This abbreviated labelling standard (AbLS) is a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It includes generalized claims and is not intended to be a comprehensive review of the medicinal ingredient. Wording of the claim on the PLA and label must therefore be identical to this labelling standard.

This AbLS cannot be used to support probiotic or prebiotic claims. The use of the words “probiotic” or “prebiotic” on product labels, in brand names, or in marketing material is not supported by this AbLS.

Date August 30, 2011

<table>
<thead>
<tr>
<th>Field</th>
<th>Field content</th>
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<tr>
<td>Proper and common name(s)</td>
<td>The bacterial strain must be identified, e.g. <em>Lactobacillus rhamnosus</em> GG, for each of the following microorganism: <em>Bifidobacterium adolescentis</em> <em>Bifidobacterium animalis</em> (including <em>B. animalis</em> subsp. <em>animalis</em> and <em>B. animalis</em> subsp. <em>lactis</em>) <em>Bifidobacterium bifidum</em> <em>Bifidobacterium breve</em> <em>Bifidobacterium longum</em> (including <em>Bifidobacterium longum</em> subsp. <em>infantis</em>) <em>Lactobacillus acidophilus</em> <em>Lactobacillus amylovorus</em> <em>Lactobacillus casei</em> <em>Lactobacillus delbrueckii</em> subsp. <em>bulgaricus</em> <em>Lactobacillus fermentum</em> <em>Lactobacillus gasseri</em> <em>Lactobacillus johnsonii</em> <em>Lactobacillus paracasei</em> <em>Lactobacillus plantarum</em> <em>Lactobacillus reuteri</em> <em>Lactobacillus rhamnosus</em> <em>Lactobacillus salivarius</em> <em>Streptococcus salivarius</em> subsp. <em>thermophilus</em></td>
<td>Skerman et al. 1980 Skerman et al. 1980 Skerman et al. 1980 Masco et al. 2004 Mattarelli 2008 Skerman et al. 1980 Nakamura et al. 1981 JCICSB 2008; Skerman et al. 1980 Validation List No. 14 1984 Skerman et al. 1980 Validation List No. 4 1980 Fujisawa et al. 1992 JCICSB 2008; Collins et al. 1989 Skerman et al. 1980 Validation List No. 8 1982 Collins et al. 1989 Li et al. 2006; Skerman et al. 1980 Farrow et al. 1984; Validation list No. 15 1984</td>
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<tr>
<td><strong>Note:</strong></td>
<td>• The medicinal ingredient must be supported by the documentation listed in the specifications below.</td>
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<td></td>
<td>• Brand names or common names that contain implied claims are not supported by this AbLS and PLAs containing such brand names or common names must be assessed through the non-compendial process.</td>
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<tr>
<td><strong>Source material(s)</strong></td>
<td>Live microorganism – whole cell</td>
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<tr>
<td><strong>Route(s) of administration</strong></td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td><strong>Dosage form(s)</strong></td>
<td>This monograph is not intended to include foods or food-like dosage forms such as yogurts, bars, chewing gums or beverages.</td>
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<td></td>
<td>Dosage form by age group:</td>
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<td><strong>Children 1-5 years:</strong></td>
<td>The acceptable pharmaceutical dosage forms are limited to solution/ drops, or emulsion/ suspension (Giacoia et al. 2008; EMEA/CHMP 2006).</td>
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<td><strong>Children 6-12 years, Adolescents, and Adults:</strong></td>
<td>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.</td>
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<tr>
<td><strong>Use(s) or Purpose(s)</strong></td>
<td>Provides live microorganisms that temporarily modify gut flora.</td>
<td>Elli et al. 2006; FAO/WHO 2006; Bezkorovainy 2001; Conway 1987</td>
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<tr>
<td><strong>Dose(s)</strong></td>
<td>1.0 x 10⁷ to 1.0 x 10¹¹ colony forming units (cfu) from one or more strains of the bacterial species listed above, per day.</td>
<td>Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003</td>
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<tr>
<td><strong>Directions for use:</strong></td>
<td>Take at least 2–3 hours before or after antibiotics.</td>
<td>MedlinePlus 2011; APhA 2006; Biradar et al. 2005</td>
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<tr>
<td><strong>Subpopulation(s)</strong></td>
<td>Adults, adolescents, and children ≥ 1 year old.</td>
<td>Gill and Prasad 2008; Lenoir-Wijnkoop et al. 2007; Hawrelak 2006; Picard et al. 2005; Reid et al. 2003</td>
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<tr>
<td><strong>Duration of use</strong></td>
<td>No statement required.</td>
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<tr>
<td><strong>Storage conditions</strong></td>
<td>For all liquid products: Store in refrigerator in a tightly closed, light-resistant container.</td>
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| **Risk information**         | **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 (APA 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).  
- If a strain in the product possesses 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 a strain in the product has 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, a risk statement (CG 2011; HC 2009; HC 2003) 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. |
| **Non-medicinal ingredients**| Must be chosen from the current NHPD Natural Health Products Ingredients Database and must meet the limitations outlined in the 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 |
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.

A completed Finished Product Specifications form must accompany the product application.

The finished product must comply with the requirements of the current NHPD *Compendium of Monographs* guidance document which states that all aspects of manufacturing and preparing the product for sale, for example good manufacturing practices and labelling, must comply with the *Natural Health Product Regulations* (JC 2008). For more information, refer to the current guidance documents: *Evidence for Quality of Finished Natural Health Products*, the *Labelling Guidance Document*, the *Good Manufacturing Practices Guidance Document* and the *Product Licensing Guidance Document*.

In addition to the requirements in the *Compendium of Monographs*, the finished product must adhere to the following additional quality requirements:

- That the species designation of each strain in the product is current and accurate.
- That no strain harbours known virulence factors or is considered to be a pathogen in immunocompetent individuals.
- That no strain in the product possesses antibiotic resistance that is known to be transferrable.
- That all strains in the product are susceptible to therapeutic concentrations of at least two commercially available antimicrobial agents.
- That the strains as formulated in the final dosage form survive transit through the human gastrointestinal tract.
- That the total quantity of bacteria in Colony Forming Units (cfu) indicated on the product label is present in the product throughout the indicated shelf life when stored as directed.

The following documentation for each strain in the product must be maintained by the applicant or the manufacturer:

- An identification report from an internationally recognized culture collection.
- If the identification report above is greater than 12 months old, a recent attestation from the culture collection that the original species designation is still valid.
- A strain characterization report including data obtained using a

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<td>published, whole-genome sampling technique. The strain characterization report must also include any and all genotypic and phenotypic characteristics that are routinely used to distinguish the strain from others during manufacturing and in the finished product.</td>
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<tr>
<td>• If the strain designation has been issued by an internationally recognized culture collection, documentation from the culture collection that clearly links the strain in the product with the current manufacturer.</td>
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<tr>
<td>• 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).</td>
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<td>• 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.</td>
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<tr>
<td>• Results from <em>in vitro</em> testing for resistance to gastric acid and bile using published or internally verified methods.</td>
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<td>• Results from real-time stability testing using the storage conditions indicated on the product label.</td>
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<tr>
<td>• The full description and standard operating protocol (SOP) of an internally-verified assay that is used to routinely quantify the total of all strains in the product in Colony Forming Units (cfu).</td>
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</table>

Demonstrated resistance in *in vitro* testing to gastric acid and bile is considered to be reasonably predictive of survival in the human gut for the species listed above at the time of publication. Products or strains that are demonstrated to be unable to survive transit through the human gut by more reliable methods are not supported by this AbLS.

Living microorganisms consumed by humans must not harbour known virulence factors or be considered pathogens in immunocompetent individuals. The scientific principles of the EFSA’s *Qualified Presumption of Safety* process are valid and acceptable to the NHPD for this purpose. The species listed on this AbLS are currently given Qualified Presumption of Safety status by the EFSA (2010) and the safety of individual strains of these species is considered to be adequately supported provided they do not possess transferrable antibiotic resistance.

Information on the manufacturing process must be maintained and provided to Health Canada upon request. This information is expected to include product-specific details of all critical steps that may introduce significant variability in the identity, quantity or purity of the finished product. This information may be retained by licensees or maintained by a manufacturer; however the information must include all critical steps up to
and including the final dosage form.

Any or all of the documentation required by these specifications may be maintained by a manufacturer; however applicants are ultimately responsible for ensuring that this documentation is available prior to licensing.

1 See appendix 1 for full nomenclature.

References cited


Live microorganisms  Page 6 of 12


Farrow JAE, Collins MD. DNA base composition, DNA-DNA homology and long-chain fatty acid studies on Streptococcus thermophilus and Streptococcus salivarius. Microbiology 1984;130(2):357.


Fujisawa T, Benno Y, Yashima T, Mitsuoka T. Taxonomic study of the Lactobacillus acidophilus group, with recognition of Lactobacillus gallinarum sp. nov. and Lactobacillus johnsonii sp. nov. and synonymy of Lactobacillus acidophilus group A3 (Johnson et al. 1980) with the type strain of Lactobacillus amylovorus (Nakamura 1981). International Journal of Systematic and Evolutionary Microbiology 1992;42(3):487.


JCICSB 2008: Judicial Commission of the International Committee on Systematics of Bacteria. The type strain of Lactobacillus casei is ATCC 393, ATCC 334 cannot serve as the type because it represents a different taxon, the name Lactobacillus paracasei and its subspecies names are not rejected and the revival of the name 'Lactobacillus zeae' contravenes Rules 51b (1) and (2) of the International Code of Nomenclature of Bacteria. Opinion 82. International Journal of Systematic and Evolutionary Microbiology 2008;58(7):1764-1765.


References reviewed


Appendix 1  Nomenclature for medicinal ingredients
(NCBI 2009; Bisby et al. 2006; Skerman et al. 1989)

Bifidobacterium adolescentis Reuter 1963

Bifidobacterium animalis subsp. animalis (Mitsuoka 1969) Scardovi and Trovatelli 1974

Bifidobacterium animalis subsp. lactis (Meile et al. 1997) Masco et al. 2004

Bifidobacterium bifidum (Tissier 1900) Orla-Jensen 1924

Bifidobacterium breve Reuter 1963

Bifidobacterium longum subsp. infantis (Reuter 1963) Mattarelli et al. 2008

Bifidobacterium longum subsp. longum Reuter 1963

Lactobacillus acidophilus (Moro 1900) Hansen and Mocquot 1970

Lactobacillus amylovorus Nakamura 1981

Lactobacillus casei (Orla-Jensen 1916) Hansen and Lessel 1971

Lactobacillus delbrueckii subsp. delbrueckii (Leichmann 1896) Beijerinck 1901

Lactobacillus fermentum Beijerinck 1901

Lactobacillus gasseri Lauer and Kandler 1980

Lactobacillus johnsonii Fujisawa et al. 1992

Lactobacillus paracasei Collins et al. 1989

Lactobacillus plantarum (Orla-Jensen 1919) Bergey et al. 1923

Lactobacillus reuteri Kandler et al. 1982.

Lactobacillus rhamnosus (Hansen 1968) Collins et al. 1989

Lactobacillus salivarius Rogosa et al. 1953

Streptococcus salivarius subsp. thermophilus (Orla-Jensen 1919) Farrow and Collins 1984