

## 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 statements are synonymous. Either term or statement may be selected by the applicant.
- ▶ Any non-viable form of the medicinal ingredients found in Tables 1, 2, and 3 (e.g. heat-killed, thermostabilised) is excluded from this monograph and the compendial application process.
- ▶ All of the microorganisms found in Appendix I (Table 6) are excluded from this monograph and the compendial application process.

#### Date

January 27, 2023

#### Proper name(s), Common name(s), Source information(s), Strain(s)

#### Note

Refer to Appendix I, Table 6 for medicinal ingredients that are excluded from this monograph.

Table 1. Proper name(s), Common name(s), Source information, Strain(s) – BACTERIA

Proper name(s)	Common name(s)	Source Information <sup>1</sup>	
		Part(s)	Strain(s) <sup>2</sup>
<i>Bifidobacterium adolescentis</i>	<i>Bifidobacterium adolescentis</i>	Whole cell	Strain designation
<i>Bifidobacterium animalis</i> subsp. <i>animalis</i>	<i>Bifidobacterium animalis</i> subsp. <i>animalis</i>	Whole cell	Strain designation



Proper name(s)	Common name(s)	Source Information <sup>1</sup>	
		Part(s)	Stain(s) <sup>2</sup>
<i>Bifidobacterium animalis</i> subsp. <i>lactis</i>	<i>Bifidobacterium animalis</i> subsp. <i>lactis</i>	Whole cell	Strain designation
<i>Bifidobacterium bifidum</i>	<i>Bifidobacterium bifidum</i>	Whole cell	Strain designation
<i>Bifidobacterium breve</i>	<i>Bifidobacterium breve</i>	Whole cell	Strain designation
<i>Bifidobacterium longum</i>	<i>Bifidobacterium longum</i>	Whole cell	Strain designation
<i>Bifidobacterium longum</i> subsp. <i>infantis</i>	<i>Bifidobacterium longum</i> subsp. <i>infantis</i>	Whole cell	Strain designation
<i>Bifidobacterium longum</i> subsp. <i>longum</i>	<i>Bifidobacterium longum</i> subsp. <i>longum</i>	Whole cell	Strain designation
<i>Bifidobacterium longum</i> subsp. <i>suis</i>	<i>Bifidobacterium longum</i> subsp. <i>suis</i>	Whole cell	Strain designation
<i>Companilactobacillus farciminis</i>  (formerly <i>Lactobacillus farciminis</i> )	<i>Companilactobacillus farciminis</i>  (formerly <i>Lactobacillus farciminis</i> )	Whole cell	Strain designation
<i>Fructilactobacillus sanfranciscensis</i>  (formerly <i>Lactobacillus sanfranciscensis</i> )	<i>Fructilactobacillus sanfranciscensis</i>  (formerly <i>Lactobacillus sanfranciscensis</i> )	Whole cell	Strain designation
<i>Lacticaseibacillus casei</i>  (formerly <i>Lactobacillus casei</i> )	<i>Lacticaseibacillus casei</i>  (formerly <i>Lactobacillus casei</i> )	Whole cell	Strain designation
<i>Lacticaseibacillus paracasei</i>  (formerly <i>Lactobacillus paracasei</i> )	<i>Lacticaseibacillus paracasei</i>  (formerly <i>Lactobacillus paracasei</i> )	Whole cell	Strain designation
<i>Lacticaseibacillus rhamnosus</i>	<i>Lacticaseibacillus rhamnosus</i>	Whole cell	Strain designation



Proper name(s)	Common name(s)	Source Information <sup>1</sup>	
		Part(s)	Strain(s) <sup>2</sup>
(formerly <i>Lactobacillus rhamnosus</i> )	(formerly <i>Lactobacillus rhamnosus</i> )		
<i>Lactiplantibacillus paraplantarum</i>  (formerly <i>Lactobacillus paraplantarum</i> )	<i>Lactiplantibacillus paraplantarum</i>  (formerly <i>Lactobacillus paraplantarum</i> )	Whole cell	Strain designation
<i>Lactiplantibacillus plantarum</i>  (formerly <i>Lactobacillus plantarum</i> )	<i>Lactiplantibacillus plantarum</i>  (formerly <i>Lactobacillus plantarum</i> )	Whole cell	Strain designation
<i>Lactobacillus acidophilus</i>	<i>Lactobacillus acidophilus</i>	Whole cell	Strain designation
<i>Lactobacillus amylolyticus</i>	<i>Lactobacillus amylolyticus</i>	Whole cell	Strain designation
<i>Lactobacillus amylovorus</i>	<i>Lactobacillus amylovorus</i>	Whole cell	Strain designation
<i>Lactobacillus crispatus</i> <sup>3</sup>	<i>Lactobacillus crispatus</i>	Whole cell	Strain designation
<i>Lactobacillus delbrueckii</i>	<i>Lactobacillus delbrueckii</i>	Whole cell	Strain designation
<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i>	<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i>	Whole cell	Strain designation
<i>Lactobacillus delbrueckii</i> subsp. <i>delbrueckii</i>	<i>Lactobacillus delbrueckii</i> subsp. <i>delbrueckii</i>	Whole cell	Strain designation
<i>Lactobacillus gallinarum</i> <sup>3</sup>	<i>Lactobacillus gallinarum</i>	Whole cell	Strain designation
<i>Lactobacillus gasseri</i>	<i>Lactobacillus gasseri</i>	Whole cell	Strain designation
<i>Lactobacillus helveticus</i>	<i>Lactobacillus helveticus</i>	Whole cell	Strain designation
<i>Lactobacillus johnsonii</i>	<i>Lactobacillus johnsonii</i>	Whole cell	Strain designation
<i>Lactobacillus kefiranofaciens</i>	<i>Lactobacillus kefiranofaciens</i>	Whole cell	Strain designation
<i>Lactococcus lactis</i>	<i>Lactococcus lactis</i>	Whole cell	Strain designation



Proper name(s)	Common name(s)	Source Information <sup>1</sup>	
		Part(s)	Stain(s) <sup>2</sup>
<i>Latilactobacillus curvatus</i>  (formerly <i>Lactobacillus curvatus</i> )	<i>Latilactobacillus curvatus</i>  (formerly <i>Lactobacillus curvatus</i> )	Whole cell	Strain designation
<i>Lentilactobacillus buchneri</i>  (formerly <i>Lactobacillus buchneri</i> )	<i>Lentilactobacillus buchneri</i>  (formerly <i>Lactobacillus buchneri</i> )	Whole cell	Strain designation
<i>Lentilactobacillus hilgardii</i>  (formerly <i>Lactobacillus hilgardii</i> )	<i>Lentilactobacillus hilgardii</i>  (formerly <i>Lactobacillus hilgardii</i> )	Whole cell	Strain designation
<i>Lentilactobacillus kefir</i>  (formerly <i>Lactobacillus kefir</i> )	<i>Lentilactobacillus kefir</i>  (formerly <i>Lactobacillus kefir</i> )	Whole cell	Strain designation
<i>Leuconostoc citreum</i>	<i>Leuconostoc citreum</i>	Whole cell	Strain designation
<i>Leuconostoc lactis</i>	<i>Leuconostoc lactis</i>	Whole cell	Strain designation
<i>Leuconostoc mesenteroides</i>	<i>Leuconostoc mesenteroides</i>	Whole cell	Strain designation
<i>Leuconostoc pseudomesenteroides</i>	<i>Leuconostoc pseudomesenteroides</i>	Whole cell	Strain designation
<i>Levilactobacillus brevis</i>  (formerly <i>Lactobacillus brevis</i> )	<i>Levilactobacillus brevis</i>  (formerly <i>Lactobacillus brevis</i> )	Whole cell	Strain designation
<i>Ligilactobacillus salivarius</i>  (formerly <i>Lactobacillus salivarius</i> )	<i>Ligilactobacillus salivarius</i>  (formerly <i>Lactobacillus salivarius</i> )	Whole cell	Strain designation



Proper name(s)	Common name(s)	Source Information <sup>1</sup>	
		Part(s)	Strain(s) <sup>2</sup>
<i>Limosilactobacillus fermentum</i>  (formerly <i>Lactobacillus fermentum</i> )	<i>Limosilactobacillus fermentum</i>  (formerly <i>Lactobacillus fermentum</i> )	Whole cell	Strain designation
<i>Limosilactobacillus mucosae</i>  (formerly <i>Lactobacillus mucosae</i> )	<i>Limosilactobacillus mucosae</i>  (formerly <i>Lactobacillus mucosae</i> )	Whole cell	Strain designation
<i>Limosilactobacillus panis</i>  (formerly <i>Lactobacillus panis</i> )	<i>Limosilactobacillus panis</i>  (formerly <i>Lactobacillus panis</i> )	Whole cell	Strain designation
<i>Limosilactobacillus pontis</i>  (formerly <i>Lactobacillus pontis</i> )	<i>Limosilactobacillus pontis</i>  (formerly <i>Lactobacillus pontis</i> )	Whole cell	Strain designation
<i>Limosilactobacillus reuteri</i>  (formerly <i>Lactobacillus reuteri</i> )	<i>Limosilactobacillus reuteri</i>  (formerly <i>Lactobacillus reuteri</i> )	Whole cell	Strain designation
<i>Loigolactobacillus coryniformis</i>  (formerly <i>Lactobacillus coryniformis</i> )	<i>Loigolactobacillus coryniformis</i>  (formerly <i>Lactobacillus coryniformis</i> )	Whole cell	Strain designation
<i>Oenococcus oeni</i>	<i>Oenococcus oeni</i>	Whole cell	Strain designation
<i>Pediococcus acidilactici</i>	<i>Pediococcus acidilactici</i>	Whole cell	Strain designation
<i>Pediococcus pentosaceus</i>	<i>Pediococcus pentosaceus</i>	Whole cell	Strain designation
<i>Propionibacterium acidipropionici</i>	<i>Propionibacterium acidipropionici</i>	Whole cell	Strain designation
<i>Propionibacterium freudenreichii</i>	<i>Propionibacterium freudenreichii</i>	Whole cell	Strain designation



Proper name(s)	Common name(s)	Source Information <sup>1</sup>	
		Part(s)	Strain(s) <sup>2</sup>
<i>Propionibacterium freudenreichii</i> subsp. <i>shermanii</i>	<i>Propionibacterium freudenreichii</i> subsp. <i>shermanii</i>	Whole Cell	Strain designation

<sup>1</sup>The source material should be the same as the proper name.

<sup>2</sup>The 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).

<sup>3</sup>For “source of probiotics” claim only.

References: Zheng et al. 2020, JCICSB 2008, Mattarelli et al. 2008, Masco et al. 2004, Roos et al. 2000, Validation List No. 68 1998, Curk et al. 1996, Wiese et al. 1996, Dicks et al. 1995, Vogel et al. 1994, Fujisawa et al. 1992, Howey et al. 1990, Collins et al. 1989, Farrow et al. 1989, Fujisawa et al. 1988, Validation List no. 20, 1985, Validation List no. 16, 1984b, Validation List no. 11, 1983, Validation List No. 8, 1982, Nakamura 1981, Johnson et al. 1980, Skerman et al. 1980, Validation List No. 4 1980, Beijerinck 1901.

Table 2. Proper name(s), Common name(s), Source information, Strain(s) – BACTERIA and FUNGI

Proper name(s)	Common name(s)	Source information <sup>1</sup>	
		Part(s)	Strain(s) <sup>2</sup>
<i>Lacticaseibacillus rhamnosus</i>	<i>Lacticaseibacillus rhamnosus</i>	Whole cell	GG
<i>Lactobacillus johnsonii</i>	<i>Lactobacillus johnsonii</i>	Whole cell	La1
<i>Lactobacillus johnsonii</i>	<i>Lactobacillus johnsonii</i>	Whole cell	Lj1
<i>Lactobacillus johnsonii</i>	<i>Lactobacillus johnsonii</i>	Whole cell	NCC 533
<i>Saccharomyces boulardii</i> <sup>3</sup>	<i>Saccharomyces boulardii</i>	Whole cell	Strain designation
<i>Saccharomyces cerevisiae</i>	<ul style="list-style-type: none"> <li>▶ Baker's Yeast</li> <li>▶ Brewer's Yeast</li> <li>▶ Brewers yeast fungus</li> </ul>	Whole cell	Strain designation

<sup>1</sup>The source material should be the same as the proper name.

<sup>2</sup>The 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).

<sup>3</sup>*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; McCulloch et al. 1998; Skerman et al. 1989).

References: Euzéby 2012, McFarland 2010, NCBI 2009, Bisby et al. 2006, Hawrelak et al. 2005, Malgoire et al. 2005, Pridmore et al. 2004, Gilliland 2001, Reid 1999, Sanders 1999, McCullough et al. 1998, Fujisawa et al. 1992, Collins et al. 1989, Skerman et al. 1989, Hansen 1968, Meyen ex E.C. Hansen 1883.



Table 3. Proper name(s), Common name(s), Source information, Strain(s) – FUNGI

Proper name(s)	Common name(s)	Source information <sup>1</sup>	
		Part(s)	Strain(s) <sup>2</sup>
<i>Debaryomyces hansenii</i>	<i>Debaryomyces hansenii</i>	Whole cell	Strain designation
<i>Kluyveromyces lactis</i>	<i>Kluyveromyces lactis</i>	Whole cell	Strain designation
<i>Kluyveromyces marxianus</i>	<i>Candida pseudotropicalis</i>	Whole cell	Strain designation
<i>Saccharomyces bayanus</i>	<i>Saccharomyces bayanus</i>	Whole cell	Strain designation
<i>Saccharomyces boulardii</i>	<i>Saccharomyces boulardii</i>	Whole cell	Strain designation
<i>Saccharomyces cerevisiae</i>	<ul style="list-style-type: none"> <li>▶ Baker's Yeast</li> <li>▶ Brewer's Yeast</li> <li>▶ Brewers yeast fungus</li> </ul>	Whole cell	Strain designation
<i>Saccharomyces pastorianus</i>	<i>Saccharomyces pastorianus</i>	Whole cell	Strain designation
<i>Schizosaccharomyces pombe</i>	<i>Schizosaccharomyces pombe</i>	Whole cell	Strain designation
<i>Xanthophyllomyces dendrorhous</i>	<i>Xanthophyllomyces dendrorhous</i>	Whole cell	Strain designation

<sup>1</sup>The source material should be the same as the proper name.

<sup>2</sup>The PLA and label must identify the strain designation as the source material for each microorganism (e.g. *Saccharomyces cerevisiae* ABC123 where "ABC123" is the strain designation).

References: Golubev 1995, van der Walt 1971, Lodder 1952, Saccardo 1895, Lindner 1893, Meyen ex E.C. Hansen 1883, Reess 1870.

### Route of administration

Oral

### Dosage form(s)

This monograph excludes foods or food-like dosage forms as indicated in the Compendium of Monographs Guidance Document.

### Acceptable dosage forms by age group:

**Children 1-2 years:** The acceptable pharmaceutical dosage forms are limited to emulsion/suspension and solution/ liquid preparations (Giacoaia et al. 2008; EMEA/CHMP 2006).

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

**Children 6-11 years, Adolescents 12-17 years, and Adults 18 years and older:** Acceptable dosage forms for oral use are indicated in the dosage form drop-down list of the web-based Product Licence Application form for Compendial applications.





### Use(s) or Purpose(s)

Medicinal ingredients from Tables 1, 2, and 3

Source of probiotics.

Medicinal ingredients from Tables 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).

Table 4. Medicinal ingredients from Table 2 with specific use(s) or purpose(s)

Medicinal ingredients	Strains	Uses or Purposes
<i>Lacticaseibacillus rhamnosus</i>	GG	Helps to manage acute infectious diarrhoea
		Helps to manage and/or reduce the risk of antibiotic-associated diarrhoea
<i>Lactobacillus johnsonii</i>	<ul style="list-style-type: none"> <li>▶ La1</li> <li>▶ Lj1</li> <li>▶ NCC 533</li> </ul>	An adjunct to physician-supervised antibiotic therapy in patients with <i>Helicobacter pylori</i> infections
<ul style="list-style-type: none"> <li>▶ <i>Saccharomyces boulardii</i></li> <li>▶ <i>Saccharomyces cerevisiae</i></li> </ul>	All	Helps to reduce the risk of antibiotic-associated diarrhoea

References: Canani et al. 2007, Bergonzelli et al. 2006, Kotowska et al. 2005, Can et al. 2006, Cruchet et al. 2003, Pantoflickova et al. 2003, Cremonini et al. 2002, Armuzzi et al. 2001, Felley et al. 2001, Guandalini et al. 2000, Vanderhoof et al. 1999, Guarino et al. 1997, McFarland et al. 1995, Surawicz et al. 1989.

### Dose(s)

#### Subpopulation(s)

Children 1 to 11 years, Adolescents 12 to 17 years and Adults 18 years and older (Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003).





**Quantity(ies)**

Method of preparation: Live

*Medicinal ingredients from Tables 1 and 3*

1.0 x 10<sup>7</sup> total Colony Forming Units (CFU) or more, per day (Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003).

**Note**

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.

Table 5. Medicinal ingredients from Table 2

Medicinal ingredients	Strains	Uses or Purposes	Doses (CFU/day)	
			Minimum	Maximum
<i>Lactocaseibacillus rhamnosus</i>	GG	Management of acute infectious diarrhoea	6.0 x 10 <sup>9</sup>	1.2 x 10 <sup>10</sup>
		Management/risk reduction of antibiotic-associated diarrhoea	1.0 x 10 <sup>10</sup>	2.0 x 10 <sup>10</sup>
	All	All other uses <sup>1</sup>	1.0 x 10 <sup>7</sup>	N/A
<i>Lactobacillus johnsonii</i>	▶ La1 ▶ Lj1 ▶ NCC 533	<i>H. pylori</i> infections	1.25 x 10 <sup>8</sup>	3.6 x 10 <sup>9</sup>
	All	All other uses <sup>1</sup>	1.0 x 10 <sup>7</sup>	N/A
▶ <i>Saccharomyces boulardii</i> ▶ <i>Saccharomyces cerevisiae</i>	All	Risk reduction of antibiotic-associated diarrhoea	1.0 x 10 <sup>10</sup>	3.0 x 10 <sup>10</sup>
		All other uses <sup>1</sup>	1.0 x 10 <sup>7</sup>	N/A

<sup>1</sup>For ‘All other uses’, the total recommended daily CFU count must meet the minimum of 10<sup>7</sup> either as a single ingredient or in combination.

References: Gill and Prasad 2008, Canani et al. 2007, Lenoir-Wijnkoop et al. 2007, Bergonzelli et al. 2006, Hawrelak 2006, Can et al. 2006, Picard et al. 2005, Pantoflickova et al. 2003, Reid et al. 2003, Cremonini et al. 2002, Armuzzi et al. 2001, Felley et al. 2001, Vanderhoof 1999, Guarino et al. 1997, McFarland et al. 1995.

**Notes**

- ▶ 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.
- ▶ Multiple microorganisms cultured together with only one combined microorganism count



(i.e., blends) are not included in this monograph.

- ▶ Gravimetric or volumetric amounts (e.g. g, mL) are not acceptable.

### **Direction(s) for use**

*All medicinal ingredients found in Tables 1 and 2 except *Saccharomyces cerevisiae* and *S. boulardii**

Take at least 2-3 hours before or after antibiotics (NIH 2011; APhA 2006; Biradar et al. 2005).

*All medicinal ingredients found in Table 3*

Take at least 2-3 hours before or after taking antifungal medications (NIH 2011; APhA 2006; Biradar et al. 2005).

### **Duration(s) of use**

No statement required.

### **Risk information**

#### **Caution(s) and warning(s)**

- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you have fever, vomiting, bloody diarrhoea or severe abdominal pain (APhA 2006; WHO 2005; CPhA 2002).
- ▶ Stop use and consult a health care practitioner/health care provider/health care professional/doctor/physician if symptoms of digestive upset (e.g. diarrhea) occur, worsen and/or persists beyond 3 days (APhA 2006; WHO 2005).

#### **Contraindication(s)**

Do not use this product 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).

#### **Known adverse reaction(s)**

No statement required.

### **Non-medicinal ingredients**

Must be chosen from the current 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 need to be disclosed as non- medicinal ingredients.

## Storage condition(s)

### *Liquid products*

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

## Note

This requirement does not apply to shelf-stable liquid dosage form preparations (i.e. oil suspensions and emulsions indicated in the Compendium of Monographs Guidance Document).

### *Non-liquid products (optional)*

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

## Specifications

- ▶ The medicinal ingredients must comply with the requirements outlined in the NHPID and 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.

► Regarding risk information:

- 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:

- Do not use this product if you have a XXX allergy (CG 2011; HC 2009);

OR

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

- 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 PLA form and label as follows:

- Do not use this product if you are taking XXX (e.g. Do not use this product if you are taking ampicillin).

**Note:** The above risk statement is not applicable to Class I (compendial) and Class II applications. If applicable to the strain attesting to this monograph, additional evidence must be provided and reviewed under the Class III stream.

► The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) 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.
- 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.

## References cited

Abe S, Takayama K, Kinoshita S. Taxonomic studies on glutamic acid-producing bacteria. *Journal of General and Applied Microbiology* 1967;13(3):279-301.

Adiloğlu AK, Gönülateş N, İşler M, Senol A. The effect of kefir consumption on human immune system: a cytokine study. *Mikrobiyoloji Bulteni* 2013;47(2):273-281.

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## Appendix I

Table 6. Excluded live microorganisms from this monograph

Proper and Common name(s)	References
<i>Bacillus clausii</i>	Nielsen et al. 1995
<i>Bacillus coagulans</i>	Skerman et al. 1980
<i>Bacillus indicus</i>	Suresh et al. 2004
<i>Bacillus subtilis</i>	Skerman et al. 1980
<i>Bacillus subtilis</i> subsp. <i>inaquosorum</i>	Rooney et al. 2009
<i>Clostridium butyricum</i>	Skerman et al. 1980
<i>Enterococcus faecalis</i>	Schleifer et al. 1984
<i>Enterococcus faecium</i>	Schleifer et al. 1984
<i>Escherichia coli</i>	Skerman et al. 1980
<i>Streptococcus salivarius</i>	Skerman et al. 1980
<i>Streptococcus salivarius</i> subsp. <i>thermophilus</i>	Farrow and Collins 1984