

**New substances proposed for expedited evaluation or risk assessment:
Responses from member consultation**

CMA has long advocated for a streamlining of new substance applications for use in listed medicines in Australia. We are active in working with the TGA in the review of business processes for complementary medicines, with the aim of gaining efficiencies within current legislation for new substance applications and registered complementary medicines applications.

In the CMA response to the Government's de-regulation agenda, we recommended the TGA streamline the evaluation of new substances for use as permitted ingredients for listed medicines. This may be achieved by information sharing with regulatory counterparts, for example the outcomes of evaluation reports produced by Health Canada.

We have been working to put forward a list of potential new substances that may be subject to an expedited evaluation or risk assessment, including potential substances approved by Health Canada and or where substances have been subject to previous TGA review.

Previous proposals for ingredients have been put forward that would require consideration of the scheduling status of the substance and consideration of indications suitable for use in listed medicines (e.g. melatonin and DHEA are Schedule 4 (prescription only medicines). Other suggestions have included substances that have previously been considered by the TGA and determined not suitable for use in listed medicines (e.g. L-tryptophan - CMEC Meeting 28, 27 July 2001).

Instead, it was suggested that ingredients that have been approved by other comparable regulators could be used as a source for expedited approval in Australia. TGA provided a recent example of this with the approval of *Garcinia cambogia* based of information from Health Canada and TGA internal information.

The purpose of this draft list was to provide industry with a list of evaluations and risk assessments completed by or pending completion by the TGA and a list of substances that could be considered to be suitable for an expedited evaluation or risk assessment. In anticipation of future work, CMA sought industry feedback on the draft list, specifically any advice in relation to the prioritisation of these substances (see table 1).

The following TGA draft document provides some guidance on the [potential information sources to support expedited new substance evaluations](#).

Note: Where the list of substances refers to Health Canada monographs, they are herbal. Nutritional appear as "HC available"; # - proposed for inclusion by CMA.
Pre-cleared information (PCI) is any form of information supporting the safety, efficacy or quality of a medicinal ingredient or natural health product that NHPD has reviewed and determined to be acceptable. PCI can be used to speed up the evaluation of the NHP, and serves as a reliable source of product information for consumers.

Table 1		
Proposed ingredient	Known regulatory status	Comments / additional information
Betaine hydrochloride #	<p>Health Canada available, initial TGA review.</p> <p>TGA: Betaine hydrochloride was "grandfathered" onto the register for use in listed medicines as an excipient, which is supported by a USP monograph ensuring a minimal quality standard for this ingredient.</p> <p>Canada: Monograph: Betaine / Betaine Hydrochloride - Under Consultation. Classified as an NHP under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations.</p>	<p>Orally, betaine hydrochloride is used as a supplemental source of hydrochloric acid, used to help support digestion / digestive aid and as a liver protectant.</p>
Calcium and magnesium pyruvate	<p>Initial TGA review</p> <p>Canada: Calcium pyruvate is classified as an NHP, because it is used as a source of Calcium and Pyruvic acid, and therefore is considered an NHP under Schedule 1, item 2 (an isolate), of the Natural Health Products Regulations.</p>	<p>Orally, pyruvate is used for weight loss and obesity, improving athletic performance, etc.</p>
Chrysin	<p>Initial TGA review</p>	<p>Chrysin is a flavonoid commonly extracted from passion flower (<i>Passiflora incarnata</i>) and occurs naturally in other botanicals. Chrysin is a member of the flavone subclass of flavonoids. Flavonoids as a group are widely present in plants, including fruits and vegetables. They serve primarily as pigments and may have antimicrobial properties. Flavonoids are biologically active, though generally with less prodigious effects than alkaloids.</p>
d-ribose #	<p>Health Canada available, Initial TGA review</p> <p>Canada: Classified as an NHP under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations.</p> <p>FSANZ – non-traditional, novel food. Safety no established for proposed pattern and level of use.</p>	<p>Ribose- (D-ribosa, D-ribose, Ribosaa) – could be indicated for use in listed medicines for indications around athletic performance generally.</p>
Grifola frondosa (whole plant aqueous ethanol extract) Maitake Mushroom	<p>Initial TGA review</p> <p>Canada: Classified as an NHP under Schedule 1 item 1 (fungus) of the NHP Regulations. Maitake - Grifola frondosa (under consultation) available here,</p>	<p>Used in Herbal Medicine to support the immune system.</p>

Table 1		
Proposed ingredient	Known regulatory status	Comments / additional information
	Pre-cleared information.	
Kunzea ericoides (Manuka oil) essential oil – topical use only	Initial TGA review	Attention has been given to the antiseptic and antimicrobial actions of the essential oil.
Methylcobalamin #	Initial TGA review TGA allow this substance to be used as an Active ingredient for Export Only; Over The Counter; Prescription Medicines; Biologicals. It can be used as an Excipient ingredient for Prescription Medicines; Devices; Biologicals.	Classified as an NHP under Schedule 1, item 3 (a vitamin) of the Natural Health Products Regulations (the active form of vitamin B12).
Methylfolate (5MHF) # 5-Methyltetrahydrofolate	Health Canada available here , Classified as a Natural Health Product in Canada (active, natural form of folate). Proper names - L-Glutamic acid Initial TGA review	
N-Acetyl-L-cysteine (NAC) #	Health Canada (under consultation) available here , Pre-cleared information Initial TGA review In Australia N-Acetyl-L-cysteine is a derivative of the amino acid L-cysteine. It is restricted to topical use only in Listed Medicines, but can be used as an active ingredient for Biologicals; Export Only; Over The Counter; and Prescription Medicines. N-Acetyl-L-cysteine can also be used as an excipient ingredient for Listed Medicines and Prescription Medicines.	Statement of purpose- provides antioxidants.
Grape seed extract	Health Canada monograph available here .	<i>Vitis vinifera</i> (grape)' is already available for use in listed medicines as long as it meets the definition of a herbal substance. TGA wish to clarify that this includes extract of grape seed, and the dry/powdered seeds from grapes.
Acai (Euterpe oleracea)	Health Canada monograph available here Pre-cleared information FSANZ- not novel food, non-traditional. No safety concerns identified.	Açaí (acai) is a berry grown on the açai palm tree (Euterpe oleracea), which is native to tropical Central and South America. Orally, acai is used for osteoarthritis, weight loss, detoxification, aging skin, metabolic syndrome, and for improving general health (antioxidant).

Table 1		
Proposed ingredient	Known regulatory status	Comments / additional information
Deglycyrrhizinated Licorice – buccal	Health Canada monograph available here Pre-cleared information	
Bitter Fennel (Foeniculum vulgare subsp. Vulgare var. vulgare)	Health Canada monograph available here Pre-cleared information	

Industry prioritisation of ingredients at table 1:

Response from members has indicated the prioritisation of the above substances as follows:

1. Methylfolate (5MTHF)
2. Methylcobalamin
3. N-Acetyl-L-Cysteine (NAC)
4. Betaine hydrochloride (including entire digestive enzyme monograph)
5. d-Ribose
6. Grifola frondosa
7. Kunzea ericoides (Manuka oil) Essential Oil
8. Any order thereafter

Other ingredients proposed by industry for inclusion to the list of potential substances for expedited evaluation (Table 2):

Table 2: Other ingredients proposed by industry	Known regulatory status	Comments/additional information
Digestive Enzymes	Adoption of the full digestive enzyme monograph pre-cleared by Health Canada.	
Cognitive function	Adoption of the full cognitive function monograph pre-cleared (under consultation) by Health Canada	
5-Hydroxytryptophan	TGA: Tryptophan is currently specifically excluded from use in listed medicines – refer CMEC 28. Qld Only available See note on L-tryptophan above. Canada:	5-HTP is the intermediate metabolite of the essential amino acid L-tryptophan in the biosynthesis of serotonin. 5-Hydroxytryptophan is derived from <i>Griffonia simplicifolia</i> .

<p>Also known as: Butterfly Enzyme, Enzyme de Ver de Soie, Extrait de Ver de Soie, SER, Serrapeptidase, Serratiopeptidase, Silk Worm Enzyme, Silkworm Extract</p>	<p>Canada - Serrapeptase - Under consultation . Pre-cleared information</p>	<p>inflammatory, antiedemic, and fibrinolytic effect.</p> <p>Effectiveness – found possibly effective for Post-operative swelling, considered insufficient reliable evidence to rate its use for other conditions.</p> <p>Orally, serrapeptase is used for back pain, osteoarthritis, rheumatoid arthritis, osteoporosis, carpal tunnel syndrome, sinusitis, laryngitis, pharyngitis, diabetes, leg ulcers, migraine headache, tension headache, asthma, fibromyalgia, cardiovascular disease, post-operative swelling, and otitis media.³</p>
<p>Melatonin</p>	<p>TGA: Schedule 4 prescription only medicine. Only unscheduled substances are eligible for listing.</p> <p>Canada: Classified as an NHP under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations. Melatonin monograph available. Pre-cleared information</p>	<p>AU: Indications/Claims. TGA guidance on potential restricted representations – sleeplessness is not a RR, cannot refer to insomnia.</p> <p>Canada: Statement of purpose - helps increase the total sleep time in people suffering from sleep restriction or altered sleep schedule (e.g. shift-work and jet lag). Helps to prevent and/or reduce the effects of jet lag. Helps to reduce the time it takes to fall asleep in people with delayed sleep phase disorder. Helps re-set the body's sleep-wake cycle.</p>
<p>Hyaluronic acid (Glycoaminoglycan)</p>	<p>Canada: Classified as an NHP under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations. Hyaluronic acid/Sodium hyaluronate obtained from <i>Gallus gallus</i>. Sodium hyaluronate obtained from the extracellular capsule of <i>Streptococcus</i>,</p> <p>Approved by the FDA for treatment of osteoarthritis by intra-articular injection.</p> <p>TGA - Serious forms of osteoarthritis may be excluded by including “mild”, “minor” or words to that effect. Must be medically uncomplicated</p>	<p>Hyaluronic acid is a naturally occurring polysaccharide that belongs to the glycosaminoglycan family and consists of a basic unit of two sugars, glucuronic acid and N-acetyl-glucosamine. It is an important component of articular (joint) cartilage, where it is present as a coat around each cell (chondrocyte).</p> <p>Orally, hyaluronic acid is used for various joint disorders, including osteoarthritis and preventing the effects of aging. Topically, hyaluronic acid is used for healing wounds, burns, skin ulcers, stomatitis, and moisturizing the skin</p> <p>Considered possibly effective for osteoarthritis and aging skin⁴.</p>
<p>Calcium malate</p>	<p>Form not currently approved for use in listed medicines</p>	<p>Different from calcium citrate malate Calcium salt of malic acid. As a food additive, it has</p>

³ Natural Medicines – professional monographs - accessed 110215

⁴ Natural Medicines – professional monograph Hyaluronic acid – accessed 110215

		the E number E352.
Magnesium malate	<p>TGA: Form not currently approved for use in listed medicines.</p> <p>Canada: Magnesium malate is classified as an NHP, because it is used as a source of Magnesium, and therefore is considered an NHP under Schedule 1, item 7 (a mineral), of the Natural Health Products Regulations.</p>	
l-Threonine	<p>TGA – Threonine (syn L-Threonine) approved as A, E for listed medicines. DL- Threonine approved as A, E in listed medicines.</p> <p>Canada - Classified as an NHP under Schedule 1, item 4 (an amino acid) of the Natural Health Products Regulations. As per Natural Health Products Ingredients database. Workout supplements monograph available.</p>	<p>Threonine is a large, neutral, essential amino acid that is a precursor of the amino acids glycine and serine in the human body. L-threonine is found in collagen, elastin, and enamel proteins, and in the heart, skeletal muscles, and central nervous system. Active isomer is the L-form.</p>
d-mannose	<p>TGA: sodium mannose phosphate (syn d-mannose) is restricted to dermal use only. Can be used as an active ingredient for prescription medicines. Can be used as an excipient ingredient in OTC, Export only and Listed medicines.</p> <p>FSANZ: non-traditional, novel food. Safety not established for proposed pattern and level of use.</p> <p>Canada: Classified as an NHP under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations</p> <p>US - dietary supplement.</p>	<p>D-mannose is a 6-carbon sugar and an isomer of dextrose. Orally, d-mannose is used for urinary tract infections (UTIs). Supplemental d-mannose is well absorbed from the gastrointestinal tract⁵</p>
Beta-alanine (3-aminopropanoic acid)	<p>TGA: Can be used as an active ingredient in prescription medicines</p> <p>Canada: Classified as an NHP under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations. Workout supplements monograph available.</p>	<p>Beta-alanine is a beta-amino acid. Orally, beta-alanine is used for improving athletic performance and exercise capacity, building lean muscle mass, and improving physical functioning in the elderly.³</p>
Beta-glucan	<p>TGA: for dermal use only in listed medicines and OTC. Active ingredient for prescription medicines, excipient for listed, EO, OTC, prescription.</p> <p>Canada: Classified as an NHP under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations. Pre cleared information available</p>	<p>Beta-glucan is a soluble fiber derived from the cell walls of algae, bacteria, fungi, yeast, and plants. As a type of dietary fiber, it constitutes an edible plant part that is resistant to digestion and intestinal absorption. Statement of purpose: Helps reduce/lower (LDL) cholesterol, Provides support for healthy (postprandial) glucose metabolism, source of dietary fiber to help support and</p>

⁵ Natural Medicines – professional monograph d-mannose – accessed 110215

	here.	maintain a healthy digestive system, Helps support and maintain a healthy digestive system
Fulvic acid	Canada: Classified as an NHP under Schedule 1, item 2 (an isolate) of the Natural Health Products Regulations	Fulvic acid is defined as a “humic substance,” meaning that it is a major component of organic matter.
<i>Streptococcus salivarius</i> K12	TGA: <i>S.salivarius</i> K12 is considered highly related to <i>S.thermophilus</i> , an ingredient that is approved as an active in Listed medicines. FSANZ – traditional, not novel food. Already used as an ingredient in the food industry in Australia and New Zealand. It has been approved for use in foods and dietary supplements/health products in a number of other international markets. Canada: Classified as an NHP under Schedule 1 item 1 (bacterium) of the NHP Regulations.	A separate application in support of this substance will be included in CMA’s formal response to TGA.
Chitosan from <i>Aspergillus niger</i>	Chitosan from <i>Deacetylchitin Poliglusam</i> approved for use in listed medicines.	
Docosahexaenoic acid # (DHA) 3 - rich oil derived from microalgae <i>Ulkenia</i> sp.	FSANZ approved as a novel food in 2005. Docosahexaenoic acid (DHA) - rich oil derived from microalgae <i>Schizochytrium</i> sp. is approved as an active for listed medicines in AU.	
3,3'-Diindolymethane (DIM)	Health Canada monograph available here. Pre cleared information	Health Canada Statement of purpose: Source of/Provides antioxidants. Helps to support/promote healthy estrogen metabolism/balance
<i>Pelargonium sidoides</i>	Registered CM in 2011 for the treatment of acute bronchitis and acute sinusitis. EMA available. In the instance when an ingredient is only in use in registered CMs and is proposed for use in listed medicine, the TGA advise that ingredients used in registered medicines have only been considered in the context of a particular medicine. This is very different to the listed medicine context where very broad safety and quality considerations have to be made for a proposed ingredient. Therefore, the TGA expressed that there is no simplified or expedited route expected for existing registered medicine ingredients if they were to be proposed for the	New substance application would need to be provided to the TGA.

	<p>listed medicine framework, unless they meet category 1 or 2 criteria of the BPR framework (attached).</p> <p>(TGA BPR meeting 25 February 2015)</p>	
Red Rice Yeast	<p>TGA: CMEC recommends to the TGA that red yeast rice is not suitable for use as an active ingredient in listable therapeutic goods as the safety associated with its use in these goods could not be established on the evidence provided to the Committee (CMEC Meeting 34, 3 May 2002)</p> <p>US FDA available.</p>	Revised evidence would need to be provided to the TGA based on past CMEC decision.
<p>African mango</p> <p><i>Irvingia gabonensis</i>, synonyms <i>Irvingia barteri</i>, <i>Mangifera gabonensi</i></p>	<p>Health Canada available. Pre cleared information available here.</p>	<p>Orally, <i>Irvingia gabonensis</i> is used for obesity and weight loss, hyperlipidemia, diabetes, and pain.</p> <p>Health Canada statement of purpose.</p> <ul style="list-style-type: none"> • Could be a complement to a healthy lifestyle that incorporates a calorie-reduced diet and regular physical activity for individuals involved in a weight management program • Helps support healthy cholesterol levels/Helps support cardiovascular health by reducing total and LDL cholesterol • Helps support healthy glucose levels
L-Arginine	<p>TGA: Arginine (syn L-Arginine) can be used as an active ingredient in prescription, listed and EO.</p> <p>CMEC 21 considered the safety of oral l-arginine and recommended to the TGA that it was not suitable for inclusion in listed therapeutic goods intended for oral ingestion.</p> <p>CMEC 34 recommended to the TGA that L-arginine is suitable for use as an active ingredient for use in listable therapeutic goods, with the condition that it is for topical application only, and not for mucosal, vaginal or rectal use. (CMEC Meeting 34, 3 May 2002)</p> <p>Health Canada: available pre-cleared information (Workout supplements)</p>	<p>Proposed for use in listed medicines due to l-arginine role in supporting health blood flow. Other use for L-arginine have been indicated for its perceived benefit with regard to growth, sexual function, cardiovascular and immune function.</p> <p>Health Canada statement of purpose:</p> <ul style="list-style-type: none"> • May help support a modest improvement in exercise capacity in individuals with stable cardiovascular diseases (CVD). • L-Arginine is a non-essential amino acid that is involved in protein

		synthesis.
Conjugated linoleic acid CLA	<p>TGA: Conjugated linoleic acid 75% approved for use as in active in listed medicines, EO, prescription and OTC. Conjugated linoleic acid 80% triglycerides- approved for use as an active in Export Only (EO).</p> <p>Health Canada: available pre-cleared monograph information here.</p>	<p>Health Canada statement of purpose</p> <ul style="list-style-type: none"> • May help to support a modest improvement to body composition when used with a program of reduced intake of dietary calories and increased physical activity. • May help to support a modest reduction in fat mass when used with a program of reduced intake of dietary calories and increased physical activity.
<p>Maca</p> <p><i>Lepidium meyenii</i></p>	<p>TGA: approved for use as an active ingredient in Export only, solely for export</p> <p>New substance evaluation tabled at ACCM meeting 7 2011</p> <p>Application was initially submitted to the TGA in 2008, but was rejected for evaluation at this time due to insufficient information being provided. In 2009 a supplemented data package was accepted for evaluation. This current application has been the subject of numerous requests for additional information and the applicant's last response was received in June 2011.</p> <p>The TGA noted that after four rounds of evaluation of the chemistry, manufacturing and quality control data, a number of critical issues remain unresolved. The TGA proposed that the application for evaluation of 'pregelatinised <i>Lepidium meyenii</i> root powder' be rejected as the applicant has been given ample opportunity to address outstanding issues, but this has not been achieved.</p> <p>ACCM advises the TGA that data submitted for evaluation in the current application for pregelatinised <i>Lepidium meyenii</i> root powder are inadequate to support the safety and quality of the substance as a new complementary medicine substance for use in listed medicines. In particular, there is inadequate identification of the starting</p>	<p><i>L. meyenii</i> (maca) is a perennial plant from the Brassicaceae family and exists as a number of differently coloured phenotypes. Like other cruciferous vegetables, maca is reported to contain glucosinolates (which are hydrolysed to glucose and isothiocyanates upon disruption of the plant tissue). Maca is a staple in the diets of people indigenous to the Andes and used in folk medicine for increasing energy and enhancing fertility. Maca is currently sold as a food in Australia and is available as a dietary supplement in a number of other countries.</p> <p>Processed maca is widely used as a food in Australia.</p>

	<p>material, inadequate assurance of the quality of the final product and concern regarding the level of certain components (e.g. isothiocyanates and possible contaminants).</p> <p>Health Canada: available pre-cleared monograph information here.</p>	<p>Health Canada statement of purpose:</p> <ul style="list-style-type: none"> • Provides antioxidants • Helps to support healthy mood balance during menopause • Helps to support emotional aspects of sexual health
<i>Salacia reticulata</i>	<p>Health Canada: Classified as an NHP under Schedule 1 item 1 (plant or plant material) of the NHP Regulations.</p>	<p>Used in traditional systems of medicine such as Ayurveda and Unani to treat diabetes, obesity, gonorrhea, rheumatism, itching, and asthma. Other uses include weight loss¹.</p> <p>CMA -Consideration required for evidence to support indications for use in listed medicines in Australia.</p>
<i>Lagerstroemia speciosa</i> Banaba	<p>Health Canada: Classified as an NHP under Schedule 1 item 1 (plant or plant material) of the NHP Regulations</p>	<p>Banaba is a medicinal plant that grows in India, Southeast Asia, and the Philippines. Banaba is traditionally used for blood sugar control. The hypoglycemic effect of banaba leaf extract is thought to occur through a mechanism of action similar to that of insulin.</p> <p>CMA -Consideration required for evidence to support indications for use in listed medicines in Australia.</p>
<i>Eurycoma longifolia</i> TongKat Ali	<p>Health Canada: Classified as an NHP under Schedule 1 item 1 (plant or plant material) of the NHP Regulations.</p>	<p>Commonly grows wild in Southeast Asian countries such as Malaysia, Indonesia, Thailand, and Myanmar.</p> <p>Orally <i>Eurycoma longifolia</i> is used for a wide range of applications including: erectile dysfunction, impotence, infertility, and increasing libido, increase athletic performance, increase physical strength, increase testosterone levels, hypogonadism, reduce belly fat, and as a general "adaptogen" to resist stress. It is also used for fever, malaria, ulcers, hypertension, tuberculosis, bone pain, cough, diarrhea, headache, syphilis, and cancer.</p> <p>CMA -Consideration required for evidence to support indications for use in listed medicines in Australia.</p>
<i>Cissus quadrangularis</i> <i>synonym Vitis quadrangularis</i>	<p>Health Canada: Classified as an NHP under Schedule 1 item 1 (plant or plant material) of the NHP Regulations.</p>	<p><i>Cissus quadrangularis</i> is a succulent vine native to Africa, Southeast Asia, and India with a long-standing history of use in traditional therapeutic practices.</p> <p>Orally, <i>Cissus quadrangularis</i> is used for</p>

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		<p>obesity and weight loss, diabetes, metabolic syndrome, and hyperlipidemia. It has also been used for bone fractures, osteoporosis, scurvy, cancer, dyspepsia, hemorrhoids, peptic ulcer disease (PUD), dysmenorrhea, asthma, malaria, and pain. <i>Cissus quadrangularis</i> is also used in body building supplements as an alternative to anabolic steroids.</p> <p>CMA -Consideration required for evidence to support indications for use in listed medicines in Australia.</p>
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ⁱ Natural Medicines – professional monograph *Salacia reticulata*, *Lagerstroemia speciosa*, *Eurycoma longifolia*, *Cissus quadrangularis* accessed 250315