Submission for Selenium

Part A
1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine.

Selenium.

2. Proprietary name(s).

Not applicable.

3. Name of the company / organisation / individual requesting a reclassification.

Not applicable. This request is made on behalf of the natural health products industry.

4. Dose form(s) and strength(s) for which a change is sought.

Not applicable. This request is made on behalf of the natural health products industry.

5. Pack size and other qualifications.

Not applicable. This request is made on behalf of the natural health products industry.

6. Indications for which change is sought.

Not applicable. This request is made on behalf of the natural health products industry.

7. Present classification of the medicine.

At the present time, selenium is:

- Unscheduled when in products for oral use, containing 150 µg or less.
- Unscheduled when in products for external use, containing 3.5% or less of selenium sulphide.
- Pharmacy-only medicine when in products for oral use containing more than 150 µg and less than 300 µg selenium per recommended daily dose (RDD).
- Prescription medicine except when specified elsewhere in the Medicines schedule.

8. Classification sought.

It is proposed that selenium acid is scheduled as:

- Pharmacy-only medicine in products for oral use and the recommended daily dose exceeds 200 µg.
- Prescription medicine when for injection, except in parenteral nutrition replacement preparations.

9. Classification status in other countries (especially Australia, UK, USA, Canada).

Australia

- Unscheduled below 150 µg.
- Pharmacy medicine in preparations containing more than 150 µg of selenium per recommended daily dose.
- Prescription only medicine in preparations containing more than 300 µg of selenium per recommended daily dose.

Canada

- Unscheduled at 200 µg and below.
- Prescription drug in oral dosage form containing more than 200 µg selenium per maximum daily dose.

UK

Unscheduled, except for Selenium sulphide, which is a Pharmacy medicine.

Selenium recommendations internationally

The dietary selenium intake varies geographically as soil in some parts of the world is deficient in selenium. For example, selenium deficiency is rare in the United States where soils are rich in selenium, but is more common in China where soils are selenium deficient. In the US, most cases of selenium depletion or deficiency are associated with severe gastrointestinal problems, such as Crohn's disease, or with the surgical removal of part of the stomach, and are therefore a result of impaired selenium absorption. It is well established that most New Zealand soils are deficient in selenium.

10. Extent of usage in New Zealand and elsewhere (eg sales volumes) and dates of original consent to distribute.

Selenium is commonly available in dietary supplement tablets at less than 150 µg.

There are no medicines for internal use containing selenium currently registered in New Zealand.

11. Labelling or draft labelling for the proposed new presentation(s).

In a consultation draft version of the Permitted Substances List for natural health products, the following label statements are currently proposed for natural health products containing selenium:

> *Selenium is toxic in high doses.*
> *Do not exceed the maximum daily dose of 150 micrograms.*

These same statements are required on the labels of Listed Medicines containing selenium in Australia. If the requested change is accepted, the proposed dose statement will be changed to 200 micrograms.

12. Proposed warning statements if applicable.

In Canada, the following statement is required on products with a daily dose of 200 µg or more of selenium:

> *If you have a history of non-melanoma skin cancer, consult a health care practitioner prior to use* (Duffield-Lillico et al. 2003).

However, a review of the literature (see Part B 2 below) indicates that a link between selenium and cancer is still unclear.

It is proposed that the risks of selenosis and the potential risk [if it actually does exist] of non-melanoma skin cancer could be mitigated by including label advisory statements to the effect:

> *Selenium is toxic in high doses.*
> *Do not exceed the maximum daily dose of 200 micrograms.*
> *If you have a history of non-melanoma skin cancer, consult a health care practitioner prior to use.*

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

There are no registered pharmacy-only or prescription medicines containing selenium.

Manufacturers of current dietary supplement-type products will likely increase the quantity of selenium in their products. It should be noted that all dietary supplement products will be regulated under the NHP Bill. When the NHP Bill is passed, natural health products containing selenium up to the requested level (200 µg a day) will have to meet a Code of Manufacturing Practice for natural health products.

Part B Reasons for requesting classification change including benefit-risk analysis. This section should be supported by the following:

1. A statement of the benefits to both the consumer and to the public expected from the proposed change.

Multi-ingredient supplements such as trace elements and essential nutrient formulations are usually taken to complement dietary intake of essential vitamins and minerals. Such products are generally regarded as dietary supplements.

At the present time, under the current Dietary Supplements Regulations regime, therapeutic claims are not permitted for dietary supplements. This creates a peculiar situation where, for example, iron supplements are recognised to aid in the treatment of iron deficiency and iron deficiency anaemia, and are taken for these purposes, yet such products cannot provide advice on their labels on how they should be used. The NHP Bill is intended to address this situation.

When the NHP Act comes into effect, certain health benefits will be able to be claimed for allowed health conditions, provided the manufacturer of the natural health product holds evidence to support the claim(s) being made. For example, iron deficiency anaemia is one of the allowed conditions permitted by the NHP Bill. Similarly, a claim that selenium can help with rhinitis could be allowed if there was sufficient evidence.

The clear benefit of allowing the requested change is that it will enable easier implementation of the NHP system by allowing the essential vitamin or mineral to be present in effective quantities or in effective doses in natural health products.

Selenium is an essential trace element, used in particular in the glutathione peroxidase enzyme system which protects intracellular structures against oxidative damage. In foods it is present largely as the amino acids selenomethionine and selenocysteine, in which it replaces the usual sulphur atom.

It is important for general health and has been suggested to reduce prostate cancer risk, particularly in men with a low selenium status (Nicastro and Dunn, 2013; Yang et al. 2013). The amount of selenium in foods depends on the selenium content in soil and varies between countries. In New Zealand, the soil generally has low levels of selenium and in turn dietary intakes and selenium status are lower than in many countries. However, the selenium status of New Zealanders has improved over the past years due to imported wheat and cereals from Australia, which contain higher selenium levels, and farming animals are fed with foods with higher selenium levels (Thomson, 2004). From the 2009 New Zealand Total Diet Survey, selenium intake in New Zealand males over 25 was 78 µg/day, which is above the estimated average requirement of 60 µg/day) Vannoort et al, 2009). The dose recommended on the label of selenium supplements is usually 50-200 µg daily (Medsafe, 2000). The Dietary Supplements Regulations 1985 require selenium supplements to be manufactured and labelled so that the recommended daily dose is no more than 150 µg.

Selenium deficiency in itself usually does not cause illness, but it can make the body more susceptible to other illnesses. Selenium deficiency in combination with a second, as yet undetermined stress (possibly a viral infection) leads to Keshan disease, an endemic cardiomyopathy occurring in low selenium areas of China. Other conditions such as Kashin-Beck disease, a cartilage condition, also occur in selenium-deficient areas (Yang et al, 1988), although it has not been shown to respond to selenium supplementation. Selenium deficiency in conjunction with iodine-deficiency has also been reported to increase the risk of cretinism (Vaderpas et al, 1992).

2. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk.

The Ministry of Health's 2006 publication Nutrient Reference Values for Australia and New Zealand's are the same as those recommended by the Institute of Medicine (IOM). The recommended intakes for selenium are:

Age group and gender		Selenium µg / day		
		EAR	RDI	UL
Children	1-3 years	20	25	90
	4-8 years	25	30	150
Boys	9-13 years	40	50	280
	14-18 years	60	70	400
Girls	9-13 years	40	50	280
	14-18 years	60	60	400
Men	19-30 years	60	70	400
	31-50 years	60	70	400
	51-70 years	60	70	400
	> 70 years	60	70	400
Women	19-30 years	50	60	400
	31-50 years	50	60	400
	51-70 years	50	60	400
	> 70 years	50	60	400
Pregnancy	14-18 years	55	65	400
	19-30 years	55	65	400
	31-50 years	55	65	400
Lactation	14-18 years	65	75	400
	19-30 years	65	75	400
	31-50 years	65	75	400

EAR estimated average requirement
RDI recommended daily intake
UL upper level of intake

The main dietary sources of selenium are seafood, poultry and eggs (Thomson 2004), as the level in plant foods is markedly variable.

Possible risks from high doses of selenium

Selenosis
High blood levels of selenium (greater than 100 µg/dL) can result in a condition called selenosis (Koller and Exon, 1986). Symptoms of selenosis include gastrointestinal upsets, hair loss, white blotchy nails, garlic breath odour, fatigue, irritability, and mild nerve damage (Goldhaber, 2003).

Excess selenium intake from selenate, selenite or selenocysteine is excreted in the urine. The kidneys account for 50-60% of total excretion of selenium. There is also some faecal excretion of unabsorbed selenium and losses through skin, hair and, at high intakes, expired air.

The Ministry of Health has set an upper limit of 400 µg a day for adults, and 280 µg a day for children aged 9-13 years. These limits are the same as set by the Institute of Medicine. The proposed dose of 200 µg a day falls within these upper limits for adults and children aged 9-13 years even after the recommended dietary intake is taken into account.

Diabetes

There has been concern raised that taking a selenium supplement 200 µg /day long-term, for an average of 7.7 years, increases the risk of developing type 2 diabetes (Stranges et al, 2007). Higher serum levels of selenium has also been reported to be associated with an increased risk of developing diabetes and increase mortality (Bleys et al, 2007; Bleys et al, 2008, Yang et al, 2013). However, a study published in Diabetes Care involving 3,630 women and 3,535 men indicated that increasing levels of selenium in toenails appeared to be associated with a lower risk of diabetes, with the relationship appearing to be linear (Park et al, 2012). A link of high selenium levels to diabetes is still inconclusive.

The following discussion on other risks is taken from the American Nutrition Association website http://americannutritionassociation.org/newsletter/what-selenium

Cancer

Observational studies indicate that death from cancer, including lung, colorectal, and prostate cancers, is lower among people with higher blood levels or intake of selenium (Russo et al 1997; Patterson and Levander 1997; Knekt et al 1998; Fleet 1997; Shamberger 1985; Young and Lee 1999; Burguera et al, 1990). In addition, the incidence of non-melanoma skin cancer is significantly higher in areas of the United States with low soil selenium content (Fleet 1997).

The effect of selenium supplementation on the recurrence of different types of skin cancers was studied in seven dermatology clinics in the U.S. from 1983 through the early 1990s. Taking a daily supplement containing 200 mcg of selenium did not affect recurrence of skin cancer, but significantly reduced the occurrence and death from total cancers. The incidence of prostate cancer, colorectal cancer, and lung cancer was notably lower in the group given selenium supplements (Combs et al, 1997).

Research suggests that selenium might affect cancer risk in two ways. As an anti-oxidant, selenium can help protect the body from damaging effects of free radicals. Selenium may also prevent or slow tumour growth. Certain breakdown products of selenium are believed to prevent tumour growth by enhancing immune cell activity and suppressing development of blood vessels to the tumour (Combs et al, 2001).

However, not all studies have shown a relationship between selenium status and cancer. In 1982, over 60,000 participants of the Nurse's Health Study with no history of cancer submitted toenail clippings for selenium analysis. Toenails are thought to reflect selenium status over the previous year. After three and a half years of data collection, researchers compared toenail selenium levels of nurses with and without cancer. Those nurses with higher levels of selenium in their toenails did not have a reduced risk of cancer (Garland et al, 1995).

Two long-term studies, the SU.VI.MAX study in France and the Selenium and Vitamin E Cancer Prevention Trial (SELECT) in the United States and Canada, investigated whether selenium combined with at least one other dietary supplement could reduce the risk of prostate cancer in men. The SU.VI.MAX study examined the effects of a supplement package containing moderate doses of vitamins E and C, beta-carotene, zinc, and selenium

(100 mcg/day) versus placebo on the risk of chronic diseases such as cancer and cardiovascular disease (Hercberg et al, 1998, NIcastro and Dunn, 2013).

Among the 5,141 men enrolled, those randomized to the supplements who began the study with a normal (<3 ng/ml) PSA (prostate specific antigen) level at baseline had their risk of prostate cancer reduced by half (Meyer et al, 2005).

Among the men whose PSA levels were elevated at baseline, however, use of the supplements was associated with an increased incidence of prostate cancer of borderline statistical significance compared to placebo.

The SELECT trial was a very large randomized clinical trial beginning in 2001 that was specifically designed to determine whether 7–12 years of daily supplementation with selenium (200 mcg, as L-selenomethionine), with or without synthetic Vitamin E (400 IU, as dl-alpha-tocopheryl acetate), reduced the number of new prostate cancers in healthy men age 50 and older (PSA ≤4 ng/ml at baseline) (Lippman et al, 2009; National Cancer Institute).

The trial, which had enrolled 35,533 men, was discontinued in October 2008 when an analysis found that the supplements, taken alone or together for an average of 5.5 years, did not prevent prostate cancer. Results from an additional 1.5 years of follow-up from this trial (during which the subjects no longer received vitamin E or selenium) showed that men who had taken the selenium alone or selenium plus vitamin E had a slightly increased risk of developing prostate cancer compared with men who took a placebo, but the differences were not statistically significant (Klein et al, 2011).

Men taking only vitamin E, however, had a 17% increased risk of prostate cancer that was not likely due to chance. No differences were found among groups in the incidence of lung or colorectal cancers or all cancers combined.

Heart disease

Some population surveys have suggested an association between lower antioxidant intake and a greater incidence of heart disease (National Cancer Institute). Evidence also suggests that oxidative stress from free radicals, which are natural by-products of oxygen metabolism, may promote heart disease (Ozer et al, 1995; Lapenna et al, 1998; Neve 1996).

For example, it is the oxidized form of low-density lipoproteins (LDL, often called "bad" cholesterol) that promotes plaque build-up in coronary arteries (Lapenna et al, 1998). Selenium is one of a group of antioxidants that may help limit the oxidation of LDL cholesterol and thereby help to prevent coronary artery disease (Ozer et al, 1995; Lapenna et al, 1998; Neve 1996).

Currently there is insufficient evidence available to recommend selenium supplements for the prevention of coronary heart disease.

Arthritis

Surveys indicate that individuals with rheumatoid arthritis, a chronic disease that causes pain, stiffness, swelling, and loss of function in joints, have reduced selenium levels in their blood (Kose et al, 1996; Heliovaara et al, 1994). In addition, some individuals with arthritis have a low selenium intake (Stone et al, 1997). The body's immune system naturally makes free radicals that can help destroy invading organisms and damaged tissue, but that can also harm healthy tissue (Grimble, 1994).

Selenium, as an antioxidant, may help to relieve symptoms of arthritis by controlling levels of free radicals (Aaseth et al, 1998). Current findings are considered preliminary, and further research is needed before selenium supplements can be recommended for individuals with arthritis.

HIV
HIV/AIDS malabsorption can deplete levels of many nutrients, including selenium. Selenium deficiency is associated with decreased immune cell counts, increased disease progression, and high risk of death in the HIV/AIDS population (Look et al, 1997; Singhal and Austin 2002).

HIV/AIDS gradually destroys the immune system, and oxidative stress may contribute to further damage of immune cells. Antioxidant nutrients such as selenium help protect cells from oxidative stress, thus potentially slowing progression of the disease (Romero-Alvira and Roche 1998). Selenium also may be needed for the replication of the HIV virus, which could further deplete levels of selenium (Patrick 1994). An examination of 125 HIV-positive men and women linked selenium deficiency with a higher rate of death from HIV (Baum et al, 1997).

In a small study of 24 children with HIV who were observed for five years, those with low selenium levels died at a younger age, which may indicate faster disease progression (Campa et al, 1999). Results of research studies have led experts to suggest that selenium status may be a significant predictor of survival for those infected with HIV (Baum and Shor-Posner, 1998).

Comment
The main concerns other than selenium toxicity (selenosis) are its effect on diabetes, and prostate cancer. These do not appear to be supported by the reported studies, or at least the evidence appears still inconclusive. It is well-established that dietary selenium intake in New Zealand is lower than in other countries. The reported absorption of selenium from food is about 55-70% (Whanger 1998). Most excess selenium is excreted via urine. There is also some faecal excretion of unabsorbed selenium and losses through skin and hair, and at high intakes, expired air.

The Word Health Organization report on trace elements and human health (1996) reviewed studies as well as reports of community outbreaks of selenosis. From these results they concluded that daily intakes of 900 µg/day could result in selenosis. The Expert Panel then set 400 µg/day as the upper limit believed to be safe for daily intake. As they state, this figure “was derived arbitrarily by dividing the mean marginal level of safe dietary selenium intake…by two”.

The proposed daily dose of 200 µg/day remains well within the upper limit of 400 µg/day. It is proposed that the selenium dose can be increased to 200 µg/day without increasing risk. If it is considered necessary to allow the requested dose to be unscheduled, it is suggested that the risks of selenosis and the potential risk of non-melanoma skin cancer could be mitigated by including a label advisory statement to the effect:

> *Selenium is toxic in high doses.*
> *Do not exceed the maximum daily dose of 200 micrograms.*
> *If you have a history of non-melanoma skin cancer, consult a health care practitioner prior to use.*

3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated.

Not applicable.

4. Relevant comparative data for like compounds.

Not applicable.

5. Local data or special considerations relating to New Zealand.

At this time the Medicines Schedule entry for selenium is harmonised with Australia.
An increase in the allowed limit to 200 µg will de-harmonise the Medicines Schedule with Australia, which is currently 150 µg.

An increase in the allowed limit to 200 µg will harmonise with the Canadian limit for natural health products, which is 200 µg.

6. Interactions with other medicines.

Selenium is thought to interact with anticoagulants/antiplatelet medications, statins, niacin and warfarin (Australian Prescriber, 2010). However, the evidence for interactions is not strong.

8. Possible resistance.

Not applicable.

9. Adverse events - nature, frequency, etc.

In double blind randomised placebo controlled clinical trials involving a multi-ingredient essential nutrient formulation also containing selenium, the following adverse events were reported (Rucklidge et al, 2014; Gordon et al 2015):

> Headache, dry mouth, sleep disruption, gastrointestinal disturbances, nausea, constipation, agitation, sedation, anxiety, rash (diagnosed by the consulting psychiatrist as being unrelated), abdominal pain, weight gain, blurred vision.

There was no reported to be no significant difference in adverse events between the trial groups and placebo groups. One absence seizure was reported in one of the trials, but further investigations were unable to determine whether there was a seizure, or whether the observer had misinterpreted the event. As the products are a multi-ingredient product, any causal link to any particular ingredient is problematic.

A study reported by Reid et al (2004) showed no acute side effects with dosing of 1600 µg selenium daily, while side effects of possible selenium toxicity were observed at doses of 3200 µg daily.

10. Potential for abuse or misuse.
Selenium is not habit-forming or a drug of abuse. No potential for abuse or misuse is anticipated.

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