Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Office of Complementary Medicines
TGA Contact Officer: Lucille Ward
Telephone: 02 6232 8229
Facsimile: 02 6232 8577

[redacted]

Attention: Regulatory Affairs Officer

Dear Sir / Madam

Notice of Cancellation of Listing
under Subsection 30(1A) of the *Therapeutic Goods Act 1989*

Medicines: [redacted]

Sponsor:

I, Hongxia Jin, a delegate of the Secretary of the Department of Health and Ageing for the purposes of Section 30 of the *Therapeutic Goods Act 1989* ('the Act'), have cancelled the listing of [redacted] ('the medicines') from the Australian Register of Therapeutic Goods ('ARTG') in reliance on paragraph 30(1A)(a) of the Act.

A. Reasons for my decision

I have cancelled the listings of these medicines because certain information, including documentation provided by [redacted] indicates that the medicines are not eligible for listing under Section 26A of the Act.

B. Action to be taken by sponsor

Supply of the above medicine should cease from **3 April 2009.** Sponsors are reminded that under Section 19D of the Act, it is an offence to supply therapeutic goods not entered in the ARTG.

C. Relevant legislation

Subsection 30(1A) of the Act relevantly provides that, the Secretary may, by notice in writing given to a person in relation to whom a medicine is listed under section 26A, cancel the listing of the medicine if:

(a) the medicine is not eligible for listing; ...
(b) ...
(c) ...

Subsection 30(5)(b) of the Act relevantly provides that where the Secretary cancels the registration or listing of goods in relation to a person, the goods cease to be registered or listed:

(a) if the cancellation is effected under subsection (1), (1A) or (1C)—on the day on which the notice of cancellation is given to the person; ...
(b) ...

D. Information reviewed:

1. The information provided by [redacted] on behalf of [redacted] dated 5 March 2008 in response to the Notice of 8 February 2008 re [redacted] under Section 31 of the Act.
2. The additional information provided by [redacted] on behalf of [redacted] dated 24 April 2008 in response to the phone call requesting further information in relation to the Notice of 8 February 2008 re [redacted] under Section 31 of the Act.
3. The information provided by [redacted] on behalf of [redacted] dated 8 July 2008 in response to clarification requested by the TGA regarding the character of the *Olea europaea* extract ('active ingredient') included in the medicine [redacted].
4. The information provided by phone and email on 25 July 2008 from [redacted] on behalf of [redacted], in response to the information requested by the TGA in the phone call between [redacted] and the TGA contact officer Lucy Ward on the same date.
5. The U.S. patents for the patent numbers included on the front panel of the medicine label ('main label').
6. The submission by [redacted] dated 10 December 2008 in response to the Proposal to Cancel dated 24 November 2008 under Section 30(1A) of the Act.
7. The records held in the ARTG for the medicines.
8. The *Therapeutic Goods Act 1989*.
9. The Therapeutic Goods Regulations 1990 ('the Regulations').

E. History of the case

[redacted] was included onto the ARTG on 18 July 2007. The following information was included on the (sole) active ingredient of this medicine:

Active Ingredient
Olea europaea 100 mg

Carrier
Maltodextrin 95.5 mg
Citric acid - anhydrous 4.5 mg

Plant details (origin)
fruit

Part Preparation
Extract dry concentrate

Equivalent
Olea europaea (Fresh) 12 g

Ratio	Type
120:1	CONCENTRATION

Extract step solvent
Water – purified 100%

This medicine was randomly selected for review to ascertain whether the medicine should have been listed under Section 26A of the Act. A Notice under the provisions of Section 31 of the Act was issued on 8 February 2008, requesting that the company provide the following information relating to the medicine:

- The actual label(s) for the medicine for all packaging types and pack sizes.
- The finished product specification for the medicine.
- The certificate of analysis for the last released batch of the medicine.
- A list of the evidence held by the company to support the indications/claims made in relation to the medicine.

[redacted] 'the agent' provided a response dated 5 March 2008 on behalf of [redacted] ('the sponsor'). The response consisted of a colour printout of the label; a Certificate of Analysis issued on 21 February 2008; a Product Specification document dated 11 September 2007; and a list of the evidence held by the sponsor to support the indications/claims made in relation to the medicine. A request was made via telephone to the agent on 17 April 2008 for provision of the actual medicine label (not a printout) including a blister foil, as originally requested in the Section 31 Notice. In this phone call the TGA contact officer Lucy Ward and [redacted] discussed a number of regulatory concerns, including that

- the website for the medicine breached a standard condition of listing by including indications not entered onto the ARTG entry;
- the website contained prohibited advertising representations under the *Therapeutic Goods Advertising Code 2007*;
- the label contained claims relating to patents, organic certification and content of the goods ('biophenols'), and that evidence or information to verify those claims had not been provided in the Claims Substantiation Document;

- the Product Specification Document did not include enough information to ascertain whether the product was consistent with the ARTG entry.

The agent was informed that some of these deficiencies were considered significant, however the sponsor had the option of addressing the issues within 5 working days if they wished to avoid further regulatory action. The agent agreed to raise the issues with the sponsor. Further information was provided dated 24 April 2008 by the agent, including provision of the actual label including blister foil; provision of an updated Product Specification Document; an assurance that the breaches relating to the medicine's website advertisement were being addressed; and an acknowledgement that other issues existed and would be addressed following formal review.

The updated Product Specification Document included an excipient ingredient 'citric acid' not included on the initial Product Specification Document, but which was consistent with the ARTG entry. Five U.S. patent numbers were included on the main label: [redacted] The full text documents were retrieved on 17 July 2008 from the Internet site http://www.patentstorm.us, a database of full-text U.S. patents from the U.S. Patent Office. Several of these patents described the use of citric acid as an agent to promote hydrolysis of oleuropein to hydroxytyrosol in olive vegetation water. Therefore, in order to better characterise the active ingredient, further information on the extraction process from whole herb to the finished extract was requested in an email to the agent dated 23 June 2008. In reply by email on 8 July 2008 the agent provided a flow chart that had been supplied by [redacted], titled '*The Process of Obtaining the Olive Vegetarian Water (Olea europaea) extract*'.

The TGA contact officer Lucy Ward contacted the agent by telephone on 25 July 2008 to ascertain whether the *Olea europaea* extract present in [redacted] Begin was the same extract present in the other medicines: [redacted] The agent confirmed during this phone call and in an email of the same date that '*the olive extract used in the 4 [redacted] products is the same material*'.

A Notice under Subsection 30(1A) of the Act proposing to cancel the medicines from the ARTG was issued the 24 November 2008 signed by Delegate of the Secretary, Hongxia Jin. The Notice outlines that certain information, including documentation provided by [redacted] indicates the medicines are not eligible for listing under section 26A of Act because the *Olea europaea* extract included as an active ingredient in the medicines does not fit the definition of a herbal substance provided for in Regulation 2 of the Regulations.

In the email dated 11 December 2008 [redacted] provided a response attached as a letter dated 10 December 2008 in pdf format. The response did not include evidence to demonstrate that the *Olea europaea* extract meets the definition of a herbal substance.

F. Material Findings of Fact

1. The medicine is not eligible for listing (Paragraph 30(1A)(a) of the Act).

[redacted]

To be eligible for use in listed medicines, the preparation of a herbal substance must be consistent with the definition of a '*herbal substance*' provided for in regulation 2 of the Therapeutic Goods Regulations 1990 ('the Regulations'). Certain information, including the documentation provided on behalf of [redacted] indicates that the medicine does not meet the definition of a herbal substance.

The initial Product Specification Document did not adequately characterise the nature of [redacted] – Begin, specifically, excipient ingredients were not included. The updated Product Specification Document included an excipient, namely citric acid, as a '*carrier*' for the active ingredient *Olea europaea*.

The inclusion of citric acid in the herbal extract, in combination with other certain information, indicates that the *Olea europaea* extract detailed above does not meet the definition of a herbal substance. The certain information includes:

- The publicly available information on the U.S. patents whose numbers were included on the main label.
- The flow chart on the sponsor's letterhead titled '*The Process of Obtaining the Olive Vegetarian Water (Olea europaea) extract*' ('the flow chart').
- The list of the evidence to support the indications/claims made in relation to the medicine ('the Claims Substantiation Document.')
- The letter from [redacted] dated 10 December 2008 ('the submission') in response to the Notice under 30(1A) proposing to cancel the medicine from the ARTG.

Two of the U.S. patents, namely [redacted] describe the treatment of '*olive-derived vegetation water*' with citric acid for the purposes of obtaining '*olive-derived hydroxytyrosol*' (U.S. patent [redacted] or '*an olive extract containing hydroxytyrosol, with low amounts or substantially free of oleoeuropein and tyrosol, and a method of obtaining the same*' (U.S. patent [redacted]). They detail that citric acid is added to olive-derived vegetation water and stored for a period of time to promote acid hydrolysis of the component oleuropein to hydroxytyrosol.

The flow chart from the sponsor describes that 'Vegetation water' is collected from the pulp of organic olives. Citric acid is added and it is then stored at room temperature, after which the material is sterilised and converted to powder. This extraction process appears to be consistent with the methods described in the above patents.

The Claims Substantiation Document includes the phrase: '... *hydroxytyrosol, the principal bio-phenol in* [redacted]...', a reference from a clinical trial by Bitler *et al.* (2003). This indicates the medicine includes a significant level of hydroxytyrosol, which is consistent with an extract *Olea europaea* that has been subject to a treatment intended to yield hydroxytyrosol as described in the above patents.

The submission from the company dated 10 December 2008 confirmed that '*in the case of olive vegetation water, as effect of lowering the pH of the solution, it* [citric acid] *expedites the hydrolysis of oleuropein into hydroxytyrosol and elenolic acid.*'

The following definition of a herbal substance is included in regulation 2 of the Regulations:

> ***herbal substance*** means all or part of a plant or substance (other than a pure chemical or a substance of bacterial origin):
>
> (a) that is obtained only by drying, crushing, distilling, extracting, expressing, comminuting, mixing with an inert diluent substance or another herbal substance or mixing with water, ethanol, glycerol or aqueous ethanol; and
>
> (b) that is not subjected to any other treatment or process other than a treatment or process that is necessary for its presentation in a pharmaceutical form.

The active ingredient of [redacted] does not meet the definition of herbal substance because:

- The expressed plant part is mixed with citric acid, a substance that causes a change in the chemical composition of the herbal material. The citric acid is therefore not an inert diluent substance or any other substance that may be mixed with a herbal substance that are outlined in point (a) of the definition.

- The step of adding and storing the citric acid to the vegetation water is a process of promoting the hydrolysis of oleuropein to hydroxytyrosol, which is a treatment or process not necessary for the presentation of the herbal substance in a pharmaceutical form.

The submission by the company discussed that an increased amount of hydroxytyrosol is found in ripe olives versus green olives and supports the notion that hydrolysis of oleuropein to hydroxytyrosol occurs naturally, most likely enzyme-mediated. This information does not alter the material fact that the *Olea europaea* plant material included in the medicine is subject to a chemical reaction caused by citric acid, a treatment not included in the definition of a herbal substance. The submission also alludes to a role of citric acid as a '*stabilizer / preservative*', because '*if no acid would be added to the olive vegetation water, the product would spoil quickly with an irreversible loss of a very valuable source of hydroxytyrosol.*' Accordingly, the U.S. patent [redacted] contains the following information:

> *B. Conversion of oleuropein to hydroxytyrosol*
>
> *... The pH of the vegetation water may be decreased by addition of acid, and the vegetation water allowed to incubate under conditions which, according to the discovery of the invention, promote acid hydrolysis of oleoeuropein to hydroxytyrosol.*
>
> ...
>
> *The addition of acid to the vegetation water serves several purposes: (i) it stabilizes the vegetation water; (ii) it prevents fermentation of the vegetation water; (iii) it slowly hydrolizes the oleoeuropein, converting it to hydroxytyrosol; ...*

The '*stabilizer / preservative*' action of citric acid appears to only relate to the phase of incubating/storing the vegetation water, which is for the purposes of promoting hydrolysis of oleuropein to hydroxytyrosol (also through the action of citric acid.) Therefore, the addition of citric acid to the 'vegetation water' is not a treatment necessary for the presentation of the *Olea europaea* plant material in a pharmaceutical form.

Paragraph 9A(4) of the Act relevantly provides that '*The regulations may prescribe: (a) the therapeutic goods, or the classes of therapeutic goods, that are required to be included in each*

part of the Register.' Regulation 10 of the Regulations relevantly provides that '*Goods to be included in parts of the Register ... For paragraph 9A(4)(a) of the Act: ... (b) therapeutic goods, and classes of therapeutic goods, of a kind mentioned in Part 1 of Schedule 4 that are included in the Register are to be included in the part of the Register for listed goods.*' Part 1 of Schedule 4 of the Regulations includes preparations that have herbal substances as their therapeutically active ingredients. Herbal substances eligible for inclusion in the Part of the Register for listed goods must meet the definition of herbal substance, which is set out in regulation 2 of the Regulations.

As [redacted] contains an extract of *Olea europaea* as an active ingredient, which is not a herbal substance for the purposes of Part 1 of Schedule 4 of the Regulations, I consider that [redacted] is not eligible for listing as a medicine in the ARTG under section 26A of the Act.

- [redacted]

The agent acting on behalf of [redacted] confirmed in a phone call and email on 25 July 2008 that the *Olea europaea* extract included as an active ingredient in [redacted] is the same *Olea europaea* extract included in [redacted]

For the reasons presented above in relation to [redacted] namely that the herbal extract of *Olea europaea* included in the medicines is not a herbal substance for the purposes of Part 1 of Schedule 4 of the Regulations, I consider that [redacted] are not eligible for listing as medicines in the ARTG under Section 26A of the Act.

Review rights

This Decision is an 'initial decision' within the meaning of Section 60 of the *Therapeutic Goods Act 1989*. This means that if your interests are affected by the decision, you may seek reconsideration by the Minister. Any appeal should be made in writing within 90 days after this decision first comes to your notice or to the notice of your company, and should be sent to the following address:

The Parliamentary Secretary to the Minister for Health and Ageing
Parliament House
CANBERRA ACT 2600

This letter should be headed 'APPEAL UNDER SECTION 60 OF THE THERAPEUTIC GOODS ACT 1989'.

The Parliamentary Secretary may either deal with the appeal personally or send it to be dealt with by one of the Minister's delegates within the Department. Should you be dissatisfied with the result of your appeal then, subject to the *Administrative Appeals Tribunal Act 1975*, you may appeal to the Administrative Appeals Tribunal for review of the Minister's/Delegate's decision.

Other matters for action and/or consideration

The *Olea europaea* extract discussed in this letter does not meet the definition of a herbal substance, however other options are available, if the sponsor wishes to supply this type of medicine in Australia. In brief, these options are:

- Submitting an '*application for an evaluation of a new complementary medicine substance*'. The application is assessed to determine suitability for use in listed medicines. If considered suitable the substance may become eligible for listing for the purposes of Part 5 and Part 1 of Schedule 4 to the Therapeutic Goods Regulations 1990.

OR

- Submitting a '*new medicine registration application form (complementary medicines).*' If approved, the medicine becomes eligible for inclusion in the part of the Register for registered (as opposed to listed) goods.

The Office of Complementary Medicines may be contacted if further information is required.

Yours faithfully

Hongxia Jin
Delegate of the Secretary

3 April 2009

cc: [redacted] Facsimile: [redacted]