PROBIOTICS

- This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredients.
- 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” (FAO/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) (JC 2008a).
- PLAs for products that contain bacterial or yeast species not listed in the Proper name(s), Common name(s), and Source material(s) section and/or do contain listed bacterial or yeast species that do not meet the recommended conditions of use set out in this monograph are to be submitted for Natural Health Products (NHP) market authorization outside of the Natural Health Products Directorate’s (NHPD) compendial stream (when accompanied by adequate supporting evidence as per Section 5 of the NHPR (JC 2008a)).
- Contact Health Canada’s Food Directorate for requirements for probiotic products which are to be marketed as foods (HC 2009a).
- 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 (JC 2008b), in accordance with Schedule 2 to the NHPR (JC 2008a) and Schedule D to the Food and Drugs Act (JC 2008c).

Notes:
- Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant’s discretion.
- The solidus (/) indicates that the terms are synonyms or that the statements are synonymous. Either term or statement may be selected by the applicant.

Date August 30, 2011

Proper name(s), Common name(s), and Source material(s)

Identity: The NHPD defines probiotic source material as the strain identifier of the bacterial or yeast species (HC 2006a,b). 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.

- Lactobacillus johnsonii La1 / Lactobacillus johnsonii Lj1 / Lactobacillus johnsonii NCC 533 (Euzéby 2011; Pridmore et al. 2004; Reid 1999; Sanders 1999)
- Lactobacillus rhamnosus GG (Euzéby 2011; Hawrelak et al. 2005; Gilliland 2001; Reid 2001, Skerman et al. 1989)
- *Saccharomyces boulardii* (McFarland 2010; NCBI 2009; Malgoire et al. 2005; McCullough et al. 1998)
  Refer to note in Appendix 1 for species information.

Note: Refer to Appendix 1 for full nomenclature for these medicinal ingredients.

**Route(s) of administration**

Oral

**Dosage form(s)**

- This monograph is not intended to include foods or food-like dosage forms such as yogurts, bars, chewing gums or beverages.

- Dosage form by age group:
  - **Children 1-5 years:**
    The acceptable pharmaceutical dosage forms are limited to solution/ drops, or emulsion/ suspension (Giacoa et al. 2008; EMEA/CHMP 2006).
  - **Children 6-12 years, Adolescents, and Adults:**
    The acceptable pharmaceutical dosage forms include, but are not limited to, chewables (eg. gummies, tablets), caplets, capsules, strips, lozenges, powders or liquids where the dose is measured in drops, teaspoons or tablespoons.

**Use(s) or Purpose(s)**

Statement(s) to the effect of:

For *Lactobacillus johnsonii* La1 or *L. johnsonii* Lj1 or *L. johnsonii* NCC 533:
- An adjunct to physician-supervised antibiotic therapy in patients with *Helicobacter pylori* infections (Bergonzelli et al. 2006; 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).

For products containing the above strains and that meet all other requirements of this monograph, one or more of the following supplemental statements may be included on the PLA, the label or in marketing material:
• 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/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/WHO 2006; Picard et al. 2005; Reid et al. 2003; Isolauri 2001; Saavedra 2001).

Dose(s)

Subpopulation:

Adults, adolescents, and children ≥ 1 year old

Quantity:

For patients with *H. pylori* infections:

1.25 x 10^8 to 3.6 x 10^9 cfu *L. johnsonii* Lj1 or *L. johnsonii* Lj1 or *L. johnsonii* NCC 533, per day (Bergonzelli et al. 2006; Pantoflickova et al. 2003; Felley et al. 2001)

For management of acute infectious diarrhoea:

6.0 x 10^9 to 1.2 x 10^10 cfu *L. rhamnosus* GG, per day (Canani et al. 2007; Guarino et al. 1997)

For management of antibiotic-associated diarrhoea:

1.0 x 10^10 to 2.0 x 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 x 10^10 to 2.0 x 10^10 cfu *L. rhamnosus* GG, per day (Cremonini et al. 2002; Armuzzi et al. 2001; Vanderhoof 1999)
1.0 x 10^{10} to 3.0 x 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):**

- Consult a health care practitioner prior to use if you have nausea, fever, vomiting, bloody diarrhoea or severe abdominal pain (APhA 2006; WHO 2005; CPA 2002).
- Discontinue use and consult a health care practitioner if symptoms of digestive upset (e.g. diarrhoea) occur, worsen, or persist beyond 3 days (APhA 2006; WHO 2005).

**Contraindication(s):**

- Do not use if you have an immune-compromised condition (e.g. AIDS, lymphoma, patients undergoing long-term corticosteroid treatment) (APhA 2006; Cukovic-Cavka et al. 2006; Ledoux et al. 2006; Riquelme et al. 2003; Lherm et al. 2002).
- If one or more strains in the product possess unexplained atypical resistance to any antibiotic (Mathur and Singh 2005), the name(s) of the antibiotic(s) must be indicated as a contraindication on the label as follows: Do not use if you are taking xxxx. (For example: Do not use if you are taking ampicillin.)
- If one or more of the strains in the product have come into contact with any priority allergen during the manufacturing process (including the use of any priority allergens or their derivatives in the culture medium) that is not listed as a medicinal or non-medicinal ingredient, the risk statement (CG 2011; HC 2009b; HC 2008) must be included on the product label as follows: This product has come into contact with XXX. If you have a XXX allergy, do not use this product.

Note: The list of priority allergens is maintained at: http://www.hc-sc.gc.ca/fn-an/label-etiquet/allergen/index-eng.php.

**Known adverse reaction(s):**

No statement required.

**Non-medicinal ingredients**

- Must be chosen from the current NHPD *Natural Health Products Ingredients Database* and must meet the limitations outlined in that database.
- Fermentable carbohydrates (e.g. transgalactooligosaccharides, lactulose and inulin-type fructans such as inulin and oligofructose) are acceptable non-medicinal ingredients provided
they are present in quantities consistent with improving the stability and viability of the medicinal ingredients.

- Ascorbic acid at a dose not greater than 0.5% is an acceptable non-medicinal ingredient if used as a preservative (Cui et al 2006; Zárate et al 2006; Zárate et al 2005).
- Ingredients that are intentionally added to the formulation for the purpose of preserving the viability of strains during lyophilization, storage or rehydration (cryoprotectants) are considered to be non-medicinal ingredients and must be listed on the PLA and the product label.

**Storage condition(s)**

For all liquid products:
Store in refrigerator in a tightly closed, light-resistant container.

**Specifications**

- The finished product must comply with the requirements of the current NHPD *Compendium of Monographs* guidance document.
- In addition to the requirements in the *Compendium of Monographs*, the finished product must adhere to the following 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;
  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.
  iii) That no strain in the product possesses antibiotic resistance that is known to be transferrable.
- The following information on the manufacturing process must be maintained by the applicant or the manufacturer and provided to Health Canada upon request:
  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;
  iii) Information on the source and history of the microorganism, confirmation of identity of the species, strain, etc.
  iv) The measured minimal inhibitory concentrations obtained for the antibiotic panel published by the European Food Safety Authority (EFSA), obtained with the EFSA broth microdilution method. (EFSA 2008); and,
  v) For strains that demonstrate atypical resistance to one or more antibiotic listed by EFSA, data demonstrating unambiguously that the genetic mechanism of resistance is non-transferrable or a list of all known genetic mechanisms of resistance to the antibiotic that have been verified to be absent from the strain.
References cited


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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.


Appendix 1  Nomenclature for medicinal ingredients

NCBI 2009; Bisby et al. 2006; Skerman et al. 1989:

*Lactobacillus johnsonii* Fujisawa et al. 1992 (Lactobacillaceae)

*Lactobacillus rhamnosus* (Hansen 1968) Collins et al. 1989 (Lactobacillaceae)

*Saccharomyces boulardii* Seguela, Bastide & Massot 1984 (Saccharomycetaceae)

**Note:**
*Saccharomyces boulardii* is not a valid proper name for a genetically distinct subtype within the species of *Saccharomyces cerevisiae* (Posteraro et al. 2005). This name is still used in the scientific literature however and pending a more thorough review, will continue to be accepted as a proper name in probiotic products to prevent confusion with non-probiotic subtypes of *S. cerevisiae* (Malgoire et al. 2005, van der Aa Kühle et al. 2003, McFarland 2010, McCullogh et al. 1998, and de Llanos et al. 2004).