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Product Licence Applications for Natural Health Products containing Probiotics

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The following information is intended to clarify some basic concepts that will help applicants in the preparation of Product Licence Applications for natural health products containing probiotics.

Definition of probiotic:

The Natural Health Products Directorate (NHPD) has adopted the internationally accepted Food and Agriculture Organization (FAO) / World Health Organization (WHO) (2006) definition of a probiotic: “live microorganisms which when administered in adequate amounts confer a health benefit to the host.” This includes probiotics that might confer a health benefit in humans by benefiting the microbiota indigenous to humans as in the *Natural Health Products Regulations* (NHPR).

Dosage form and the probiotics monograph:

Please note that the NHPD Probiotics Monograph (February 11, 2009) includes only natural health products in pharmaceutical dosage forms such as pills, capsules, or liquids measured in teaspoons or tablespoons. It excludes probiotics in food formats such as yogurts, cheeses, beverages, etc. Products with probiotics in food formats are subject to classification on a case by case basis in accordance with the Guidance Document on the Classification of Products at the Food–Natural Health Products Interface: Products in Food Formats (<http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/food-nhp-aliments-psn-guide-eng.php>).

The NHPD recommends that applicants review Health Canada’s recently published Guidance Document, “The Use of Probiotic Microorganisms in Food”, (http://www.hc-sc.gc.ca/fn-an/legislation/guide-ld/probiotics_guidance-orientation_probiotiques-eng.php) and the further guidance, “Accepted Claims about the Nature of Probiotic Microorganisms in Food” (http://www.hc-sc.gc.ca/fn-an/label-etiquet/claims-reclam/probiotics_claims-allegations_probiotiques-eng.php) for information regarding the use of probiotic health claims for foods. The purpose of these guidance documents is to clarify the acceptable use of health claims about microorganisms represented as “probiotics” on food labels and in advertising. It also provides guidance on the safety, quality (stability) and labelling aspects of food products containing probiotic microorganisms. These guidance documents are being used by the Canadian Food Inspection Agency (CFIA) to administer and assess compliance of food products containing probiotic microorganisms with the *Food and Drugs Act* and with the food provisions of the *Food and Drug Regulations*.

The difference between “species” and “strain”:

The NHPD has encountered many applications with probiotic ingredients that demonstrate confusion over the use of the term “species” and the term “strain”.

In the context of product licence assessment for probiotics, the term “species” refers to the combination of the Latin name for the genus of the organism (i.e. *Lactobacillus*) and the specific epithet (i.e. *acidophilus*) (see Chapter 4.3.1 of the Product Licence guidance document for additional information) for a complete species designation of *Lactobacillus acidophilus*. Note that in cases where probiotic activity has been demonstrated for a particular subspecies (i.e. *Lactobacillus animalis* subsp. *lactis*), the subspecies name is considered to be part of the species designation and thus the proper name of the medicinal ingredient.

The term “strain” is used to define a particular taxonomic isolate within the species. Evidence to support strain identification refers to characterization that distinguishes one particular isolate from another within the species. (i.e. strain *L. acidophilus* La1 has a characteristic profile that is different from strain *L. acidophilus* BAB1). The differences that designate one strain from another occur at both the phenotypic and genotypic level.

Further, applicants should be aware that a change in the strain is considered a fundamental change to the medicinal ingredients. Such a change would require resubmission of the product licence application.

The importance of including the strain indicator on the Product Licence Application form and proposed label:

The inclusion of a strain indicator (strain number) for each probiotic strain is essential information (see Chapter 4.3.6 of the Product Licensing guidance document) that must appear on both the Product Licence Application form and proposed label. The NHPD uses the presence of a strain indicator designation or number as a screening criterion for all bacterial ingredients. Therefore, Product Licence Application (PLA) forms missing a strain indicator in the source field for bacteria ingredients will be considered incomplete and subject to a Processing Deficiency Notice.

The strain indicator is used to ensure that any strain specific evidence provided matches the ingredient appearing in the formulation. In cases where the evidence provided does not match the strain indicator on the Product Licence Application (PLA) form, applicants should provide the NHPD with a rationale as to how the evidence is relevant to the application. Alternatively, the applicant can submit documents demonstrating that the strain for which a product licence is requested is identical to that in the evidence submitted. Any evidence provided to demonstrate the equivalence of any particular strain with another should be clearly outlined in a cover letter accompanying the application. Additional evidence supporting equivalency may be required (i.e. evidence comparing strain sequencing or documents to support strain origin).

Health Canada has always required that companies producing probiotic health products have strain identification information. For example, in the TPD “Labelling Standard: Intestinal Flora Modifiers” (1995) the following requirements are set out:

As a minimum, the manufacturer must have data available to support the identity, potency*, purity and quality of the product as follows:

* Note that the potency must reflect the number of viable organisms to which a consumer will be exposed upon consumption within the established timeframe to expiry.

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

ii) Details on the fermentation process such as information on the culture medium(s), pH, temperature, isolation techniques, etc.

iii) Appropriate finished product specifications such as information on the purity, safety of the product (including contaminants), potency, etc. The specifications for all dosage forms should include a description of the dosage form including organoleptic properties as well as physico-chemical testing e.g., pH, specific gravity, viscosity, appropriate to the dosage form.

Requirements for strain specific evidence:

A consistent conclusion of scientific evidence available on probiotics is that the strain of the microorganism is important since within any one species there is genetic diversity and not all strains of a given species have probiotic activity.

Similarly, the safety profile for a strain may be strain-specific and, therefore, the safety assessment conducted by the Natural Health Products Directorate for probiotic products will include evaluation of the safety of the strain, in addition to the safety of the species. Failure to provide strain-level evidence will be considered a deficiency which will result in the refusal to issue a product licence. As per Chapter 5 of the Evidence for Safety and Efficacy of Finished Natural Health Products guidance document, evidence¹ to support the efficacy of at least one of the probiotic strains in the natural health product according to the recommended conditions of use is required (i.e. to support the daily dose, sub-population, route of administration and dosage form). For claims implying a measurable health benefit, primary evidence must come from strain specific, scientific studies in humans. Furthermore, applicants must provide sufficient strain specific evidence to support the safety of each strain. Evidence from *in vitro* and animal studies is considered supportive but not sufficient without human evidence. Market history may be supportive human evidence where related specifically to the product under assessment. Further information on the requirements for safety and efficacy evidence for probiotics can be found in Chapter 7 of the Evidence for Safety and Efficacy of Finished Natural Health Products guidance document.

¹ Copies of full-text scientific articles of studies conducted in humans are required.



Requirement for counts in colony forming units:

Applicants must present the viable counts of probiotic microorganisms in the product (as obtained by appropriate methodology) in colony forming units (CFU) in the quantity field on the Product Licence Application form and proposed label. Provision of quantities in “milligrams” or “teaspoonfuls” only is insufficient and may result in the rejection of an application. When a combined count can be justified by the evidence provided, the applicant can include the blend as a mixture on the PLA form. Full proper names as well as full strain indicators should be indicated in the source description while the quantity/dosage unit can be represented as a combined count in CFU. The quantity intended is the guaranteed quantity that will be available to the consumer over the shelf-life of the product and under the recommended conditions of use for the product. The quantity in CFU required for product efficacy should be the label claim. The number of viable organisms as per the label claim must be present in the product at the end of the expiry period (allowing for analytical error).

Declaration of non-medicinal ingredients:

All non-medicinal ingredients present in the finished product in any significant quantity (i.e. including cryoprotectants and raw material fermentation ingredients) must be listed on the PLA form and in the proposed label text. Applicants should work with the raw material manufacturer to determine which fermentation ingredients or other ingredients such as stabilizers, should be declared in the finished product and thus ensure that any label statements regarding the absence of allergens can be adequately supported.

Citation of the TPD Labelling Standard for Intestinal Flora Modifiers (1995):

The TPD Labelling Standard for Intestinal Flora Modifiers (TPD, 1995) is no longer accepted as sufficient evidence to support the recommended purpose or use “For restoring and/or normalizing and/or stabilizing the intestinal flora”. It is expected that such claims will be supported by strain specific evidence in humans showing a significant beneficial effect on the microfloral populations of the intestine. To expedite the licensing process, applicants may refer to the NHPD monograph for Probiotics (http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_probioti-eng.php) which has replaced the TPD labeling standard.