims require scientific substantiation from human intervention or observational studies\textsuperscript{90}

• Strains from either the \textit{Lactobacillus} or \textit{Bifidobacterium} genus are generally approved for safety and intestinal health claims (Japan\textsuperscript{104}, Korea\textsuperscript{93}, Malaysia\textsuperscript{96}, Philippines)

• Claims must be strain specific and not overly general or leave room for misinterpretation\textsuperscript{90}
## List of allowable probiotic strains

### Malaysia

**Bifidobacterium sp.** – B. bifidum Bb-02, B. breve strain Yakult, B. breve M-16V, B. animalis subsp. lactis (BB-12), B. lactis HNO19, B. lactis BI-04, B. lactis Bi-07, B. lactis 420, B. lactis CNCM I-3446, **Lactobacillus sp.** – L. acidophilus LA-5, L. acidophilus NCFM, L. acidophilus La-14, L. acidophilus Rosell-52, L. casei Shirota, L. johnsonii La 1/Lj 1, L. johnsonii CNCM I-1225, L. paracasei subsp. paracasei (L. CASEI 01), L. paracasei subsp. paracasei (L. CASEI 431), L. paracasei Lpc-37, L. paracasei CNCM I-2116, L. plantarum Lp-115, L. rhamnosus (LGG), L. rhamnosus Lr-32, L. rhamnosus HNO01, L. rhamnosus Rosell-11, L. rhamnosus CGMCC 1.3724, L. salivarius Ls-33, L. reuteri DSM 17938*

### Taiwan

**Bacillus coagulans**, **Bifidobacterium bifidum**, B. breve, B. infantis, B. lactis, B. animalis subsp. lactis, B. longum, B. adolescentis, **Enterococcus faecalis**, E. faecium, **Lactobacillus acidophilus**, L. bifidus, L. brevis, L. bulgaricus, L. casei, L. casei subsp. rhamnosus, L. cremoris, L. delbrueckii, L. delbrueckii subsp. bulgaricus, L. fermentum, L. gasseri, L. helveticus, L. kefir, L. lactis, L. lactis subsp. lactis, L. paracasei, L. plantarum, L. reuteri, L. rhamnosus, L. salivarius, L. sporogenes, L. pentosus, L. johnsonii, L. paraplantarum, **Sporolactobacillus inulinus**, **Streptococcus lactis**, Streptococcus salivarius subsp. thermophilus, S. thermophilus, S. faecalis, **Lactococcus lactis** subsp. cremoris, Lactococcus lactis subsp. lactis, Lactococcus lactis subsp. lactis biovar diacetylactis, **Leuconostoc mesenteroides** subsp. cremoris

### Thailand

**Bacillus** coagulans, **Bifidobacterium** adolescentis, B. animalis, B. bifidum, B. breve, B. infantis, B. lactis, B. longum, B. pseudolongum, **Enterococcus** durans, Enterococcus faecium, **Lactobacillus** acidophilus, L. crispatus, L. gasseri, L. johnsonii, L. paracasei, L. reuteri, L. rhamnosus, L. salivarius, L. zeae, **Propionibacterium arabinosum**, **Staphylococcus** sciuri, **Saccharomyces cerevisiae** subsp. boulardii

### Singapore

Species that are acceptable for health products Probiotics (In non-milk based products) including **Bacillus**, **Lactobacillus**, **Streptococcus thermophilus**, **Bifidobacteria**

### Indonesia

**Bifidobacterium** breve, B. lactis, B. logum, B. lagum NCC 3001, **Lactobacillus** acidophilus, L. bulgaricus, L. casei, L. helveticus, L. paracasei, L. reuteri, L. rhamnosus NCC 4007, **Lactococcus** lactis, **Streptococcus** cremoris, S. lactis, S. thermophilus

### S. Korea

**Lactobacillus** acidophilus, L. casei, L. gasseri, L. delbrueckii ssp. bulgaricus, L. helveticus, L. fermentum, L. paracasei, L. plantarum, L. reuteri, L. rhamnosus, L. salivarius, **Lactococcus** lactis, **Enterococcus faecium**, E. faecalis, **Streptococcus** thermophilus, **Bifidobacteria** bifidum, B. breve, B. longum, B. animalis spp. lactis
III. Advances in Genomics
- Friedrich Miescher discovered DNA
- Walter Sutton & Theodor Boveri proposed the "Chromosome Theory"
- Albrecht Kossel discovered 5 nucleotides
- Marshall Nirenberg & Har Gobind Khorana discovered codon – triplets of DNA bases
- James Gusella identified gene for Huntington’s disease
- Kary Mullis developed PCR
- Human Genome Project was launched with aimed to sequence the entire human genome in 15 years
- Full sequence of mouse completed
- Scientists used a technique for testing embryos in-situ for genetic diseases
- First bacterium genome sequencing was completed for Haemophilus influenza
- International team completed sequencing of Saccharomyces cerevisiae
- First cloned sheep was borne
- John Sulston sequenced genome of nematode worm
- First human chromosome 22 sequenced
- Scientists used a technique for testing embryos in-situ for genetic diseases
- First draft of human genome sequence released
- New sequencing technology 70-folds DNA sequencing output/year
- Genome sequencing of large number of people
- Completed full genome sequence of fruit fly
- First draft of human genome sequence released
- Full sequence of mouse completed
- International HapMap project launched
- Completed full sequence of Plasmodium falciparum
- Human Genome Project Completed
- The ENCODE Project is launched
- Draft of rat genome was published
- Chimpanzee genome is completed
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- The ENCOD...
Advances in Genomic Tools

Development of highly affordable, reliable, efficient and rapid genomic tools:

- High throughput DNA sequencing techniques and equipment
- Polymerase Chain Reaction
- DNA Cloning systems - in vivo
- High throughput hybridization techniques – in situ
- Multilocus sequence typing
- Representational Difference Analysis (combination of several molecular techniques)
- High throughput micro-array technology (analyzing mRNA, proteins, metabolites and interactions of these cellular constituents)
- Bioinformatics (analyze patterns of biological data, determining mechanisms for the patterns)
Genetic-Mapping of Microflora in Humans

Culture, genetics, environmental factors, age, and gender cause variation in intestinal microflora composition.

From a study of gut microbial genes in Americans, Chinese, and Europeans:

<table>
<thead>
<tr>
<th>Genes particular to Asians included</th>
<th>Genes particular to Asians and Europeans included</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ahpC: may contribute to higher rates of gastritis caused by <em>Helicobacter pylori</em></td>
<td>• EAM_2103: derived from a bacteria (<em>Erwinia</em>)</td>
</tr>
<tr>
<td>• Ffh: (<em>Bacteroides</em> spp.) evidence of a high protein diet</td>
<td>• Gura_R0049: unique iron metabolic mechanism in <em>Bacteroides</em>; related to areas with historic heavy-metal mining practices</td>
</tr>
<tr>
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<td>• HemE (<em>Chlorobium</em>), Ndas_1062 (<em>Nocardiopsis</em>), SORBIDRAFT_01g014353 (<em>Salmonella</em>): regional genes particular to Europe and Asia</td>
</tr>
</tbody>
</table>

Chen et al., 2016
IV. Advocacy Strategies
Herbalife’s Advocacy Strategies

- Science is moving fast, while regulations are rather static or not up-to-date with science

- There is a need to work with industry alliances, academia, and NGOs to reach out to policy makers and/or regulators through:
  - Education
  - Outreach
  - Engagement
Herbalife’s Advocacy Strategies (con’t)

- **Company’s Product Policy**
- **Relationships with Ingredient / Product Companies**
- **Customer Advocates & Creating Demands & Training**

**Promote & Protect Way to Market Through Education**

**Build and Maintain Corporate Reputation Through Outreach**

**Reputation – Alliance building (e.g. ILSI)**

**Reputation – Thought Leadership (e.g. Science)**

**Reputation - Advocacy**

**Scientific Non-Government Organizations (Nutrition Assc)**

**Trade Associations (i.e. IADSA, IPA)**

**Company-Level Functional Departments**

**Advocacy Directed To Regulation and Policy Makers by Beneficiary Stakeholders**

Relative Importance of Internal players increases
Advocacy-Strategy Funnel

Agenda Setting
- Enhancing product portfolio
  - Product concepts & positioning
  - Working with ingredient vendors
  - Safety / efficacy documentations
- Work toward customers’ expectations

Education
- Equipping via internal training
  - Narrative & media
  - Creating demands for customers

Outreach
- Building foundations & reputation
  - CSR (RBF)
  - Science (ILSI, academia)

Engagement
- Build bridges with policy makers & regulators
  - Trade Gps
  - NGOs
  - Functional Dept

Outcomes
- Reasonable regulations


References


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96. Malaysia FOOD REGULATIONS 1985

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102. Australia New Zealand Therapeutic Goods Administration

103. Singapore A Guide to Food Labelling and Advertisements
   https://www.ava.gov.sg/docs/default-source/tools-and-resources/resources-for-businesses/auditfoodlabellingandadvertisementversionjuly2

104. Japan Specifications and Standards for Foods, Food Additives, etc. Under the Food Sanitation Act

105. Health food control act

Notification of the Ministry of Public Health, Thailand Food and Drug Administration (2011). Use of Probiotic Microorganisms in Foods
   http://food.fda.moph.go.th/law/data/announ_moph/V.English/No.%20339%20Use%20of%20Probiotic%20Microorganisms%20in%20Foods.pdf

Taiwan Food and Drug Administration. List of Food Raw Material Commodious.

General Classification of Health and Food Products. Classification Tree for Products in the Food-Health Product Interface
Thank you for listening!