Objectives

- Describe the different categories of how probiotics may be regulated in Canada
  - Natural Health Products (NHP)
  - Food
  - Drug
- Show the different types of claims associated with each category
- Identify the safety, efficacy, quality requirements for NHPs and food
- Provide you with useful resources for further study
Natural Health Products (NHP)
Canadian Regulations

  - January 1, 2004
NHP Definition

- A substance or combination of substances set out on Schedule 1, a **homeopathic medicine** or a **traditional medicine**, that is 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.

- **Excludes substances on Schedule 2**
Schedule 1 - Inclusions

Included Substances

1. Plant, alga, bacterium, fungus, or a non-human animal material
2. Extract or isolate of items listed in 1
3. Vitamins
4. Amino acids
5. Essential fatty acids
6. Synthetic duplicates of the items listed in 2 to 5
7. Minerals
8. Probiotics
Schedule 2 - Exclusions

- Schedule C (Radio-pharmaceuticals), D (Biologics) of the *Food & Drugs Act*
- Substances under the *Tobacco Act*
- Schedules I-V of *Controlled Drugs & Substance Act*
- Substances administered by puncturing the skin
- Antibiotics
NHP definition summary

- Substance (e.g. probiotic) plus a health claim appropriate for self-selection/self-care i.e. does not require involvement of a health care practitioner
- NHPs are available over-the-counter (OTC) in Canada
How To Sell a NHP on the Canadian Market

- Submit a complete Product Licence Application “PLA”
- Pre-market review of Safety, Efficacy and Quality
- Obtain 8 digit “NPN” via Product Licence (PL)
- Develop compliant label (bilingual)

- Post licensing communications to agency
- Pharmacovigilance (Section 24 NHPR)

- Perform real-time stability
- Manufacturing, packaging, labelling or importation sites must comply with NHP GMP (Part 3 NHPR) and obtain a Site Licence.
  - Foreign sites must demonstrate compliance with NHP GMPs and are listed on importer Site Licence
NHP General Submission Requirements

- Product License Application Form (ePLA)
- Evidence of Safety and Efficacy (e.g. a monograph, human clinical data)
- Evidence of Quality (i.e., Finished Product Specification Form as per Quality Guidance)
- No agency fee at this time
Probiotic Monograph (2015)

- **Example of Pre-Cleared Information (PCI)**
  - Qualifies for a 10 day review period

- **Available Claims**
  - For listed probiotics:
    - Source of probiotics
    - Helps support intestinal/gastrointestinal health
    - Could promote a favorable gut flora
  - **Strain-specific claims:**
    - An adjunct to physician-supervised antibiotic therapy in patients with *Helicobacter pylori* infections (*Lactobacillus johnsonii* (LA1/Lj1/NCC 533))
    - Helps to manage acute infectious diarrhea (*Lactobacillus rhamnosus GG*)
    - Helps to manage and/or reduce the risk of antibiotic-associated diarrhea (*Lactobacillus rhamnosus GG*)
    - Helps to reduce the risk of antibiotic-associated diarrhea (*Saccharomyces boulardii/Saccharomyces cerevisiae*)
Probiotic Monograph (2015) cont’d

- **Dose:**
  - General: minimum $10^7$ CFU/day (total from all strains in product)
  - Specific claims: as per monograph

- **Populations:** >1 years

- **Cautions and Warnings:**
  - *If you have fever, vomiting, bloody diarrhea or severe abdominal pain, consult a health care practitioner prior to use.*
  - *If symptoms of digestive upset (e.g. diarrhea) occur, worsen, or persist beyond 3 days, discontinue use and consult a health care practitioner.*

- **Contraindications:**
  - *If you have an immune-compromised condition (e.g. AIDS, lymphoma, patients undergoing long-term corticosteroid treatment), do not use this product.*
  - *If you are taking [an antibiotic with unexplained atypical resistance], do not use this product (as applicable).*
Non-medicinal Ingredients (NMIs):
- Must be listed in the Natural Health Products Ingredient Database (NHPID) [http://webprod.hc-sc.gc.ca/nhpid-bdipsn/search-rechercheReq.do](http://webprod.hc-sc.gc.ca/nhpid-bdipsn/search-rechercheReq.do)
- Cryoprotectants should be listed as NMIs

Storage:
- All liquids: Store in refrigerator in a tightly closed, light-resistant container.

Specifications: not submitted as part of a monograph submission but information is to be available upon request

Dosage forms by age group
- Children 1-2 years: limited to emulsion/suspension and solution/drops
- Children 3-5 years: limited to chewables, emulsion/ suspension, powders and solution/drops
- Children 6-12 years, Adolescents 13-17 years, and Adults ≥ 18 years: The acceptable pharmaceutical dosage forms include, but are not limited to capsules, chewables (e.g. gummies, tablets), liquids, powders, strips or tablets.
Specifications for each live microorganism

- The species **Latin binominal identification** must be up to date and validated.

- **Survivability** of the microorganisms in the human gut must be demonstrated. In-vitro gastric acid and bile resistance testing is considered acceptable.

- The microorganism must be identified by **phenotype and genotype**:
  - Phenotyping must be assessed based on characteristics routinely used to distinguish the species from others. This includes a series of testing for sufficient confirmation of observable traits of the species.
  - Genotyping must be assessed as follows:
    - Species identification by comparison of genome sequence homology in percentage, to both "identical" and "closely related" type strains - obtained from an internationally recognized culture collection; AND
    - Strain characterization through an up to date complete/whole genome sequencing method.
Probiotic Monograph (2015) cont’d

- Specifications for each live microorganism cont’d
  - Absence of virulence of each live microorganism must be established through the following:
    - Comparison of antibiotic/antifungal resistance profile to typical species resistance - as published by an internationally recognized panel; AND
    - Explanation of the genetic basis of each atypical antibiotic/antifungal resistance to the species OR demonstration of the absence of all known genetic mechanisms of resistance; AND
    - Demonstration of lack of horizontal antibiotic/antifungal resistance transfer ability; AND
    - Demonstration of susceptibility to therapeutic concentrations of at least two commercially available antimicrobial/antifungal agents; AND
    - Demonstration of the absence of genetic elements responsible for the production of virulence factors characteristic to the genus; AND
    - Demonstration of lack of toxigenic activity (i.e. production of toxins) known to the genus.
Probiotic Monograph (2015) cont’d

- General Specifications
  - Must meet all quality requirements as detailed in NNHPD's Quality of Natural Health Products Guide.
    - Stability/viability measures put into place must ensure that a minimum of 80% of the quantity declared on the product label is present at the end of shelf life
  - Refer to Appendix 4 of the Quality of Natural Health Products Guide
  - Finished Product Specification Form (FPS Form) is not submitted with a monograph submission.
Non-‘Monograph’ Submissions

- Also called ‘non-traditional PLA’, 210 day review
- Evidence for safety and efficacy is required
  - Strain specific evidence is required
  - Totality of evidence must support all conditions of use of the product (dose, subpopulation etc)
  - *Pathway for Licensing Natural Health Products Making Modern Health Claims*
  - — Evidence requirements are proportional to the level of risk of the NHP:

- Examples of approved NHP probiotic claims as per Licensed Natural Health Products Database (LNHPD)
  - “Improves abdominal symptoms and pain in irritable bowel syndrome”
  - “Helps to reduce the risk of Clostridium Difficile associated diarrhea (CDAD) in hospitalized patients”
Non-’Monograph’ Submissions cont’d

- Submit a **Finished Product Specification Form** (FPS Form) as part of the submission
  - Same specification requirements as listed in the Probiotic Monograph (available upon request)
  - FPS Form outlines specification, tolerances and test methods used for identification, quantification, purity testing of finished product, as well as other applicable test
    - See Appendix 4 of the Quality of Natural Health Products Guide (2015)
  - Stability data is not submitted but *may* be requested during review
Schedule A Claims

- Prohibition from ‘treatment’ ‘prevention’ and ‘cure’ claims of diseases listed on Schedule A (of the Food and Drugs Act)
- NHPs (and OTC drugs) are exempt from the prohibition of advertising of ‘prevention’ claims for Schedule A to the general public
- The exact wording of the claim must be approved by Health Canada

Dosage form: NHP/food interface

- NHPs generally do not include food-like dosage forms such as bars, beverages, chewing gums and yogurts.

- Guidance: *Classification of Products at the Food – Natural Health Product Interface: Products in Food Formats* (2010)
  - Product composition
  - Product Representations
  - Product Format
  - Public perception and history of use
Guidance for Industry

- **Probiotic Monograph (2015)**
  

- **Pathway for Licensing Natural Health Products Making Modern Health Claims**
  

- **Quality of Natural Health Products Guide (2015)**
  

- **Licensed Natural Health Products Database (LNHPD)**
  

- **Natural Health Products Ingredient Database (NHPID)**
  

- **Classification of Products at the Food – Natural Health Product Interface: Products in Food Formats (2010)**
  
Background

- Probiotics - Discussion Paper (2005)
  
Probiotics in Foods
Canadian Regulations

- Food and Drugs Act (FDA) (http://laws-lois.justice.gc.ca/eng/acts/F-27/)

- Section 2 FDA, Definition of ‘food’
  - Includes 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

- Consumed *ad libitum*

- A product is in food format if it is sold in a format and serving size consistent with food use.
  - chewing gums, hard candies, candy bars, tea, juices and beverages.
    - Capsules, pills and tablets are considered non-food formats.
Definition of Probiotics in Foods

- According to the Expert Consultation (2001) conducted by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), probiotics are:

  “Live microorganisms which when administered in adequate amounts confer a health benefit on the host.”

- In the case of foods, the FAO/WHO Expert Consultation limited the scope of the definition to:

  “Live microorganisms which when consumed in adequate amounts as part of food confer a health benefit on the host.”
Probiotic Health Claims

- A probiotic health claim can consist of one of the following examples:
  - the term "probiotics" and similar terms or representations;
  - "with beneficial probiotic cultures";
  - "contains bacteria that are essential to a healthy system"; and
  - 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.
Conditions for Any ‘Probiotic’ Claim

- The use of "probiotic" and other similar terms and representations (including trade names that suggest a health benefit) should be accompanied by specific, validated statements about the benefits or effects of the probiotic.

- Validated health claims are statements that are supported by strain-specific evidence.

- When making any probiotic claim, the manufacturer or importer of the product should have documentation supporting:
  - identification, safety, viability, concentration and stability of the probiotic strain added to the food product.

- The manufacturer or importer should follow all requirements applicable to the sale of food, including novel food regulations.

- The food should contain, at a minimum, the amount of the probiotic microorganism(s) required to result in the claimed effect or health benefit throughout the shelf life of the product.
  - Documentation to support the functionality aspects of the product (i.e. stability and viability of the probiotic strain or mixed culture) should be maintained.
Probiotic Functional Claims

- Most probiotic claims are ‘functional claims’
- Functional claims refer to the specific beneficial effects that the consumption of a food or food constituent has on normal functions or biological activities of the body. Such claims relate to a positive contribution to health or performance.
  - For example, "[Naming the food or food constituent] promotes regularity or laxation".

- 2 Types
  - Non-strain-specific claims
  - Strain-specific claims
Non-strain-specific functional claims

- Eligible claims
  - Probiotic that naturally forms part of the gut flora
  - Provides live microorganisms that naturally form part of the gut flora
  - Probiotic that contributes to healthy gut flora
  - Provides live microorganisms that contribute to healthy gut flora

- Eligible species: one or more organisms on next slide
  - Probiotic microorganisms generally have been isolated from the gastrointestinal tract of healthy individuals

- Minimum levels in the product
  - A serving of stated size of a product should contain a minimum level of $1.0 \times 10^9$ cfu of one or more of the eligible microorganism(s) that is (are) the subject of the claim

- Documentation available regarding
  - Identification e.g., ATCC
  - Safety
  - Viability
  - Concentration
  - Stability
### Acceptable Strains for Non-Strain Specific Claims

<table>
<thead>
<tr>
<th>Bifidobacterium adolescentis</th>
<th>Bifidobacterium animalis subsp. animalis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bifidobacterium animalis subsp. Lactis</em></td>
<td><em>Bifidobacterium bifidum</em></td>
</tr>
<tr>
<td><em>Bifidobacterium breve</em></td>
<td><em>Bifidobacterium longum subsp. infantis</em></td>
</tr>
<tr>
<td><em>Lactobacillus acidophilus</em></td>
<td><em>Bifidobacterium longum subsp. Longum</em></td>
</tr>
<tr>
<td><em>Lactobacillus casei</em></td>
<td><em>Lactobacillus fermentum</em></td>
</tr>
<tr>
<td><em>Lactobacillus gasseri</em></td>
<td><em>Lactobacillus johnsonii</em></td>
</tr>
<tr>
<td><em>Lactobacillus paracasei</em></td>
<td><em>Lactobacillus plantarum</em></td>
</tr>
<tr>
<td><em>Lactobacillus rhamnosus</em></td>
<td><em>Lactobacillus salivarius</em></td>
</tr>
</tbody>
</table>
Strain-specific functional claims

- Strain-specific claims are claims about the health benefits or effects of specific strains of probiotics.
- At the present time, no strain-specific claims have been accepted by Health Canada.
- As these claims are reviewed and accepted, Health Canada will create a list of acceptable strain-specific claims.
Therapeutic claims on Foods containing Probiotics

- Claims that are therapeutic in nature are required to undergo a pre-market assessment by the Food Directorate of Health Canada and a regulatory amendment to the *Food and Drug Regulations* to allow their use.

- For Health Canada to consider such a proposed regulatory amendment, scientific evidence acceptable to Health Canada that supports the claimed effect must be submitted.

- Currently there are no approved therapeutic claims related to probiotics in the *Food and Drug Regulations*

- *However, A product in food format is generally classified as an NHP when a probiotic microorganism in the product is represented as having a therapeutic use.*
  - Refer to the Guidance Document “Classification of Products at the Food-Natural Health Product Interface: Products in Food Format”
Novel food (Division 28, FDR)

- ‘Novel food’ means (a) a substance, including a microorganism, that does not have a history of safe 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 microorganism that has been genetically modified such that (i) the plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism, (ii) the plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism, or (iii) one or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for that plant, animal or microorganism.

- Pre-market safety assessment is required
Guidance for Industry

- Guidance Document – The Use of Probiotic Microorganisms in Food

- Chapter 8 (Health Claims: Probiotic Claims) of the CFIA Guide to Food Labelling and Advertising (Guide)
  [Link](http://inspection.gc.ca/food/labelling/food-labelling-for-industry/health-claims/eng/1392834838383/1392834887794?chap=9)

- Guidance Document for Preparing a Submission for Food Health Claims
Probiotics as Drugs
When does a probiotic become a drug?

- In short, when it has been determined that the indication and conditions of use are not suitable for ‘self-care’ or ‘self-selection’
- In these cases, it becomes a *prescription drug*: NHP ingredient with a Rx indication
- Drug submission process i.e. New Drug Submission (NDS) submitted in eCTD
  - Principle 1: Supervision by a practitioner is necessary
  - Principle 2: The level of uncertainty respecting the drug, its use or its effects justifies supervision by a practitioner.
  - Principle 3: Use of the drug can cause harm to human or animal health or a risk to public health and the harm or the risk can be mitigated by a practitioner's supervision.
Recommendations
Recommendations

- Probiotic Monograph (2015)
- Pathway for Licensing Natural Health Products Making Modern Health Claims
  - Safety/efficacy
- Quality of Natural Health Products Guide
  - Appendix 4: Finished Product Specifications for Products containing live microorganisms
- Reference List for Probiotic Claims [in foods]
  - [http://inspection.gc.ca/food/labelling/food-labelling-for-industry/health-claims/eng/1392834838383/1392834887794?chap=15#s33c15](http://inspection.gc.ca/food/labelling/food-labelling-for-industry/health-claims/eng/1392834838383/1392834887794?chap=15#s33c15)
Thank you

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