Submission for Iron

Part A

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

Iron.

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.

One applicant has commented that acute toxicity occurs starting at 100 mg and that a therapeutic dose is 15-50 mg daily (Osiecki, 2014).

Another applicant has requested an increase to the scheduled limit of iron for internal use for:

Children 0-8 years:	NMT 20 mg/day
Children 9-14 years:	NMT 40 mg/day
Adolescents 14+ years and Adults:	NMT 45 mg/day

These values are based on the Upper Limit for iron in the Nutrient Reference Values published by the Ministry of Health (MOH, 2005).

No dose forms were specified in either application.

5. Pack size and other qualifications.

Not applicable. However, the current medicines schedule entry for iron requires that when the dose unit contains more than 5 mg of iron, the pack must not contain more than 750 mg of elemental iron. For a solid dose unit containing 5 mg elemental iron, the pack would contain 150 dose units.

The Medicines Regulations 1985 requires that medicines containing more than 24 mg of elemental iron to be packaged in safety containers.

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, iron is:

- Unscheduled when in medicines for oral use containing 24 milligrams or less per recommended daily dose, either in medicines containing not more than 5 milligrams per dose unit or in medicines containing more than 5 milligrams per dose unit and in packs containing not more than 750 milligrams of iron.
- Unscheduled when in parenteral nutrition replacement preparations.
- A pharmacy medicine when in medicines for oral use containing more than 24 milligrams per recommended daily dose or in medicines containing more than 5 milligrams per dose unit and more than 750 milligrams of iron per pack; except in parenteral nutrition replacement preparations.
- A prescription medicine when in products for injection, except in parenteral nutrition replacement preparations.

8. Classification sought.

It is proposed that the classification of iron is changed to:

- Unscheduled when in medicines for oral use containing 45 milligrams or less per recommended daily dose, either in medicines containing not more than 5 milligrams per dose unit or in medicines containing more than 5 milligrams per dose unit and in packs containing not more than 750 milligrams of iron.
- Unscheduled when in parenteral nutrition replacement preparations.
- A pharmacy medicine when in medicines for oral use containing more than 45 milligrams per recommended daily dose or in medicines containing more than 5 milligrams per dose unit and more than 750 milligrams of iron per pack; except in parenteral nutrition replacement preparations.
- A prescription medicine when in products for injection, except in parenteral nutrition replacement preparations.

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

Australia
Iron (excluding iron oxides) is:

- Unscheduled when labelled with a recommended daily dose of 24 mg or less of iron:
  (a) in undivided preparations supplied in packs each containing 750 mg or less of iron, or
  (b) in divided preparations containing more than 5 mg of iron per dosage unit in packs each containing 750 mg or less of iron; or
  (c) in divided preparations containing 5 mg or less of iron per dosage unit.
- Schedule 2 (ie pharmacy medicine) when present as an excipient, in divided preparations containing 10 mg or less of total iron oxides per dosage unit or in undivided preparations containing 1 per cent or less of total iron oxides) for human internal use.
- Schedule 4 (ie prescription medicine) except in the above circumstances.

Canada
Iron and its salts and derivatives are:

- Unscheduled when in preparations containing 30 mg or less elemental iron per solid dosage unit or 5 ml oral liquid.
- Schedule II (ie pharmacy medicine) when in preparations containing more than 30 mg elemental iron per solid dosage unit or 5 ml oral liquid.
- Schedule I (ie prescription medicine) for iron derivatives for parenteral use.

Where the package contains more than the equivalent of 250 mg of elemental iron, the following label statement is required:

> *Keep out of reach of children. There is enough iron in this package to seriously harm a child.* (Note: this must be preceded by a prominently displayed symbol that is octagonal in shape, conspicuous in colour and on a background of a contrasting colour).

UK
Iron is a prescription medicine above 24 mg.
Below this, it is unscheduled.

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

No information was provided by either applicant.

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

No labels or package information was provided by either applicant.

12. Proposed warning statements if applicable.

In order to manage the potential for poisoning posed by an increase in the maximum daily dose, it is proposed that label warning statements could be used where the pack contents exceed 750 mg, including use of a similar statement to that required by Health Canada:

> *Keep out of reach of children. There is enough iron in this package to seriously harm a child.*
> *Do not exceed the recommended dose.*
> *Consult a healthcare practitioner before use if you are already taking products containing iron.*

For products targeted to pregnant women, providing iron at doses 16-35 mg per day, a statement similar to the following is proposed:

> *Taking a daily prenatal multi-vitamin mineral supplement along with this product may result in constipation, diarrhoea, and/or vomiting due to the high intake of iron* (IOM 2001; IOM 2006).

For all products providing iron at doses greater than 35 mg per day, a statement similar to the following is proposed:

> *Some people may experience constipation, diarrhoea, and/or vomiting* (IOM 2001; IOM 2006).

If it is considered necessary in order to allow the requested maximum daily dose of 45 mg, it is proposed that iron supplements sold as natural health products could be required to be packaged in a safety container.

If it is necessary for the proposed changes to the recommended daily dose to be accepted in order for iron to be allowed in oral natural health products at a higher content, the dosage restriction section of the Permitted Substances List database could reflect the age-related dosing recommendations as follows:

MDD: NMT 45mg iron for adults.
MDD: NMT 40mg iron for children aged 9-14yrs.
MDD: NMT 20mg iron for children aged 0-8yrs.

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

Manufacturers of current dietary supplement-type products will likely increase the quantity of iron compounds in their products, or change their dosing instructions to deliver the maximum dose.

It should be noted that all dietary supplement products will be regulated under the Natural Health Products Bill (NHP Bill). When the NHP Bill is passed, natural health products will have to be manufactured according to a Code of Manufacturing Practice.

Approved medicines containing iron as the active ingredient

Addaven solution for infusion
Venofer injection
Ferrum H injection

FerroTab tablet	200 mg ferrous fumarate
Ferro-F-Tab tablet	310 mg ferrous fumarate
Elevit with Iodine tablet	183 mg ferrous fumarate
Iron-Aid tablet	310 mg ferrous fumarate
Ferrograd modified release tablet	325 mg ferrous sulfate
Ferrograd F	325 mg ferrous sulfate
Ferro liquid oral solution	30 mg/mL ferrous sulfate
Ferodan oral solution	30 mg/mL ferrous sulfate
Ferrograd-C tablet	325 mg ferrous sulfate

All these medicines are currently scheduled as a pharmacy medicine or a prescription medicine. Products for injection are not permitted under the NHP regulatory scheme.

The proposed change to increase the recommended dose for iron to 45 mg/day will not affect these medicines.

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 to treat the common cold with zinc tablets could be allowed.

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.

Iron supplements are usually taken to combat iron deficiency, which can lead to iron deficiency anaemia. Iron can also help with symptoms associated with iron deficiency, such as fatigue, and to enhance athletic performance. It has also been used in the treatment of some other health conditions, such as attention deficit hyperactivity disorder (ADHD), restless legs syndrome, heart failure, Crohn’s disease, depression, female infertility and menorrhagia.

Iron deficiency anaemia is one of the allowed conditions permitted by the NHP Bill.

Health Canada recognises that iron supplementation from natural health products is effective for iron deficiency and iron deficiency anaemia. In particular, Health Canada requires the following statements on product labels of natural health products providing 16-20 mg iron, per day:

> *Helps pregnant women meet (the) (Health Canada's/Institute of Medicine) recommended intake for iron, when taken in conjunction with a healthy diet.*

Health Canada will allow the following statements, which must be verbatim, only if iron is present at dosages at or above the Recommended Dietary Allowance (RDA) or Adequate Intake (AI):

> *Helps to prevent iron deficiency.*
> *Helps to prevent iron deficiency anaemia.*
> *Helps to prevent iron deficiency anaemia and associated tiredness and fatigue.*

Risk groups for iron deficiency
People that are the most likely to have inadequate intakes of iron are pregnant women, infants and young children, women with heavy menstrual bleeding, frequent blood donors, people with colon cancer, people who have gastrointestinal disorders and people who have heart failure (ODS, 2016).

McEvoy (1998) has proposed that 300 mg/day [or 4.2 mg/kg bw/day for a 70 kg person] can be safely taken by most people to treat iron deficiency.

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 recommended intakes for iron are:

Age group and gender		Iron mg / day		
		EAR	RDI	UL
Children	1-3 years	4	9	20
	4-8 years	4	10	40
Boys	9-13 years	6	8	40
	14-18 years	8	11	45
Girls	9-13 years	6	8	40
	14-18 years	8	15	45
Men	19-30 years	6	8	45
	31-50 years	6	8	45
	51-70 years	6	8	45
	> 70 years	6	8	45
Women	19-30 years	8	18	45
	31-50 years	5	18	45
	51-70 years	8	8	45
	> 70 years	8	8	45
Pregnancy	14-18 years	23	27	45
	19-30 years	22	27	45
	31-50 years	22	27	45
Lactation	14-18 years	7	10	45
	19-30 years	6.5	9	45
	31-50 years	6.5	9	45

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

Health Canada has made the following recommendations for iron intake:

Life Stage Group		Iron (mg/day)	
		Min*	Max
Infants	0-12 months	0.6	40
Children	1-3 years	0.6	40
	4-8 years	0.6	40

Adolescents	9-13 years	0.6	40
	14-18 years	1.4	45
Adults (incl. pregnant and breastfeeding women)	≥ 19 years	1.4	45

[* Minimum value is based on 5 percent of the highest RDA or AI.]

The National Institutes of Health Office of Dietary Supplements recommends that the RDA for vegetarians should be increased by 1.8 times compared to people who eat meat (ODS, 2016). This is because heme iron from meat is more bioavailable than non-heme iron from plant-based foods, and meat, poultry, and seafood increase the absorption of non-heme iron [IOM, 2001]. The RDA values from the Office of Dietary Supplements differ only very slightly from the Ministry of Health's values reproduced above.

Iron toxicity

The main concern over iron is iron toxicity. Iron is unsafe when used orally in large doses. Doses greater than the UL of 45 mg frequently cause gastrointestinal side effects such as constipation and nausea (IOM, 2002, Singhi et al, 2003). Doses of 30 mg/kg are associated with acute toxicity. Long-term use of high doses of iron can cause haemosiderosis and multiple organ damage. The estimated lethal dose of iron is 180-300 mg/kg (or 12.6-21 g for a 70 kg person). However, doses as low as 60 mg/kg (or 4.2 g for a 70 kg person) have also been reported to be lethal (McEvoy, 1998).

At doses below the tolerable upper intake level (UL) of 45 mg per day of elemental iron in adults with normal iron stores, gastrointestinal adverse effects are uncommon (IOM, 2002). Higher doses can be taken safely in adults with iron deficiency, but gastrointestinal side effects may occur. Taking iron supplements with food seems to reduce gastrointestinal side effects (IOM, 2002)). However, food can also significantly reduce iron absorption. The IOM recommends that iron should be taken on an empty stomach, unless it cannot be tolerated.

Iron overload

Iron overload may occur in the elderly, particularly in people with hereditary haemochromatosis. Excess iron is stored in the major organs, particularly the liver. Over a period of years, this may lead to organ failure and other complications.

However, the elderly are less likely to have a deficiency of iron, unless they are in one of the risk groups described in Part B1 above. The genes that cause haemochromatosis are inherited, but only a minority of the people who have the genes ever develop serious problems. Treatment of iron overload includes regularly removing blood (phlebotomy), chelation, and reducing iron intake by modifying the diet.

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

Symptoms of iron deficiency include general fatigue, weakness, pallor, shortness of breath, dizziness, tingling in extremities, coldness of hand and feet, restless legs, brittle nails, swelling or soreness of the tongue, cracks in the sides of the mouth. These symptoms can be easily recognised and the condition self-managed once a person has been diagnosed as a risk for iron deficiency and iron deficiency anaemia.

4. Relevant comparative data for like compounds.

Not applicable.

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

No information was provided or is available.

6. Interactions with other medicines.

The National Institutes of Health Office of Dietary Supplements cautions that iron may reduce the absorption of levodopa or levothyroxine, and that proton pump inhibitors such as omeprazole may reduce iron absorption because they reduce the acidity of stomach contents (ODS, 2016).

The data sheet for Elevit with Iodine (Bayer New Zealand, 2014) states that the absorption of iron may be decreased by concurrent administration with antacids, gastric acid suppressive medications, fluoroquinolone, bisphosphonates, levodopa, levothyroxine, penicillamine, tetracycline antibiotics or trientine.
Products containing calcium, magnesium, iron, copper or zinc may interact with orally administered antacids, antibiotics (tetracyclines, fluoroquinolones), levodopa, bisphosphonates, penicillamine, thyroxine, trientine, digitalis, antiviral agents and thiazide diuretics.

However, no regulatory authority has currently considered it necessary to require a warning statement about interactions with medicines to be placed on labels of dietary supplements or natural health products containing iron.

The potential of interaction with medicines can be managed by separating the administration of iron supplements and these medicines by a few hours.

7. Contraindications and precautions.

No information was provided by the applicants. Health Canada's monograph on iron states that a statement is not required (Health Canada, 2009).

8. Possible resistance.

Not applicable.

9. Adverse events - nature, frequency, etc.

Liquid preparations containing iron have been reported to blacken teeth (Martindale, 1999). Adverse effects of the gastrointestinal tract, including nausea, vomiting, heartburn, epigastric or abdominal pain, constipation, and diarrhoea, have been reported in clinical trials on pregnant women using high doses of 200 – 300 mg/day (Macedo & Cardoso, 2010; Ortiz et al, 2011). More of these adverse effects are reported with ferrous sulphate than other forms of iron (Ortiz et al, 2011; Zhang, Ouyang, Wieczorek, & DeSoto, 2009).

Constipation has been occasionally reported with the use of iron supplements. With use in children, as children may not report being constipated for several days, an applicant recommends that the dose for children under 9 years old should not exceed 20 mg/day in order to reduce the risk of possible toxicity.

To manage these risks, label advisory statements are proposed.

For products targeted to pregnant women, providing iron at doses 16-35 mg per day, the statement similar to the following is proposed:

> *Taking a daily prenatal multi-vitamin mineral supplement along with this product may result in constipation, diarrhoea, and/or vomiting due to the high intake of iron.*

For all products providing iron at doses greater than 35 mg, per day, a statement similar to the following is proposed:

> *Some people may experience constipation, diarrhoea, and/or vomiting.*

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

References

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