PROMETHEAN CORP

April 3, 2009

Office of Nutritional Products, Labeling,
and Dietary Supplements (HFS-800)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 02740-3835

To Whom It May Concern:

This letter serves as the Premarket Notification to the United States Food and Drug Administration for the New Dietary Ingredient to be included in a product that will be introduced for distribution in the United States and other global markets. The required information is as follows:

1.) The name and complete address of the distributor of the dietary supplement that contains the new dietary ingredient.

(b) (4)

2.) The name of the new dietary ingredient that is the subject of the premarket notification.

Resveratrol also known as *trans*-3,5,4'-Trihydroxystilbene; 3,4',5-Stilbenetriol; *trans*-Resveratrol; (*E*)-5-(*p*-Hydroxystyryl)resorcinol (*E*)-5-(4-hydroxystyryl)benzene-1,3-diol

3.) Description of the dietary supplement.

AIO Premium Cellular Health is a liquid nutraceutical dietary supplement which includes 75 mgs of the new dietary ingredient, Resveratrol. Suggested use is 1-2 ounces daily with recommended daily maximum usage not to exceed 4 ounces for men and 3 ounces for women. As with all dietary supplements, consultation with the individual's doctor is recommended before

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use. If an individual is taking prescription medication, has an ongoing medical condition, is pregnant, nursing or under the age of 18, they should consult their doctor before using the product.

4.) The history of use or other evidence of safety establishing Resveratrol, when used under the conditions recommended or suggested in the labeling of AIO Premium Cellular Health, will reasonably expected to be safe.

Resveratrol (trans-resveratrol) is a phytoalexin produced naturally by several plants when under attack by pathogens such as bacteria or fungi. Resveratrol has also been produced by chemical synthesis and is sold as a nutritional supplement derived primarily from Japanese knotweed. It currently is included in many dietary supplements sold over the counter in health food and nutritional stores. Attached is information made publicly available on the website of Memorial Sloan-Kettering Cancer Center. References are made to the many source documents used for the compilation of the information provided.

5.) Signature of an officer of the distributor.

See the signature below of the Chairman and Chief Executive Officer of the holding company parent of the distributor of the dietary supplement.

Respectfully,

Matthew T Henninger, Chairman & CEO
212-355-5134 (direct)
mth@prmncorp.com

Memorial Sloan-Kettering Cancer Center

About Herbs

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Resveratrol

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Scientific Name

3,5,4'-trihydroxystilbene

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Common Name

Resveratrols, Trans-3,5,4'trihydroxystilbene, 3,5,4'-trihydroxy-trans-stilbene

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Clinical Summary

Resveratrol is a polyphenolic compound found in the skins of red grapes. It is also found in peanuts, mulberries, spruce, eucalyptus, and some Chinese herbs. Resveratrol has antioxidant and anti-inflammatory properties as evidenced by its cardioprotective effects. It reduces the oxidation of low density lipoproteins (LDL) and inhibits aggregation of platelets and may offer protection against atherogenesis and coronary heart disease [1] [2].Several cell culture and animal studies have shown that resveratrol inhibits proliferation of cancer cells by apoptosis and by exerting antiestrogenic effects [3] [4] [5] [6]. However, there is contradicting data from another study which showed that it acts as a phytoestrogen and could activate genes that are normally regulated by estrogen [7]. According to other studies, resveratrol was found to inactivate some enzymes of the CYP450 family in tumor cells [8] [9]. Recently, resveratrol has

been implicated in enhancing longevity based on preliminary data from experiments done in yeast cells [10] [11]. However, there is no data from clinical trials to verify these effects in humans. Women with hormone sensitive diseases, such as estrogen receptor-positive cancer should avoid resveratrol as it may stimulate the proliferation of certain tumor cells.

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Food Sources

- Grape skin
- Peanuts
- Mulberries
- Spruce
- Eucalyptus
- *Polygonum cuspidatum* or Japanase knowtweed

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Purported uses

- Atherosclerosis
- Cancer prevention
- Coronary heart disease
- Inflammation

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Mechanism of Action

Resveratrol acts as an antioxidant and inhibits the oxidation of low density lipoproteins (LDL) [1], aggregation of platelets, and eicosanoid synthesis, thereby may help to protect against atherosclerosis and coronary heart disease [2]. It also acts as an anti-inflammatory agent by inhibiting cyclooxygenase (COX) activity [12] as well as the release of cytokines from macrophages in chronic obstructive pulmonary disease (COPD) [13]. Laboratory studies have shown that resveratrol has estrogen-like properties and activates expression of genes that are regulated by estrogen [7]. Other data from cell culture and animal experiments suggest that it plays a role in cancer chemoprevention during initiation, promotion, and progression of carcinogenesis [12] [14]. In vivo studies have also demonstrated the inhibitory effects of resveratrol on the growth of oral squamous carcinoma cells [3], human promyelocytic leukemia cells [4], human breast cancer cells [5], and neuroblastoma cells [6] resulting from induction of apoptosis and antiestrogenic property. Resveratrol was also found to inhibit the enzymes CYP1A1, CYP1A2, and CYP1B1 in tumor cells. This may be one of the mechanisms by which resveratrol exerts anti-tumor effects as some of these enzymes are known to be involved in the activation of procarcinogens and toxins [8] [9]. Preliminary data from recent experiments in yeast cells suggests that resveratrol may have a role in increasing life span which it does by activating a set of genes known as sirtuins [10] [11].

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Pharmacokinetics

Upon oral administration, resveratrol is rapidly absorbed in the gastrointestinal tract and undergoes glucoronidation and sulfation in the liver microsomes. More than 50% of the ingested resveratrol is eliminated in urine in 24 hrs [15].

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Adverse Reactions

As resveratrol exhibits estrogen-like properties and activates transcription by estrogen receptor that leads to stimulation of cancer cell proliferation, women with estrogen receptor-positive cancers should avoid resveratrol [7].

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Herb-Drug Interactions

- Because resveratrol inhibits platelet aggregation, concurrent use of other antiplatelet drugs may increase the risk of bleeding.
- Since resveratrol inactivates certain enzymes of the CYP450 family, the concentration of drugs that are metabolized by the same enzymes may increase in the body.

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Literature Summary and Critique

There is no data from clinical trials to support the beneficial effects of resveratrol in humans.

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References

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Memorial Sloan-Kettering Cancer Center

About Herbs

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Resveratrol

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How It Works

Bottom Line: In laboratory studies, resveratrol was shown to reduce inflammation, but human data is lacking.

A naturally occurring compound in the skins of red grapes and other botanicals, resveratrol has been shown to reduce inflammation. It also has antioxidant properties and may help to protect against atherosclerosis (thickening of arterial walls) and heart disease. Animal studies have shown that resveratrol has the ability to prevent certain cancer cells from dividing. Researchers now believe that it may also play a role in increasing life span in yeast cells. However, it is not clear if similar effects will be seen in humans.

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Purported Uses

- **Atherosclerosis**

Laboratory studies have shown that resveratrol helps in preventing atherosclerosis

- **Coronary heart disease**

There is limited scientific evidence to support this use

- **Cancer prevention**

Several laboratory studies have demonstrated the ability of resveratrol in preventing growth of cancer cells. However, it is not clear if similar effects will be seen in humans.

- **Inflammation**

This use is supported by data from laboratory studies.

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Research Evidence

Clinical trials have not been conducted so far to test the efficacy of resveratrol in humans.

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Do Not Take If

- You are taking antiplatelet drugs (resveratrol may increase the risk of bleeding)
- You are taking drugs that are metabolized by CYP450 (Cytochrome P450) enzymes (resveratrol inactivates some CYP450 enzymes which may lead to accumulation of such drugs in the body).

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Side Effects

Women who have estrogen receptor-positive cancers should not take resveratrol because it may cause certain cancer cells to multiply.

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