PROBIOTICS

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Background:

- This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) for natural health product (NHP) market authorization of probiotics. It is not intended to be a comprehensive review of all probiotic organisms and possible health claims associated with them.
- For the purpose of this monograph, probiotics are defined as “live microorganisms which when administered in adequate amounts confer a health benefit to the host” (Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) 2006). One means through which probiotics might confer a health benefit in humans is through benefiting the microbiota indigenous to humans as described in the Natural Health Products Regulations (NHPR) (Justice Canada 2008a).
- PLAs for probiotic products that contain one or more of the bacterial or yeast species listed in the Proper and common name(s) section and meet the recommended conditions of use (e.g. use or purpose, route of administration, dose, etc.) set out in this monograph, can be submitted for NHP market authorization through the Natural Health Products Directorate’s (NHPD) compendial application stream. PLAs for products that contain bacterial or yeast species not contained in the Proper and common name(s) section and/or do not meet the recommended conditions of use set out in this monograph can be submitted for NHP market authorization outside of the NHPD’s compendial stream (when accompanied by adequate supporting evidence as per Section 5 of the NHPR) (Justice Canada 2008a). Detailed information on safety and efficacy requirements for non-compendial probiotic PLAs can be found in the NHPD’s Evidence for Safety and Efficacy of Finished Natural Health Products guidance document (Health Canada 2006).
- This monograph is not intended to include NHPs in food formats such as beverages, cheeses or yogurts. PLAs for NHPs in food formats can be submitted for market authorization outside of the NHPD’s compendial application stream (when accompanied by adequate supporting evidence as per Section 5 of the NHPR) (Justice Canada 2008a).
- Guidance regarding the use of probiotic health claims for foods (e.g. yogurt) will be provided in an upcoming amendment to the Canadian Food Inspection Agency’s “Guide to Food Labelling and Advertising”
- This monograph does not cover probiotics containing bacteria or fungi created by recombinant DNA procedures as these are classified as biologics and are subject to the Food and Drug Regulations (Justice Canada 2008b), in accordance with Schedule 2 to the NHPR (Justice Canada 2008a) and Schedule D to the Food and Drugs Act (Justice Canada 2008c).
Proper and common name(s):¹, ²

- *Bifidobacterium adolescentis* Reuter
- *Bifidobacterium animalis* subsp. *animalis* (Mitsuoka) Scardovi and Trovatelli
- *Bifidobacterium animalis* subsp. *lactis* synonym: *B. lactis* Mele et al.
- *Bifidobacterium bifidum* (Tissier) Orla-Jensen
- *Bifidobacterium breve* Reuter
- *Bifidobacterium infantis* Reuter
- *Bifidobacterium longum* Reuter
- *Lactobacillus acidophilus* (Moro) Hansen and Mocquot
- *Lactobacillus amylovorus* Nakamura³
- *Lactobacillus casei* (Orla-Jensen) Hansen and Lessel
- *Lactobacillus fermentum* Beijerinck
- *Lactobacillus gasseri* Lauer and Kandler
- *Lactobacillus johnsonii* Fujisawa et al.
- *Lactobacillus paracasei* Collins et al.
- *Lactobacillus plantarum* (Orla-Jensen) Bergey et al.
- *Lactobacillus reuteri* Kandler et al.³
- *Lactobacillus rhamnosus* (Hansen) Collins et al.
- *Lactobacillus salivarius* Rogosa
- *Saccharomyces boulardii* Seguela, Bastide & Massot³

Source material(s):

Identity:

The NHPD defines probiotic source material as the strain identifier of the bacterial or yeast species (Health Canada 2006). Product licence applicants must identify the strain of each bacterial or yeast species in their product in both the PLA and on the product label.

As strain identity is necessary for post-market surveillance, product licence applicants must determine the strain of each bacterial or yeast species in their product unambiguously (e.g. by a combination of genotypic and phenotypic methods):

- Examples of genotypic methods include, but are not limited to, the following: Pulsed Field Gel Electrophoresis of the DNA sequence encoding 16S rRNA for *Lactobacillus* spp. or the DNA sequence encoding Heat Shock Protein HSP 60 for *Bifidobacterium* spp., polymerase chain reaction-based analyses, DNA-DNA hybridization (Holzapfel et al. 2001; Tannock 1999; Klein et al. 1998);

¹ The following references were reviewed for proper nomenclature: American Type Culture Collection (ATCC) 2008, Euzéby 2008, Skerman et al. 1989

² The following references were used to select the species included in this monograph: Reid 2001, Gilliland 2001

³ Not derived from human intestinal microflora
• Examples of phenotypic methods include, but are not limited to, the following: patterns generated from the fermentation of a range of sugars, final fermentation products obtained from glucose utilization (Holzapfel et al. 2001; Tannock 1999; Klein et al. 1998);
• All strains should be deposited in an internationally recognized culture collection (e.g. American Type Culture Collection) (FAO and WHO 2006; Salminen et al. 1998).

Probiotic activity:

Product licence applicants attesting to this monograph are not to submit the following data with their PLA forms. It is to be submitted to the NHPD upon request only (either directly or by authorized citation of an approved Master File).

Since some strains of bacterial or yeast species listed in this monograph do not have probiotic activity (either at all or under certain conditions of use), applicants attesting to this monograph must have data available to support the following criteria for the strain or strains that are identified as medicinal ingredients in their product (FAO and WHO 2006):
• In vitro data demonstrating the strain’s resistance to gastric acid;
• In vitro data demonstrating the strain’s resistance to bile acid;
• In vitro data demonstrating the strain’s ability to hydrolyze bile salts;
• In vitro data demonstrating the strain’s adherence to mucus and/or human epithelial cells;
• In vitro data determining the strain’s antibiotic resistance pattern;
• In vitro data determining the strain’s D-lactate production;
• Evidence from tests or scientific literature that the strain is not a significant risk with regard to transferable antibiotic resistance or other opportunistic virulence properties; and
• Evidence to support that the strain is safe for use in humans and can provide one or more of the health benefits in healthy or non-healthy humans listed in the Use or Purpose section (Note: evidence in non-healthy humans is acceptable only when the product indicates a specific use or purpose for a non-healthy population, e.g. patients with diarrhoea).
Alternatively, the applicant may have evidence available demonstrating that the strain is identical to a strain that meets all of the above criteria.

Route(s) of administration:

Oral

Dosage form(s):

Those pharmaceutical dosage forms suited to oral administration, including but not limited to chewable tablets, caplets, capsules, strips, lozenges, powders or liquids where the dose is measured in drops, teaspoons, or tablespoons are acceptable. This monograph is not intended to include foods or food-like dosage forms such as beverages, bars or chewing gums.

Use(s) or Purpose(s):
General:

The following general use or purpose statements can be used in reference to any single bacterial or yeast species or combination of bacterial and yeast species listed in the **Proper and common name(s)** section, provided that the information requirements on activity and identity listed under the **Source material(s)** section above have been satisfied. However, in order to state one of the first four use or purpose statements listed below, products must contain at least one bacterial species derived from the human intestinal microflora. See footnote 3 listed in the **Proper and common name(s)** section for species not derived from human intestinal microflora.

Statement(s) to the effect of:

- Probiotic that forms part of a natural healthy gut flora (Tappenden and Deutsch 2007; Reid et al. 2003; Isolauri 2001; Lu and Walker 2001; Saavedra 2001)
- Provides live microorganisms that form part of a natural healthy gut flora (Tappenden and Deutsch 2007; Reid et al. 2003; Isolauri 2001; Lu and Walker 2001; Saavedra 2001).
- Probiotic that contributes to a natural healthy gut flora (Tappenden and Deutsch 2007; Reid et al. 2003; Isolauri 2001; Lu and Walker 2001; Saavedra 2001).
- Provides live microorganisms that contribute to a natural healthy gut flora (Tappenden and Deutsch 2007; Reid et al. 2003; Isolauri 2001; Lu and Walker 2001; Saavedra 2001).
- Probiotic to benefit health and/or to confer a health benefit (Gill and Prasad 2008; Othman et al. 2008; Lenoir-Wijnkoop et al. 2007; O’Hara and Shanahan 2007; FAO and WHO 2006; Picard et al. 2005; Reid et al. 2003; Isolauri 2001; Saavedra 2001).
- Provides live microorganisms to benefit health and/or to confer a health benefit (Gill and Prasad 2008; Othman et al. 2008; Lenoir-Wijnkoop et al. 2007; O’Hara and Shanahan 2007; FAO and WHO 2006; Picard et al. 2005; Reid et al. 2003; Isolauri 2001; Saavedra 2001).

Specific:

In order to use a specific use or purpose statement, products must meet the minimum monograph dose for the species and strains listed below. One or more specific use or purpose statements can be used, as applicable.

Statement(s) to the effect of:

For *Lactobacillus johnsonii* La1 (synonym: *L. johnsonii* Lj1 (Reid 1999; Sanders 1999)):
- An adjunct to physician-supervised antibiotic therapy in patients with *Helicobacter pylori* infections (Cruchet et al. 2003; Pantoflickova et al. 2003; Felley et al. 2001)

For *Lactobacillus rhamnosus* GG:
- Helps to manage acute infectious diarrhoea (Canani et al. 2007; Guandalini et al. 2000; Guarino et al. 1997).
- Helps to manage antibiotic-associated diarrhoea (Cremonini et al. 2002; Armuzzi et al. 2001; Vanderhoof 1999).
• Helps to reduce the risk of antibiotic-associated diarrhoea (Cremonini et al. 2002; Armuzzi et al. 2001; Vanderhoof 1999).

For *Saccharomyces boulardii*:
• Helps to reduce the risk of antibiotic-associated diarrhoea (Can et al. 2006; Kotowska et al. 2005; Cremonini et al. 2002; McFarland et al. 1995; Surawicz et al. 1989).

**Dose(s):**

**Subpopulation:**
• Adults, adolescents, and children ≥ 1 year old

**Quantity:**

For general use or purpose statements:
• $1.0 \times 10^7$ to $1.0 \times 10^{11}$ colony forming units (cfu) from one or more of the bacterial or yeast strains contained in this monograph, per day (Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelek 2006; Picard et al. 2005; Reid et al. 2003)

For patients with *H. pylori* infections:
• $1.25 \times 10^8$ to $3.6 \times 10^9$ cfu *L. johnsonii* Lj1, per day (Pantoflickova et al. 2003; Felley et al. 2001)

For management of acute infectious diarrhoea:
• $6.0 \times 10^9$ to $1.2 \times 10^{10}$ cfu *L. rhamnosus* GG, per day (Canani et al. 2007; Guarino et al. 1997)

For management of antibiotic-associated diarrhoea:
• $1.0 \times 10^{10}$ to $2.0 \times 10^{10}$ cfu *L. rhamnosus* GG, per day (Cremonini et al. 2002; Armuzzi et al. 2001; Vanderhoof 1999)

For risk reduction of antibiotic-associated diarrhoea:
• $1.0 \times 10^{10}$ to $2.0 \times 10^{10}$ cfu *L. rhamnosus* GG, per day (Cremonini et al. 2002; Armuzzi et al. 2001; Vanderhoof 1999)
• $1.0 \times 10^{10}$ to $3.0 \times 10^{10}$ cfu *S boulardii*, per day (Can et al. 2006; Kotowska et al. 2005; Cremonini et al. 2002; McFarland et al. 1995)

**Duration of use:**

No statement required.

**Risk information:**
Statement(s) to the effect of:

Caution(s) and warning(s):
- Discontinue use and consult a health care practitioner if symptoms of digestive upset (e.g. diarrhoea) occur, worsen, or persist beyond 3 days (WHO 2005; Berardi et al. 2002).

Contraindication(s):
- Do not use if you are experiencing nausea, fever, vomiting, bloody diarrhoea or severe abdominal pain (WHO 2005; Berardi et al. 2002; Canadian Pharmacists Association (CPA) 2002).
- Do not use if you have an immune-compromised condition (e.g. AIDS, lymphoma, patients undergoing long-term corticosteroid treatment) (Cukovic-Cavka et al. 2006; Ledoux et al. 2006; Riquelme et al. 2003; Lherm et al. 2002).

Known adverse reaction(s):
- No statement required.

Non-medicinal ingredients:
- Must be chosen from the current NHPD List of Acceptable Non-medicinal Ingredients and must meet the limitations outlined in the list.
- Fermentable carbohydrates (e.g. transgalactooligosaccharides, lactulose and inulin-type fructans such as inulin and oligofructose) are acceptable non-medicinal ingredients.
- Lactobacillus delbrueckii (Leichmann) Beijerinck subsp. bulgaricus (Orla-Jensen) Weiss et al. (synonym: Lactobacillus bulgaricus (Orla-Jensen) Rogosa and Jensen), Lactobacillus helveticus (Orla-Jensen) Bergey et al. and Streptococcus thermophilus Orla-Jensen (synonym: Streptococcus salivarius Andrewes and Horder subsp. thermophilus comb. nov.) (Callanan et al. 2007; Senok et al. 2005) are acceptable non-medicinal ingredients.

Specifications:
- Must comply with the minimum specifications outlined in the current NHPD Compendium of Monographs.
- In addition to the requirements in the Compendium of Monographs, finished products must adhere to the following additional quality requirements:
  i) The identity of species and strain must be confirmed by both genotypic and phenotypic characterization at the master cell bank and/or the raw material and/or the finished product stage; and
  ii) The quantity and dose frequency cited on the PLA and product label must reflect the total number of viable organisms, as measured by cfu, to which a consumer will be exposed within the shelf life period.
- Upon request only, product licence applicants will be required to submit the following information to the NHPD:
i) Information on purity including details of the fermentation process such as culture medium(s), pH, temperature, isolation technique etc.;

ii) Appropriate finished product specifications including identity, purity and quantity along with corresponding tolerances and physicochemical tests (pH, specific gravity, viscosity etc.) appropriate to the dosage form; and

iii) Information on the source and history of the microorganism, confirmation of identity of the species, strain, etc.

References cited:


References reviewed:


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Taylor AL, Dunstan JA, Prescott SL. 2007. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. Journal of Allergy and Clinical Immunology 119(1):184-191.


