

NATURAL HEALTH PRODUCT

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.

Notes

- ▶ By submitting a PLA referencing this monograph, the applicant is attesting that the product will comply fully with the recommended conditions of use and specifications section outlined in this monograph. These include species identification, strain characterization, quantification in colony forming units (CFU), and a complete assessment of virulence properties (including but not limited to: antibiotic resistance profile, virulence factor production, and toxigenic activity).
- ▶ 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 and/or the statements are synonymous. Either term or statement may be selected by the applicant.
- ▶ Any non-viable form of the medicinal ingredients found in Appendix I (e.g. heat-killed, thermostabilised) is excluded from this monograph and the compendial application process.

Date

May 26, 2015

Proper name(s) and Common name(s)

Refer to Appendix I for lists of acceptable bacterial (Table 1), bacterial and fungal (Table 2), and fungal (Table 3) proper and common names.

Refer to Appendix I, Table 4 for medicinal ingredients that are excluded from this monograph.

Source material(s)

Whole cell AND Strain Designation

Note

The Product Licence Application (PLA) and label must identify the strain designation as the source material for each microorganism (e.g. *Lactobacillus acidophilus* ABC123 where "ABC123" is the strain designation).

Route(s) of administration

Oral

Dosage form(s)

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

Dosage forms by age group

- Children 1-2 years:
The acceptable pharmaceutical dosage forms are limited to emulsion/suspension and solution/drops (Giacchia et al. 2008; EMEA/CHMP 2006).
- Children 3-5 years:
The acceptable pharmaceutical dosage forms are limited to chewables, emulsion/suspension, powders and solution/drops (Giacchia et al. 2008; EMEA/CHMP 2006).
- 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.

Use(s) or Purpose(s) Statement to the effect of

Medicinal ingredients from Appendix I, Table 1, 2, and 3

Source of probiotics.

Medicinal ingredients from Appendix I, Table 1, 2, and 3 except *Lactobacillus crispatus* and *Lactobacillus gallinarum*

- Helps support intestinal/gastrointestinal health (Alonso and Guarner 2013; DuPont and DuPont 2011; WGOGG 2011; Rolfe 2000).
- Could promote a favorable gut flora (Bezkorovainy 2001; Morelli 2000; Collins et al. 1998).

Medicinal ingredients from Appendix I, Table 2 with specific use(s) or purpose(s)

Name(s)	Strain(s)	Use(s) or Purpose(s)	References
<i>Lactobacillus johnsonii</i>	La1/Lj1/ NCC 533	An adjunct to physician-supervised antibiotic therapy in patients with <i>Helicobacter pylori</i> infections	Bergonzelli et al. 2006; Cruchet et al. 2003; Pantoflickova et al. 2003; Felley et al. 2001
<i>Lactobacillus rhamnosus</i>	GG	Helps to manage acute infectious diarrhoea	Canani et al. 2007; Guandalini et al. 2000; Guarino et al. 1997

Dose(s)

Subpopulation(s)

- ▶ Adults (≥ 18 y) (Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003)
- ▶ Adolescents (13-17 y) (Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003)
- ▶ Children (1-12 y) (Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003)

Medicinal ingredients from Appendix I, Table 1 and 3

Minimum: 10^7 Colony Forming Units (CFU) per day (Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003).

The minimum daily dose is the total CFU count per day provided from all live microorganisms present in the product formulation; it is not to be interpreted as a minimum quantity for individual microorganisms.

Medicinal ingredients from Appendix I, Table 2

Name(s)	Strain(s)	Quantity(ies) Colony Forming Units (CFU) per day	References
<i>Lactobacillus johnsonii</i>	La1/Lj1/ NCC 533	<i>H. pylori</i> infections: 1.25 x 10 ⁸ to 3.6 x 10 ⁹	Bergonzelli et al. 2006; Pantoflickova et al. 2003; Felley et al. 2001
	All	All other uses ¹ : Minimum: 10 ⁷	Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003
<i>Lactobacillus rhamnosus</i>	GG	Management of acute infectious diarrhoea: 6.0 x 10 ⁹ to 1.2 x 10 ¹⁰	Canani et al. 2007; Guarino et al. 1997
		Management/risk reduction of antibiotic-associated diarrhoea: 1.0 x 10 ¹⁰ to 2.0 x 10 ¹⁰	Cremonini et al. 2002; Armuzzi et al. 2001; Vanderhoof 1999
	All	All other uses ¹ : Minimum: 10 ⁷	Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003
<i>Saccharomyces boulardii</i> / <i>Saccharomyces cerevisiae</i>	All	Risk reduction of antibiotic- associated diarrhoea: 1.0 x 10 ¹⁰ to 3.0 x 10 ¹⁰	Can et al. 2006; Kotowska et al. 2005; Cremonini et al. 2002; McFarland <i>et al.</i> 1995
		All other uses ¹ : Minimum: 10 ⁷	Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003

¹ For 'All other uses', the total recommended daily CFU count must meet the minimum of 10⁷ either as a single ingredient or in combination.

Note

- ▶ All individual strain quantities of live microorganisms must be indicated on the PLA form, label and finished product specifications in Colony Forming Units (CFU) per dosage unit.
- ▶ In the case of blends where multiple live microorganisms have been cultured together, only the total microorganism count in CFU per dosage unit must be provided.
- ▶ Volumetric amounts (e.g. g, mL) are not acceptable.

Directions for use

All acceptable medicinal ingredients found in Appendix I, Table 1 and 2 except *Saccharomyces cerevisiae*/*S. boulardii*

If you are on antibiotic(s), take at least 2-3 hours before or after (NIH 2011; APhA 2006; Biradar et al. 2005).

All acceptable medicinal ingredients found in Appendix I, Table 3 and *Saccharomyces cerevisiae*/*S. boulardii*

If you are on antifungal(s), take at least 2-3 hours before or after (NIH 2011; APhA 2006; Biradar et al. 2005).

Duration of use

No statement required.

Risk information

Statement to the effect of

Caution(s) and warning(s)

- ▶ If you have fever, vomiting, bloody diarrhoea or severe abdominal pain, consult a health care practitioner prior to use (APhA 2006; WHO 2005; CPhA 2002).
- ▶ If symptoms of digestive upset (e.g. diarrhea) occurs and/or persists beyond 3 days, discontinue use and consult a health care practitioner (APhA 2006; WHO 2005).

Note

If any bacterial/fungal strain in the product has come into contact with a priority allergen or derivative (e.g. soy, gluten, milk, fish via the culture media) (list available at: <http://www.hc-sc.gc.ca/fn-an/securit/allerg/fa-aa/index-eng.php>) that is not listed as a medicinal or non-medicinal ingredient, one of the following risk statements must be included on the product label:

- ▶ If you have a XXX allergy, do not use this product (CG 2011; HC 2009);

OR

- ▶ (May) contain(s) XXX (HC 2012a; HC 2012b; CG 2011; HC2009; HC 2003)

Contraindication(s)

- ▶ If you have an immune-compromised condition (e.g. AIDS, lymphoma, patients undergoing long-term corticosteroid treatment), do not use this product (APhA 2006; Cukovic-Cavka et al. 2006; Ledoux et al. 2006; Riquelme et al. 2003; Lherm et al. 2002).
- ▶ If any bacterial/fungal strain in the product possesses unexplained atypical resistance to any antibiotic/antifungal agent (Mathur and Singh 2005), the name(s) of the antibiotic(s)/antifungal(s) agent(s) must be indicated as a contraindication on the label as follows:
If you are taking XXX, do not use this product (e.g. If you are taking ampicillin, do not use this product).

Known adverse reaction(s)

No statement required.

Non-medicinal ingredients

Must be chosen from the current NHPD Natural Health Products Ingredient Database (NHPID) and must meet the limitations outlined in the database.

Note

Cryoprotectants: All ingredients that are intentionally added during the manufacturing process of a live microorganism to preserve its stability/viability are non-medicinal ingredients.

Storage condition(s) Statement to the effect of

All liquid preparations

Store in refrigerator in a tightly closed, light-resistant container.

Note

This requirement does not apply to shelf-stable liquid preparations such as oil suspensions and emulsions.

All non-liquid preparations (optional)

Store in refrigerator in a tightly closed container (Liu 2009; Juarez Thomas 2004; Shillinger 1999).

Specifications

The following requirements are expected to be met by each live microorganism attesting to this monograph:

- ▶ The species Latin binomial 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.
- ▶ 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.

The finished product must meet all quality requirements as detailed in NHPD’s *Quality of Natural Health Products Guide*. In the case of live microorganisms, this includes the following:

- ▶ 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; this applies to single ingredient counts for live microorganisms cultured separately, or total counts for blends where multiple live microorganisms have been cultured together.
- ▶ In the case where the live microorganism can interfere with microbial impurity testing, a detailed rationale on how the final product complies is required. Such rationale should include measures for live microorganism distinguishing at the finished product stage, along

with a detailed explanation on how quality assurance measures are put into place to ensure microbial purity.

Note

Information on the manufacturing process, including but not limited to the above, must be maintained by the applicant or the manufacturer and provided to Health Canada upon request.

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Appendix I

Table 1: Medicinal Ingredients – BACTERIA

Proper and Common names	References
<i>Bifidobacterium adolescentis</i>	Masco et al. 2004; Skerman et al. 1980
<i>Bifidobacterium animalis</i> (including <i>B. animalis</i> subsp. <i>animalis</i> and <i>B. animalis</i> subsp. <i>lactis</i>)	Masco et al. 2004; Skerman et al. 1980
<i>Bifidobacterium bifidum</i>	Skerman et al. 1980
<i>Bifidobacterium breve</i>	Skerman et al. 1980
<i>Bifidobacterium longum</i> (including <i>Bifidobacterium longum</i> subsp. <i>infantis</i> , <i>Bifidobacterium longum</i> subsp. <i>longum</i> and <i>Bifidobacterium longum</i> subsp. <i>suis</i>)	Mattarelli et al. 2008
<i>Lactobacillus acidophilus</i>	Johnson et al. 1980; Skerman et al. 1980
<i>Lactobacillus amylolyticus</i>	Validation List No. 68 1998
<i>Lactobacillus amylovorus</i>	Nakamura 1981
<i>Lactobacillus brevis</i>	Skerman et al. 1980
<i>Lactobacillus buchneri</i>	Skerman et al. 1980
<i>Lactobacillus casei</i>	JCICSB 2008; Skerman et al. 1980
<i>Lactobacillus coryniformis</i>	Skerman et al. 1980
<i>Lactobacillus crispatus</i> ¹	Skerman et al. 1980
<i>Lactobacillus curvatus</i>	Skerman et al. 1980
<i>Lactobacillus delbrueckii</i> (including <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> & <i>Lactobacillus delbrueckii</i> subsp. <i>delbrueckii</i>)	Beijerinck 1901; Howey et al. 1990
<i>Lactobacillus farciminis</i>	Validation List no. 11, 1983
<i>Lactobacillus fermentum</i>	Skerman et al. 1980
<i>Lactobacillus gallinarum</i> ¹	Fujisawa et al. 1992
<i>Lactobacillus gasseri</i>	Validation List No. 4 1980
<i>Lactobacillus helveticus</i>	Skerman et al. 1980
<i>Lactobacillus hilgardii</i>	Skerman et al. 1980
<i>Lactobacillus johnsonii</i>	Fujisawa et al. 1992
<i>Lactobacillus kefiranoferiens</i>	Fujisawa et al. 1988
<i>Lactobacillus kefir</i>	Validation List no. 11, 1983
<i>Lactobacillus mucosae</i>	Roos et al. 2000
<i>Lactobacillus panis</i>	Wiese et al. 1996
<i>Lactobacillus paracasei</i>	JCICSB 2008; Collins et al. 1989
<i>Lactobacillus paraplantarum</i>	Curk et al. 1996
<i>Lactobacillus plantarum</i>	Skerman et al. 1980
<i>Lactobacillus pontis</i>	Vogel et al. 1994
<i>Lactobacillus reuteri</i>	Validation List No. 8, 1982
<i>Lactobacillus rhamnosus</i>	Collins et al. 1989

Proper and Common names	References
<i>Lactobacillus salivarius</i>	Skerman et al. 1980
<i>Lactobacillus sanfranciscensis</i>	Validation List no. 16, 1984b
<i>Lactococcus lactis</i>	Validation List no. 20, 1985
<i>Leuconostoc citreum</i>	Farrow et al. 1989
<i>Leuconostoc pseudomesenteroides</i>	Farrow et al. 1989
<i>Leuconostoc lactis</i>	Skerman et al. 1980
<i>Leuconostoc mesenteroides</i>	Skerman et al. 1980
<i>Oenococcus oeni</i>	Dicks et al. 1995
<i>Pediococcus acidilactici</i>	Skerman et al. 1980
<i>Pediococcus pentosaceus</i>	Skerman et al. 1980
<i>Propionibacterium freudenreichii</i> (including <i>Propionibacterium freudenreichii</i> subsp. <i>shermanii</i>)	Skerman et al. 1980
<i>Propionibacterium acidipropionici</i>	Skerman et al. 1980

¹For “source of probiotics” claim only

Table 2: Medicinal Ingredients – BACTERIA and FUNGI

Proper and Common names	Strain	References
<i>Lactobacillus johnsonii</i> ¹	La1	Euzéby 2012; Pridmore et al. 2004; Sanders 1999
<i>Lactobacillus johnsonii</i> ¹	Lj1	Euzéby 2012; Reid 1999; Sanders 1999
<i>Lactobacillus johnsonii</i> ¹	NCC 533	Euzéby 2012; Pridmore et al. 2004
<i>Lactobacillus rhamnosus</i> ²	GG	Euzéby 2012; Hawrelak et al. 2005; Gilliland 2001; Reid 1999, Skerman et al. 1989
<i>Saccharomyces boulardii</i> ³		McFarland 2010; NCBI 2009; Malgoire et al. 2005; McCullough et al. 1998; Meyen ex E.C. Hansen 1883
<i>Saccharomyces cerevisiae</i>		McFarland 2010; NCBI 2009; Malgoire et al. 2005; McCullough et al. 1998; Meyen ex E.C. Hansen 1883;

¹ *Lactobacillus johnsonii* Fujisawa et al. 1992 (Lactobacillaceae) (NCBI 2009; Bisby et al. 2006; Skerman et al. 1989)

² *Lactobacillus rhamnosus* (Hansen 1968) Collins et al. 1989 (Lactobacillaceae) (NCBI 2009; Bisby et al. 2006; Skerman et al. 1989)

³ *Saccharomyces boulardii* Seguela, Bastide & Massot 1984 (Saccharomycetaceae) 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* (McFarland 2010; NCBI 2009; Bisby et al. 2006; Malgoire et al. 2005; de Llanos et al. 2004; van der Aa Kühle et al. 2003; McCullough et al. 1998; Skerman et al. 1989).

Table 3: Medicinal Ingredients – FUNGI

Proper and Common names	References
<i>Debaryomyces hansenii</i>	Lodder 1952
<i>Kluyveromyces lactis</i>	van der Walt 1971
<i>Kluyveromyces marxianus</i>	van der Walt 1971
<i>Saccharomyces bayanus</i>	Saccardo 1895
<i>Saccharomyces cerevisiae</i> (including <i>Saccharomyces boulardii</i>)	Meyen ex E.C. Hansen 1883
<i>Saccharomyces pastorianus</i>	Reess 1870
<i>Schizosaccharomyces pombe</i>	Lindner 1893
<i>Xanthophyllomyces dendrorhous</i>	Golubev 1995

Table 4: The following live microorganisms are excluded from this monograph

Proper and Common names	References
<i>Escherichia coli</i>	Skerman et al. 1980
<i>Bacillus coagulans</i>	Skerman et al. 1980
<i>Bacillus subtilis</i>	Skerman et al. 1980
<i>Clostridium butyricum</i>	Skerman et al. 1980
<i>Enterococcus faecium</i>	Schleifer et al. 1984
<i>Streptococcus salivarius</i>	Skerman et al. 1980