

## Criteria for adding Substances to the List of Substances

This document is intended to provide information on the criteria that need to be met for any substance to be added to the List of Substances (*The List*). *The List* is a list of substances that are acceptable in a Low Risk Veterinary Health Product (LRVHP) intended for use in cats, dogs and horse not intended for food under the Interim Notification program (INP).

LRVHP can contain two different types of ingredients: active (medicinal) and inactive (non-medicinal, excipient) substances. An active substance is a substance known to contribute to the LRVHP health claim and its contribution is supported by adequate scientific evidence. An inactive substance is a substance added to a LRVHP formulation to confer suitability or form to the active ingredients. They may include, but are not limited to, binders, lubricants, preservatives, antioxidants, colouring agents, fragrances and flavours. In some cases substances may have both active and inactive properties depending on the level at which it is included in the LRVHP (e.g. peppermint oil may act as a flavour enhancer, but at higher doses may have an effect on digestion).

A veterinary health product is considered low risk if certain requirements are met. One of the requirements is that ingredients in the product are not expected to present a significant risk to the animal to which the product is administered. Ingredients that meet this requirement are added to the List. In some cases ingredients have qualifications associated with them to mitigate risk, e.g. some substances should not be used in certain species or subpopulations or they only meet the criteria when used as an inactive ingredient. Admissible inactive substances are not expected to result in adverse events in the animal under the intended conditions of use (eg, as a flavouring, binder, etc.) and when the quantity in the LRVHP does not exceed the amount reasonably required to accomplish its intended effect.

In general, a substance can be added to the List if the following criteria have been met:

1. The substance can be identified using existing nomenclature
2. The substance has sufficient history of use in a particular species for a particular purpose in the literature to provide adequate assurance that any potential adverse effect in humans or animals is understood and predictable
3. The substance is only infrequently responsible for the occurrence of mild transient adverse events, and if so, the adverse event is understood and predictable so that qualifications can be attached to its use
4. There is sufficient data to assess risks that are potentially dangerous and the risks are not considered unacceptable when taking into account the risk mitigation measures, precautions and contraindications.

If sufficient safety data is not available to assess the risk, but no immediate risk can be identified, the substance will not be added to the List until new information becomes available.

The following information describes the process of determining the appropriateness of adding an ingredient to the List and the conditions in which they can be used as well as resources that can be referred to:

### **Identification of the substance**

Proper identification of the substance is essential (ex Latin binomial name of each plant material).

Helpful websites:

- NHPD Product Ingredient Database: <http://webprod.hc-sc.gc.ca/nhpid-bdipsn/search-rechercheReq.do> )
- GRIN Taxonomy for plants: [http://www.ars-grin.gov/cgi-bin/npgs/html/tax\\_search.pl?](http://www.ars-grin.gov/cgi-bin/npgs/html/tax_search.pl?)

- Enzymes: [http://ca.expasy.org/enzyme/enzyme\\_details.html](http://ca.expasy.org/enzyme/enzyme_details.html)
- For other substances: <http://www.chem.qmul.ac.uk/iupac/>  
<http://chem.sis.nlm.nih.gov/chemidplus/>

For probiotics :

The proper name should include the species name (i.e. *Lactobacillus*), the specific epithet (i.e. *acidophilus*), subspecies if applicable ( i.e. *Lactobacillus animalis* subs *lactis*) and the strain (i.e. *L. acidophilus* BAB1)

### **Verification of eligibility exclusion**

Verification if any of the ingredients is a Controlled or Scheduled substance. For more information see <http://laws.justice.gc.ca/en/F-27/>.

They include substances listed on:

- Schedule I to V of the *Controlled Drugs and Substances Act*,
- Schedule C (radiopharmaceuticals) of the *Food and Drugs Act*,
- Biological substances, including those obtained by DNA procedures, except for
  - substances prepared from algae, bacteria or fungi,
  - substances used in acceptable homeopathic preparations, and
- Part 1 of Schedule F (prescription drugs) of the *Food and Drugs Regulations* except substances used in acceptable homeopathic preparations.

Verification that the ingredient is not considered a Specific Risk Material (SRM) as defined in the *Feeds Regulations* (i.e. the skull, brain, trigeminal ganglia, eyes, tonsils, spinal cord and dorsal root ganglia of cattle aged 30 months or older, and the distal ileum of cattle of all ages).

Verification of the List of Substances for substances already determined to be non-admissible (tagged NON). These substances have been determined to present an unacceptable health risk and/or requiring a higher level of oversight when administered to animals (with the exception of certain homeopathic preparations). These substances may have the potential risk of causing irreversible damage, potentially lethal, toxicity to major organs, carcinogenic activity, teratogenic activity, abortifacient activity, a narrow margin of safety, the likelihood of contamination, adulteration, and/or substitution.

### **Gathering of safety information**

This may include safety information obtained from evidence based reference texts, peer-reviewed published papers, websites evaluating peer-reviewed evidence, well designed analytical studies preferable from more than one centre or research group, and adverse event databases. Status classification by other jurisdictions or authorities, such as published lists of generally recognized as safe (GRAS) can also be included. Table 1 below provides examples of resources that are used for safety information for substances.

**Table 1.**

<b>Product Status in Canada and other jurisdictions</b>	
Is the substance is considered an acceptable feed ingredient in Canada?	<a href="http://laws-lois.justice.gc.ca/eng/regulations/SOR-83-593/page-16.html">http://laws-lois.justice.gc.ca/eng/regulations/SOR-83-593/page-16.html</a> <a href="http://www.inspection.gc.ca/english/anima/feebet/feebete.shtml">http://www.inspection.gc.ca/english/anima/feebet/feebete.shtml</a>
Is the substance a permitted food additive in Canada?	<a href="http://www.hc-sc.gc.ca/fn-an/securit/addit/diction/dict_food-alim_add-eng.php">http://www.hc-sc.gc.ca/fn-an/securit/addit/diction/dict_food-alim_add-eng.php</a>
Is the substance on the Canadian Cosmetic Hot List?	<a href="http://www.hc-sc.gc.ca/cps-spc/person/cosmet/info-ind-prof/hot-list-critique/prohibited-eng.php">http://www.hc-sc.gc.ca/cps-spc/person/cosmet/info-ind-prof/hot-list-critique/prohibited-eng.php</a>
Is the substance considered GRAS (generally recognized as safe) in animal feed in the US?	<a href="http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=582">http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=582</a> <a href="http://www.cfsan.fda.gov/~rdb/opa-gras.html">http://www.cfsan.fda.gov/~rdb/opa-gras.html</a>
Is the substance on the list of EAFUS (Everything Added to Food in the US)	<a href="http://www.fda.gov/Food/FoodIngredientsPackaging/ucm115326.htm">http://www.fda.gov/Food/FoodIngredientsPackaging/ucm115326.htm</a>
How is the substance categorized by the American Herbal Product Association?	<a href="http://www.ahpa.org/">http://www.ahpa.org/</a>
Is the substance exempt from tolerance studies by the EPA?	<a href="http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&amp;tpl=/ecfrbrowse/Title40/40cfr180_main_02.tpl">http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&amp;tpl=/ecfrbrowse/Title40/40cfr180_main_02.tpl</a>
Is the substance considered safe as a food additive in the EU? Does it have an E-Number?	European Food Information Council <a href="http://www.eufic.org/article/en/food-safety-quality/food-additives/expid/basics-food-additives/">http://www.eufic.org/article/en/food-safety-quality/food-additives/expid/basics-food-additives/</a>
Is the substance listed on the EFSA Compendium of botanicals that have been reported to contain toxic, addictive, psychotropic or other substances of concern?	<a href="http://www.efsa.europa.eu/en/scdocs/scdoc/280r.htm">http://www.efsa.europa.eu/en/scdocs/scdoc/280r.htm</a>
Is the substance on the GSL (general sale list) in the UK?	<a href="http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Legalstatusandclassification/Listsofsubstances/index.htm">http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Legalstatusandclassification/Listsofsubstances/index.htm</a>
Is the substance on the list of Listed Medicines in Australia?	<a href="http://www.tga.gov.au/industry/cm-listed-substances.htm">http://www.tga.gov.au/industry/cm-listed-substances.htm</a>
Is the substance considered GRAS in New Zealand?	GRAS register for Oral Nutritional Compounds: <a href="http://www.foodsafety.govt.nz/elibrary/industry/gras/index.htm">http://www.foodsafety.govt.nz/elibrary/industry/gras/index.htm</a>
Is the substance considered GRAS in Australia?	<a href="http://www.legislation.govt.nz/regulation/public/2001/0101/lates_t/whole.html?search=ts_regulation_Agricultural+compounds+and+veterinary+medicines+regulation_s_resel#DLM28471">http://www.legislation.govt.nz/regulation/public/2001/0101/lates_t/whole.html?search=ts_regulation_Agricultural+compounds+and+veterinary+medicines+regulation_s_resel#DLM28471</a>
<b>Safety profile according to</b>	

A Modern Herbal by M. Grieve, 1971	<a href="http://www.botanical.com/botanical/mgmh/mgmh.html">http://www.botanical.com/botanical/mgmh/mgmh.html</a>
American Botanical Council	<a href="http://abc.herbalgram.org/site/PageServer?pagename=Herbal_Library">http://abc.herbalgram.org/site/PageServer?pagename=Herbal_Library</a>
Complementary and Alternative Veterinary Medicine: Principles and Practice, Schoen & Wynn, 1998	
Drug Information on line: MedFacts Natural products	<a href="http://www.drugs.com/npc/">http://www.drugs.com/npc/</a>
EFSA: Study on the Assessment of Plants/Herbs, plant/Herb extract and their natural or synthetically produced components as "additives" for use in Animal Production	<a href="http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902675030.htm">http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902675030.htm</a>
Encyclopedia of Common Natural Ingredients used in food, drugs and cosmetics, 2 <sup>nd</sup> Ed, Foster, Leung, 2003	
ESCOP Monographs European Scientific Cooperative On Phytotherapy 2 <sup>nd</sup> Ed, 2003	
Handbook of Medicinal Herbs, 2 <sup>nd</sup> Ed by Duke, 2002	
Health Library	<a href="http://healthlibrary.epnet.com/GetContent.aspx?token=e0498803-7f62-4563-8d47-5fe33da65dd4&amp;chunkid=33802">http://healthlibrary.epnet.com/GetContent.aspx?token=e0498803-7f62-4563-8d47-5fe33da65dd4&amp;chunkid=33802</a>
Herb Contraindications and Drug Interactions, Brinker, 2001	
Herbal drugs and Phytopharmaceuticals. A Handbook for Practice on a Scientific Basis. 3 <sup>rd</sup> Ed. Wichtl, 2004	
Herbal Medicines: A Guide for Health Care Professionals, 2 <sup>nd</sup> Ed, Barnes 2002	
Herbal-Drug Interactions and Adverse Effects: An Evidence-based Quick Reference Guide, Philp, 2003	
International Bibliographic Information on Dietary Supplements database (IBIDs)	<a href="http://ods.od.nih.gov/Health_Information/IBIDS.aspx">http://ods.od.nih.gov/Health_Information/IBIDS.aspx</a>
Mosby's Handbook of Herbs & Natural Supplements 4 <sup>th</sup> Ed, 2010	
National institutes of Health: National center for Complementary and Alternative Medicine (NCCAM)	<a href="http://nccam.nih.gov/health/herbsataglance.htm">http://nccam.nih.gov/health/herbsataglance.htm</a>
National Animal Supplement Council (US)	<a href="http://www.nasc.cc/">http://www.nasc.cc/</a>
Natural Medicine Comprehensive Database (NMCD)	<a href="http://www.naturaldatabase.com/(S(njsoneruddi5mz55twbgj445))/home.aspx?cs=&amp;st=1&amp;li=0&amp;referer=EUPDATEPR200701&amp;s=ND">http://www.naturaldatabase.com/(S(njsoneruddi5mz55twbgj445))/home.aspx?cs=&amp;st=1&amp;li=0&amp;referer=EUPDATEPR200701&amp;s=ND</a>
Natural Standard	<a href="http://www.naturalstandard.com/">http://www.naturalstandard.com/</a>
PDR for Herbal Medicines 3 <sup>rd</sup> Ed, 2004	
PDR for Nutritional Supplements 1 <sup>st</sup> Ed, 2001	
Physicians Desk Reference for Herbal Medicines 3 <sup>rd</sup> , 2004	
Practice and Principles of Phytotherapy, Modern Herbal Medicine, Mills & Bone, 2000	
The Complete German Commission E Monographs: Therapeutic Guide to herbal Medicines, The American Botanical Council, Blumenthal, 1998	
Toxnet (National Library of Medicine)	<a href="http://toxnet.nlm.nih.gov/index.html">http://toxnet.nlm.nih.gov/index.html</a>
The Consumer's Guide to Herbal Medicine, Karch (1999)	
Treating Dairy Cows Naturally, Hubert Karreman, 2007	
Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies, Tyler & Foster, 1999	
Veterinary Herbal Medicine, Wynn & Fougere, 2007	

<b>Other Websites searches</b>	
<b>International</b>	
Google	<a href="http://www.google.ca/">http://www.google.ca/</a>
MedlinePlus	<a href="http://www.nlm.nih.gov/medlineplus/medlineplus.html">http://www.nlm.nih.gov/medlineplus/medlineplus.html</a>
Medscape	<a href="http://www.medscape.com/medscapetoday">http://www.medscape.com/medscapetoday</a>
Pub Med	<a href="http://www.ncbi.nlm.nih.gov/entrez/query.fcgi">http://www.ncbi.nlm.nih.gov/entrez/query.fcgi</a>
Scholar Google	<a href="http://scholar.google.com/">http://scholar.google.com/</a>
Veterinary Information Network	<a href="http://www.vin.com/Members/">http://www.vin.com/Members/</a>
Veterinary Information Services (IVIS)	<a href="http://www.ivis.org/home.asp">http://www.ivis.org/home.asp</a>
Vitasearch:	<a href="http://www.vitasearch.com/">http://www.vitasearch.com/</a>
<b>Canada</b>	
Compendium of Veterinary Products	<a href="http://www.naccvp.com">http://www.naccvp.com</a>
Drug Product Database	<a href="http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php">http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php</a>
NHPD Product Ingredient Database	<a href="http://webprod.hc-sc.gc.ca/nhp-id-bdipn/search-rechercheReq.do">http://webprod.hc-sc.gc.ca/nhp-id-bdipn/search-rechercheReq.do</a>
<b>United States</b>	
Compendium of Veterinary products	<a href="http://www.naccvp.com">http://www.naccvp.com</a>
National Library of Medicine	<a href="http://chem.sis.nlm.nih.gov/chemidplus/">http://chem.sis.nlm.nih.gov/chemidplus/</a>
Toxicology	<a href="http://extoxnet.orst.edu/">http://extoxnet.orst.edu/</a>