CONFIDENTIAL FAX [redacted]

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Office of Complementary Medicines
Contact Officer: Pradip Adhikari
Telephone: 02 6232 8908
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[redacted]

Facsimile: [redacted]

Attention: Regulatory Affairs Officer

Dear Sir / Madam

Re: [redacted]

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

Medicine: [redacted]
Sponsor:

I, Michael Wiseman, 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] from the Australian Register of Therapeutic Goods (ARTG) in reliance on paragraph 30(1A)(a) of the Act.

Pursuant to Subsection 30(5)(a) of the Act, this cancellation is effective from the date of this letter. You are reminded that under the provision of Section 20 of the Act, it is an offence to supply therapeutic goods not entered in the ARTG.

A. Reasons for cancellation

I have cancelled the above medicine because it is not eligible for Listing.

To be eligible for use in Listed medicines, processes used to prepare a herbal substance must be consistent with those outlined in the following definition of a herbal substance included in the Therapeutic Goods Regulations 1990 (the Regulations):

> ***herbal substance*** means all or part of a plant or substance (other than a pure chemical or a substance of bacterial origin):

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On 4 June 2007, the TGA issued a notice to the sponsor under Section 30 of the Act, proposing to cancel the medicine, on the basis that the ingredient *Piper nigrum* dry concentrated extract, known commercially as [redacted], contained in the medicine was not eligible for inclusion in Listed medicines. This Section 30 Notice gave the sponsor an opportunity to make a submission to resolve the issues.

In the submission dated 14 June 2007, and during a subsequent teleconference on 20 June 2007, the sponsor stated that:

1. there is no chemical alteration to the structure of piperine obtained following the extract manufacturer's methods,
2. the activated charcoal and neutral alumina hydroxide are used to remove/filter out impurities, and
3. the [redacted] material is typically only 95% pure and therefore should not be considered a pure chemical entity,

In response to the above three statements, I offer the following:

1. The TGA's letters to the sponsor never raised any issues in relation to the structure of piperine or the choice of solvents to manufacture piperine, other than verbally communicating to [redacted] that the solvents nominated in the ARTG are different to the solvents that are actually used during manufacture.

2. The sponsor's statement regarding the purpose of the use of activated charcoal and neutral alumina hydroxide – to remove/filter out impurities – itself confirms that these steps are designed to change the composition of the extract and isolate purified piperine.

3. In relation to the sponsor's argument that the substance is typically 95% piperine and hence can not be considered a pure chemical, the sponsor stated in its letter of 14 June 2007 that the batch of [redacted] used in [redacted] was 97.3% pure. It is also noted that the product specifications assigned by the manufacturer of [redacted] states a limit of 95-102% piperine. It is considered that, a batch found to be close to 100% piperine would fall well within the company's specifications and this batch would be used for the manufacture of the finished product. This is confirmed by a copy of the certificate of analysis for [redacted] submitted by the sponsor for batch G50287E (sampled on 18/03/2005), which reports the purity of the material as 99.2% w/w.

   According to the information publicly available on the Internet (*Piperine Fact sheet*, available at http://www.epa.gov/pesticides/biopesticides/ingredients/factsheets/factsheet_043501.htm and ChemWiki website http://www.ch.ic.ac.uk/wiki/index.php/It:Piperine), piperine for commercial use is manufactured synthetically. The online catalogue of Sigma-Aldrich, a global supplier of chemicals and reagents, lists two grades of piperine, representing 97% and greater than >=98% purity, respectively. Piperine with =>98% purity is referred to as 'piperine purum'. This demonstrates that even synthetically manufactured pure reagent grade piperine is not 100% pure. Therefore, the sponsor's argument that [redacted] can not be considered a pure chemical substance because it is claimed to be 95-102% pure, is not supported.

E. Relevant provisions under the Act

Subsection 30(1A) of the Act 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) 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.

On the basis of the information available to me, I consider that the active ingredient *Piper nigrum* extract included in the medicine is not a herbal substance as defined in the Regulations. Therefore, this medicine is not eligible for Listing in the ARTG.

B. In making this decision I have considered the following:

1. Complaints in relation to the medicine received by the TGA.
2. The information provided by [redacted] on 10 May 2007 in response to the TGA's Notice of 2 May 2007 under Section 31 of the Act.
3. Advice from the TGA Laboratories regarding the manufacturing process for the active ingredient *Piper nigrum* extract containing the herbal component which is supplied by the commercial name of [redacted]
4. The submission from [redacted] dated 14 June 2007 in response to the TGA's notice of 4 June 2007 which proposed to cancel the Listing of the medicine.
5. The teleconference between representatives of [redacted] and the TGA officers held on Wednesday 20 June 2007.
6. The records held in the ARTG for the above medicine.
7. The Therapeutic Goods Act 1989.
8. The Therapeutic Goods Regulations 1990.

D. Material Findings of Fact

A complaint was received by the TGA regarding the active ingredient *Piper nigrum* extract raising concerns that it may not meet the current definition of a herbal substance as defined in the Regulations. On 2 May 2007, the TGA issued a notice under Section 31 of the Act requesting the sponsor provide information regarding the processes used to manufacture the ingredient entered in the ARTG as 'dry concentrated extract of *Piper nigrum*'. The manufacturing information submitted by the sponsor on 10 May 2007 in response to the Section 31 notice was assessed by an evaluator at the TGA Laboratories (TGAL) to determine whether the procedures described were consistent with the current Regulation's definition of a herbal substance. The TGAL evaluator identified several steps involved in the manufacture of the active ingredient described as containing the herbal component piperine, which they believed did not meet the current Regulations' definition of a herbal substance. The issues raised by the TGAL evaluator were communicated to [redacted] by an e-mail on 23 May 2007. The questionable manufacturing steps included:

- Step 3.5, which involves treating the solution of crude material in methanol with charcoal at 70°C, is considered a purification step as its purpose appears to go beyond the filtration of undissolved materials and/or removal of only coloured materials.
- Step 3.6 is considered a further purification step in which the product of step 3.5 is treated with neutral alumina at 70°C. This step appears effectively equivalent to a chromatographic step whereby undesirable material, including those in solution, are removed from the extract in order to obtain purified piperine.

(a) the medicine is not eligible for listing.

Pursuant to subsection 30(5) of the Act, 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.

F. Review Rights

These decisions are "initial decisions" 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

The appeal to the Minister 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.

Yours faithfully,

Michael Wiseman
Delegate of the Secretary

02 July 2007