SUBMISSION FOR RECLASSIFICATION

SABADILLA

(Schoenocaulon officinale)

WELEDA NEW ZEALAND LTD.

P.O. BOX 8132

HAVELOCK NORTH

RATIONALE

Preamble

The recent recommendation to set an exemption from scheduling levels has occurred as a result of the move towards harmonisation with Australian schedules. The exemption level set has implications for some homoeopathic medicines that are on the market in New Zealand, that are produced differently to homoeopathic medicines on the market in Australia.

Our aim in this submission is:

- To clarify the classification and schedule exemption levels so that they can be clearly and objectively applied to anthroposophical and homoeopathic medicines.
- To propose classification and schedule exemption levels based on active principle concentration.
- To propose classification and schedule exemption levels that fairly reflect the actual risk of the medicine to the consumer.

To our knowledge, there have been no reports of adverse effects associated with anthroposophical or homoeopathic medicines containing sabadilla that have initiated this change.

Rationale 1: Classification of plant substances on active principles

Classification that is based only on the plant name could severely disadvantage some homoeopathic medicines. We consider that the most effective means to classify plant substances is to base the classification criteria on the "active principle" (usually alkaloids) concentration of the plant, where possible.

This would avoid the major discrepancies in alkaloid concentration and toxicity that exist between medicines made from fresh or dry plant and different plant parts, especially homoeopathic medicines. *(Refer Appendix 2)*

It would also avoid the differences in alkaloid concentration that can occur as a result of different manufacturing and extraction processes used in the preparation of herbal substances. *(Refer Reference Copy 2)*

In the case of sabadilla the homoeopathic medicines are made from the ripe seed and so the question of discrepancies between fresh and dry plant do not arise, but the classification of the plant on its active principles is still an important premise.

As can be seen from Appendix 2, a "homoeopathic potency" of a plant made following one homoeopathic pharmacopoeia would contain quite different levels of alkaloids and therefore different toxicity to the same "homoeopathic potency" of a plant produced following another pharmacopoeia. Using aconite as an example:

- Dry Plant: The highest alkaloid concentration of aconite, mentioned, is a dry root total alkaloid concentration of 1.5%. *(Refer Reference Copy 2.)*
  Aconite mother tincture made following the Homoeopathic Pharmacopoeia of the United States, although made from fresh plant contains the equivalent of 10% of the dry plant material and is called a 1x (10%) potency. *(Refer Appendix 2)*
  This 1x (10% of dry plant) potency would contain a maximum of 0.15% alkaloids.

- Fresh plant: Aconite mother tincture (50% fresh whole plant juice), made following the German Homoeopathic Pharmacopoeia, contains not less than 0.055% and not more than 0.075% of alkaloids, calculated as aconitine *(Refer Reference Copy 3.).*
  A 1x (10% of the fresh plant juice) potency made from this mother tincture would contain a maximum of 0.015% alkaloids.

As can be seen from the above two points, there is approximately a **ten fold** difference in the aconitine concentration of homoeopathic potencies originating from methods based either on a dry plant concentration or a fresh plant juice concentration.

Medsafe Precedents: Previous wording of the Medsafe classification of plants referred to the percentage strength of the alkaloids of the plant, eg. Aconite; alkaloids of and salts, except in medicines containing less than 0.02% of the alkaloids of Aconite.

Australian Precedents: Many of the classifications of herbs in the Australian Standard for the Uniform Scheduling of Drugs and Poisons refer to the percentage strength of the alkaloids of the plant, eg. Schedule 2 (Pharmacy Medicine) BELLADONNA, in preparations containing 0.25 per cent or less of the alkaloids of belladonna.

We consider that classification of plant medicines based on the active principle concentration removes the "grey" areas inherent in the present system. It provides objective and clear limits to use when classifying products.

Rationale 2: Reclassification

We consider that the general application of a Prescription Only Medicine classification to product containing sabadilla up to the general schedule exemption level of 10 mg per litre or per kilogram is not substantiated by toxicity data. We propose that a lower classification be applied to product containing lower concentrations of the alkaloids of sabadilla.

The therapeutic dose range for hyoscyamine is 0.15 mg to 0.3 mg hyoscyamine (refer to the Hyoscyamus reclassification submission). This dose range appears to have been used in the setting of the classification levels for hyoscyamine, eg.:

Pharmacist Only Medicine: Hyoscyamine; in liquid form for oral use; in solid dose form containing more than **0.3 milligrams per dose** or more than 1 milligram per recommended daily dose

We propose that the same approach be used with the classification of sabadilla.

The highest alkaloid concentrations of sabadilla referred to are 4% alkaloids *(refer Appendix 1, point 2.)* and 0.60% alkaloids in Sabadilla 10% mother tincture *(refer Appendix 1, point 4.)*, which would equate to 6% alkaloids in the ripe seed. Using 6% as the highest alkaloid content:

Toxic and therapeutic doses:

> Fatal/Toxic dose: LD50 for sabadilla is 300 mg *(refer Appendix 1, point 6.)*.
> This is equivalent to a fatal dose for a 10 kg child being equal to 3g sabadilla, which is equivalent to **180 mg alkaloids**.
>
> Therapeutic dose: 5 to 20 grains is referred to as a therapeutic dose *(refer Appendix 1, point 7.).*
> Using the definition of a "grain = 4.79891 mg *(refer Appendix 1, point 8.)*
> This is equivalent to a therapeutic dose of 24 mg to 96 mg of sabadilla, which is equivalent to **1.44 mg to 5.76 mg alkaloids**.
>
> There is more than a 100 fold difference between the possible fatal dose for a child and the therapeutic dose range.
>
> Previous classifications of Sabadilla *(refer Appendix 3.)* were based on a concentration of the alkaloids of Sabadilla at 1%. This equates to 10 mg alkaloids per 1 mL dose.
>
> Low concentration, homoeopathic medicines are commonly presented in liquid or powder form, therefore classification based on pack concentration is included.

Proposed reclassifications – refer Part A, Point 8.

> POM: Sabadilla, **alkaloids of**; for oral use in liquid or powder form in a pack containing more than 5 milligrams; in solid dose form containing more than 5 milligrams per dose.
>
> PM: Sabadilla, **alkaloids of**; for oral use in liquid or powder form in a pack containing 5 milligrams or less; in solid dose form containing 5 milligrams or less per dose.

The effect of this reclassification is that:

> Liquid or powder oral preparations in a pack containing more than a single therapeutic dose of 5 mg of the alkaloids of sabadilla, and solid dose forms containing more than 5 mg per dose are classified as Prescription Only Medicines.
>
> Liquid or powder oral preparations in a pack containing a single therapeutic dose of 5 mg or less of the alkaloids of sabadilla, and solid dose forms containing 5 mg or less per dose are classified as Pharmacy Medicines.

Rationale 3: Schedule exemption level based on active principle concentration

The aim is:

To provide an exemption level for sabadilla based on the alkaloid concentration, not the plant name.

To provide a 1000 fold difference between a therapeutic dose and the dose of a product containing the exemption level.

Alkaloid concentration of the **present** sabadilla schedule exemption level:
10 mg/L/kg (sabadilla 0.001%) at an alkaloid concentration of 6%
(0.60% alkaloids in Sabadilla 10% mother tincture (refer Appendix 1, point 4.), which would equate to 6% alkaloids in the ripe seed) results in:
600 micrograms per litre or kilogram (0.00006%) maximum alkaloids

This possible exemption level does not equate with the premise of a 1000 fold difference between the therapeutic dose and the dose of a product containing the proposed exemption level – refer following points.

Therapeutic dose: 5 to 20 grains is referred to as a therapeutic dose *(refer Appendix 1, point 7.).*
Using the definition of a "grain = 4.79891 mg *(refer Appendix 1, point 8.)*
This is equivalent to a therapeutic dose of 24 mg to 96 mg of sabadilla, which is equivalent to **1.44 mg to 5.76 mg alkaloids**.

A 1 mL oral dose of a product containing 0.00006% of the alkaloids of sabadilla would contain 0.0006 mg (0.6 microgram) alkaloids.

This is approximately a **10,000 fold** difference between the therapeutic dose range (1.44 mg to 5.76 mg) and the dose of a product containing the exemption level (0.0006 mg).

We consider that this is an excessive margin.

We would propose the following schedule exemption to meet the premise of a 1000 fold difference between the therapeutic dose and the dose of a product containing the exemption level – refer Part A, Point 8.

Sabadilla, in preparations containing 6 milligrams per litre or per kilogram of the alkaloids of sabadilla (0.0006%)
(As the largest pack size in the market is 100 mL, there is an extra safety factor of ten)

A 1 mL oral dose of a product containing 0.0006% of the alkaloids of sabadilla would contain 0.006 mg (6 microgram) alkaloids.

This is approximately a **1000 fold** difference between the therapeutic dose range (1.44 mg to 5.76 mg) and the dose of a product containing the exemption level (0.006 mg).

We consider that this is an extremely wide safety margin.

An exemption level based on the alkaloid concentration would prevent inequities occurring because of differences in alkaloid concentration of "homoeopathic potencies" made following different homoeopathic pharmacopoeia *(refer Appendix 2).*

The present schedule exemption level of 10 mg/L/kg would result in:

- Sabadilla 4x (0.01%) containing a maximum of 0.0006% alkaloids **being classified**.

The proposed schedule exemption of sabadilla at 10 mg/L/kg results in:

- Sabadilla 4x (0.01%) containing a maximum of 0.0006% alkaloids **being exempt from classification**.

Rationale 4: Safety in the market place

Weleda medicines containing sabadilla have been on the market since the early 1950's and have had wide use during those years, in the customer base to which they are directed. There have been NO adverse reactions reported.

PART A

1. International Non-proprietary Name of the medicine

Sabadilla

2. Proprietary name(s)

Non-specific change application for anthroposophical and homoeopathic products.

3. Company requesting reclassification

Weleda New Zealand Ltd.
P.O. Box 8132
Havelock North
NEW ZEALAND

4. Dose form(s) and strength(s)

Not applicable.

5. Pack size and other qualifications

Not applicable.

6. Indications for which change is sought

Not applicable.

7. Present classification of medicine

Prescription Only Medicine: Sabadilla

Recommended general schedule exemption: 10 mg per litre or per kilogram

8. Classification sought

Prescription Only Medicine: Sabadilla, **alkaloids of**; for oral use in liquid or powder form in a pack containing more than 5 milligrams; in solid dose form containing more than 5 milligrams per dose.

Pharmacy Medicine: Sabadilla, **alkaloids of**; for oral use in liquid or powder form in a pack containing 5 milligrams or less; in solid dose form containing 5 milligrams or less per dose.

Schedule exemption: **Sabadilla, in preparations containing 6 milligrams per litre or per kilogram of the alkaloids of sabadilla (0.0006%)**
(As the largest pack size in the market is 100 mL, there is an extra safety factor of ten)

9. Classification status in other countries

Germany: Sabadilla not classified.

Australia: *Schedule 4 (Prescription Only Medicine):* Sabadilla
Schedule exemption: 10 mg per litre or per kilogram

10. Extent of usage in NZ and elsewhere

Homoeopathic preparations of sabadilla are commonly used by homoeopaths and manufactured by most homoeopathic manufacturers.

11. Proposed labelling

Not applicable.

12. Proposed warning statements

Not applicable.

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

Anthroposophical and homoeopathic medicines.

PART B

Reasons for Requesting Classification Change

1. Expected benefits to both the consumer and to the public

Maintains accessibility to safe anthroposophical and homoeopathic medicines that have been used for minor, self-limiting conditions, in NZ for more than 40 years.

2. Ease of self-diagnosis or diagnosis by a pharmacist

Not applicable.

3. Relevant comparative data for like compounds

Not applicable

4. Local data or special considerations relating to NZ

Not applicable

5. Interactions with other medicines

None known.

6. Contraindications

Not applicable.

7. Possible development of drug resistance

None

8. Adverse events

Weleda medicines containing sabadilla have been on the NZ market since the early 1950's and on the European market since the early 1920's. During these years there have been, to our knowledge, no reports of any adverse events associated with these anthroposophical and homoeopathic medicines.

9. Potential for abuse or misuse

None

Glossary, Appendices and Reference Copies

Glossary

Anthroposophical medicine
The medicines specially made for anthroposophical therapy which contain herbal and homoeopathically produced preparations.

Homoeopathic medicine
Article 1 of the European Guidelines EG 92/73 and EG 92/74 on Homoeopathic Pharmaceuticals for Human respectively Veterinary Use provides the following definition [official within the 15 nations of the E.U.] of the term "homoeopathic medication":

(1) "Within the sense of this Guideline, a homoeopathic (veterinary) medication constitutes any medicinal agent, which has been prepared from products, substances, or compounds designated as homoeopathic source-material in accordance with homoeopathic manufacturing procedure as described in a European pharmacopoeia or – in absence of the corresponding monograph – according to the currently official pharmacopoeia of a member state.

(2) "Homoeopathic medication may contain multiple active constituents"
[Official Journal of European Communities No. L 297/8 of Oct.13, 1992].

Homoeopathic medicines can be the mother tincture right through the range of homoeopathic potencies.

Homoeopathic potency
A homoeopathic potency is produced from one or several source material or mother tinctures, generally followed by potentising: serial dilution and succussion (potentisation). The following are examples of the common attenuation-ratios:

- 1:10 - Decimal or D, DH, or X potencies
- 1:100 - Centesimal or C, CH potencies
- 1:50,000 - Q or LM potencies

Potentisation
Potentisation: serial dilution and succussion - a special form of shaking the liquid dilution, or triturating the powder dilution.

Mother tincture
A mother tincture is a preparation of a substance, that is used as the starting material for the preparation of a homoeopathic potency, and in some cases can also be used as a homoeopathic medicine in its own right.

Appendices

1. Appendix 1: References to Active Principle, Therapeutic and Toxicity Levels
2. Appendix 2: Concentration Differences Between Homoeopathic Medicines Using Aconite as an Example
3. Appendix 3: Previous Medsafe classifications of Sabadilla

Reference Copies

1. Reference Copy 1: pg. 405-406, Pharmacognosy 14th Ed., by Trease and Evans, published by WB Saunders Company Ltd., ISBN 0-7020-1899-6
2. Reference Copy 2: Aconite Monograph date of issue: Feb.1993, The Lawrence Review of Natural Products – Monograph System, published by Fact and Comparisons, ISSN 0734-4961
3. Reference Copy 3: pg. 103, German Homoeopathic Pharmacopoeia (GHP) (Homoopathisches Arzneibuch HAB) Official Edition, published by Deutscher Apotheker Verlag Stuttgart Govi-Verlag GmbH, Frankfur, ISBN 0946717 05 2, ISBN for German original 3-7692-0932-X
4. Reference Copy 4: pg. 807-808, German Homoeopathic Pharmacopoeia (GHP) (Homoopathisches Arzneibuch HAB) Official Edition, published by Deutscher Apotheker Verlag Stuttgart Govi-Verlag GmbH, Frankfur, ISBN 0946717 05 2, ISBN for German original 3-7692-0932-X
5. Reference Copy 5: pg. 536, Pharmacognosy 14th Ed., by Trease and Evans, published by WB Saunders Company Ltd., ISBN 0-7020-1899-6
6. Reference Copy 6: pg. 127, Handbook of Poisoning, 12th Edition, published by Appleton & Lange, a Publishing Division of Prentice-Hall, ISBN 0-8385-3643-3
7. Reference Copy 7: pg. 698, A Modern Herbal, by Mrs M, Grieve, published by Peregrine Books
8. Reference Copy 8: pg. 497, Mosby's Medical and Nursing Dictionary, 2nd Edition, Thomas A. Manning, The C.V. Mosby Company, ISBN 0-8016-5195-6