SUBMISSION FOR RECLASSIFICATION

BELLADONNA

(Atropa belladonna)

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 belladonna 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)*

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.

- Dry Plant: The highest alkaloid concentration of belladonna mentioned, is a dry root alkaloid concentration of 1%. *(Refer Appendix 1, point 2.)*
  Belladonna 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 0.1% alkaloids.

- Fresh plant: Belladonna mother tincture (50% fresh whole plant juice), made following the German Homoeopathic Pharmacopoeia, contains not less than 0.03% and not more than 0.035% per cent of non-volatile bases, calculated as hyoscyamine *(Refer Appendix 1, point 7.).*
  A 1x (10% of the fresh plant juice) potency made from this mother tincture would contain a maximum of 0.007% alkaloids.

As can be seen from the above two points, there is **more than a ten fold** difference in the alkaloid 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

Possible classification discrepancy in the present classification of belladonna

After reviewing the present classification of belladonna against the usual therapeutic ranges, we wondered if the present classification should have originally referred to the alkaloids of belladonna.

The dose levels referred to in the classification, 0.3 mg belladonna and 1 mg belladonna, appear to better reflect the usual therapeutic doses used of the alkaloids of belladonna, rather than dose levels of the plant belladonna.

At the range of active principle levels mentioned, 0.3%-1% alkaloids *(Appendix 1, point 2.),* a 0.3 mg per dose of belladonna dry plant would contain between 0.9 – 3 micrograms of belladonna alkaloids which to our knowledge would not supply a conventional therapeutic dose - dose range 0.15 mg to 0.3 mg alkaloids *(Appendix 1, point 11).*

Also all of the B.P., B.P.C. and U.S.P. belladonna preparations mentioned in Martindale specify the concentration of the alkaloids of belladonna. *(refer to Reference Copy 4)*

Classification based on dose forms

We presume that the rationale behind the present classification based on solid and liquid dose forms relates to safety, but this does cause a problem for low concentration,

homoeopathic medicines that are commonly presented in liquid form. These low concentration products do not pose the same safety issues that a conventional product may pose.

We propose a cut-off level for the liquid and powder preparations to address this situation based on a pack containing the dose used in the classification of 0.3 milligrams, being a single therapeutic dose.

> Therapeutic dose: Dose range: 0.15 mg to 0.3 mg hyoscyamine
> *(Refer Appendix 1, point.11.)*

Proposed reclassifications – refer Part A, Point 8.

> PhOM: Belladonna, **alkaloids of**; **for oral use in liquid or powder form in a pack containing more than 0.3 milligrams; ……**
>
> PM: Belladonna, **alkaloids of**; **for oral use in liquid or powder form in a pack containing 0.3 milligrams or less; …….**

The effect of this reclassification is that:

> Liquid or powder oral preparations in a pack containing more than a single therapeutic dose of 0.3 mg of the alkaloids of belladonna are classified as Pharmacist Only Medicines.
>
> Liquid or powder oral preparations in a pack containing a single therapeutic dose of 0.3 mg or less of the alkaloids of belladonna are classified as Pharmacy Medicines.

Rationale 3: Schedule exemption level based on active principle concentration

The aim is:

> To provide an exemption level for belladonna based on the alkaloid concentration, not the plant name.
>
> To provide an exemption level that is approximately equivalent in active principle concentration to the present Australian, and recommended NZ, schedule exemption of 10 mg per litre or kilogram for belladonna.
>
> 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** belladonna schedule exemption level:
10 mg/L/kg belladonna (0.001%) at a dried root alkaloid concentration of 1% *(refer Appendix 1, point 2.)* results in:
100 micrograms per litre or kilogram (0.00001%) maximum alkaloids

Proposed schedule exemption – refer Part A, Point 8.

> Belladonna, in preparations containing 100 micrograms per litre or per kilogram of the alkaloids of belladonna (0.00001%)

(As the largest pack size in the market is 100 mL, there is an extra safety factor of ten)

The proposed schedule exemption level, based on the alkaloids of belladonna (usually calculated as hyoscyamine), provides an exemption level that is equivalent in active principle concentration to the present Australian and recommended NZ schedule exemption for belladonna.

Therapeutic dose: Dose range: 0.15 mg to 0.3 mg hyoscyamine
(Refer Appendix 1, point.11.)

A 1 mL oral dose of a product containing the proposed schedule exemption of 0.00001% of the alkaloids of belladonna would contain 0.0001 mg alkaloids.

This is more than a **1000 fold** difference between the therapeutic dose range (0.15 mg to 0.3 mg) and the dose of a product containing the exemption level (0.0001 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)*.

As pointed out in Rationale 1.:

1x (10% of dry plant) potency would contain a maximum of 0.1% alkaloids
1x (10% of the fresh plant juice) would contain a maximum of 0.007% alkaloids.

Present schedule exemption level of belladonna plant at 10 mg/L/kg (0.001%) would result in:

- Belladonna, dry plant 5x (0.001%) containing a maximum of 0.00001% alkaloids **being exempt from classification**.
- Belladonna, fresh plant juice 4x (0.01%) containing a maximum of 0.000007% alkaloids **being classified**.

At present the exemption level would result in a product containing a higher level of alkaloids being exempt from classification whilst a product containing a lower level of alkaloids would be classified.

Proposed schedule exemption of alkaloids of belladonna at 100 microgram/L/kg (0.00001%) results in:

- Belladonna, dry plant 5x (0.001%) containing a maximum of 0.00001% alkaloids **being exempt from classification**.
- Belladonna, fresh plant juice 4x (0.01%) containing a maximum of 0.000007% alkaloids **being exempt from classification**.

This proposed exemption level would result in two products that both contain a concentration of alkaloids that is below the exempt level being classified in the same way, i.e. exempt.

Rationale 4: Safety in the market place

Weleda medicines containing belladonna 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

Belladonna

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

Pharmacist Only Medicine:	Belladonna; for oral use in liquid form; in solid dose form containing more than 0.3 milligrams per dose or more than 1 milligram per recommended daily dose.
Pharmacy Medicine:	Belladonna; in solid dose form containing 0.3 milligrams or less per dose and 1 milligram or less per recommended daily dose.

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

8. Classification sought

Pharmacist Only Medicine: Belladonna, **alkaloids of**; **for oral use in liquid or powder form in a pack containing more than 0.3 milligrams;** in solid dose form containing more than 0.3 milligrams per dose or more than 1 milligram per recommended daily dose.

Pharmacy Medicine: Belladonna, **alkaloids of**; **for oral use in liquid or powder form in a pack containing 0.3 milligrams or less;** in solid dose form containing 0.3 milligrams or less per dose and 1 milligram or less per recommended daily dose.

Schedule exemption: **Belladonna, in preparations containing 100 micrograms per litre or per kilogram of the alkaloids of belladonna (0.00001%)**
(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: *Prescription Only Medicine:* Belladonna up to and including D3 (3x; 0.1%)

Australia: *Schedule 4 (Prescription Only Medicine):*
BELLADONNA **except** when included in Schedule 2.
Schedule 2 (Pharmacy Medicine):
BELLADONNA in preparations containing 0.25 per cent or less of the alkaloids of Belladonna.
Schedule exemption: 10 mg per litre or per kilogram

10. Extent of usage in NZ and elsewhere

Homoeopathic preparations of Belladonna 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 belladonna 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 Belladonna

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: Copy of pg. 1475, Martindale, 30th Ed.
5. Reference Copy 5: pg. 354- 357, Pharmacognosy 14th Ed., by Trease and Evans, published by WB Saunders Company Ltd., ISBN 0-7020-1899-6
6. Reference Copy 6: pg. 1018, British Pharmacopoeia 1988, Volume II, ISBN 0 11 320837 5
7. Reference Copy 7: pg. 207, 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
8. Reference Copy 8: pg. 36, 37 British Herbal Pharmacopoeia 1983, published by the British Herbal Medicine Association, ISBN 0 903032 07 4
9. Reference Copy 9: pg. 87, The Complete German Commission E Monographs, Therapeutic Guide to Herbal Medicines, by Blumenthal, Buse, Goldberg, Gruenwald, Hall, Klein, Riggins & Rister, published in cooperation with Integrative Medicine Communications, ISBN 0-9655555-0-X
10. Reference Copy 10: pg. 427, Martindale, 30th Ed., published by The Pharmaceutical Press, ISBN 0 85369 300 5, ISSN 0263-5364