

Oral Delivery Technologies  
37 Prospect Street  
Nutley, NJ  
07110

DEC 13 2005

AIMS #  
2006-317

December 28<sup>th</sup>, 2005

Division of Standards and Labeling Regulations  
Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park Md.  
20740-3835

Dear Sirs,

Please find enclosed three 75 day premarket notifications, with respect to three new dietary supplements that Oral Delivery Technologies and Netrients.com intend to market, in accordance with Section 8 of the Dietary Supplement Health and Education Act of 1994.

Should there be any questions with respect to these filings please do not hesitate to contact the undersigned.

Yours truly,



Michael Farber MSc  
President  
Oral Delivery Technologies  
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Dear Sirs,

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, on behalf of Oral Delivery Technologies (ODT) on its own behalf and on behalf of Netrients.com, wishes to notify the Food and Drug Administration that it will market a new dietary supplement consisting of a combination of 25mg of 7ketoDHEA acetate, the acetylated form of 7-keto DHEA, a metabolite of DHEA, 25 mg of Hoodia Gordinii 20:1 extract and 25mg of citrus aurantium extract (standardized to 60% synephrine), 5 mg of pepper extract (standardized to 95% Piperines) and 5 mg of 6,7 dihydroxy bergamottins (grapefruit rind extract). The 85 mg total of components will be available as a tablet or drink to be consumed up to a maximum of three times a day to try to increase metabolism and reduce appetite.

Attached please find a summary and reports of safety studies and other information with respect to all the major ingredients in the above mentioned dietary supplement.

1. Preliminary filings with respect to 7-keto DHEA acetate by Humanetics Corp and GNC in 1997
2. Studies and current safety data with respect to citrus aurantium
3. Hoodia gordinii is an aloe type plant found in the Kalahari desert. the only studies with respect to efficacy and safety were conducted by Phytopharm in 2001. These studies showed no adverse effects. It should also be noted that the Kalahari Bushmen have consumed the hoodia gordinii for thousands of years without adverse effects and that consumers throughout the world have over the past several years have consumed millions of doses of hoodia without the reporting of adverse side effects. The use of hoodia gordinii produces a marked reduction in appetite, purportedly thru a mimetic effect of the glucose molecule in specific

binding to a site in the cerebral cortex that controls appetite. To date no reported negative side effects.

4. The appropriate cautionary warnings with regard to potential interactions, not for use by persons with elevated blood pressure, cardiovascular disease or suspected disease or history, persons taking MAO inhibitors and other possible drug interactions, not for use by persons under age 18, not for use by pregnant women or lactating women, always consult a physician before commencing any diet or supplement or exercise program, along with specific limitations as to use and the required mandatory statements for dietary supplements from the FDA will be clearly shown on all labeling and advertisements.

Should there be any questions with respect to this filing please do not hesitate to contact the undersigned.

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Michael Farber MSc  
President  
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Should you require further data p

**7-keto DHEA Acetate**  
**Basis for Concluding New Dietary Ingredient Will Reasonably Be Expected to be Safe**

**Background**

Dehydroepiandrosterone (DHEA) is a dietary ingredient which was marketed in the United States before October 15, 1994. 7-oxo-DHEA (7-keto DHEA) is a well-known metabolite of DHEA in humans. The occurrence of 7-keto-DHEA in urine of healthy and diseased persons was first reported by Lieberman et al. in 1948. They described the properties of the compound, but were unable to assign a specific structure.

In 1954, Fukushima et al. reported that 7-keto-DHEA is found in urines from both normal and abnormal subjects; it is excreted in larger amounts in adrenal abnormalities, especially those characterized by increased excretion of dehydroepiandrosterone (DHEA). Gallagher (1958) found that amphenone, an inhibitor of steroid hormone synthesis, suppressed the urinary excretion of cortisol and dehydroepiandrosterone, but had relatively little effect on the excretion of 7-keto-DHEA. Baulieu et al. 1961 showed that 7-keto-DHEA is present as the sulfate (at the 3-position) as is DHEA. Levels of 7-keto-DHEA sulfate in the blood from six patients ranged up to 40% of those of DHEA sulfate. Faredin et al. (1969) found that enzymes in human skin *in vitro* metabolized DHEA to 7-oxygenated derivatives, including 7-keto-DHEA. 7-Alpha-hydroxy-DHEA was detected in human blood and tissues (Parker, 1989), as a result of hydroxylase enzyme acting on DHEA; 7-keto-DHEA was also present.

7-keto-DHEA was first synthesized and identified by Billeter and Miescher also in 1948. 3-Beta-acetoxy-androst-5-en-7, 17 dione (7-keto-DHEA acetate) is an acetylated form of 7-keto-DHEA. The acetate group is added to protect the 3 position from oxidation that occurs during the manufacturing of 7-keto-DHEA acetate. 7-keto-DHEA acetate is readily converted to 7-keto-DHEA by esterases located in the blood and in body tissues. Similar compounds (i.e., DHEA) are manufactured and consumed as acetate esters.

## **Safety Assessments**

Several safety assessments were performed using 7-keto-DHEA acetate or 7-keto-DHEA. The mutagenic activity of 7-keto-DHEA acetate and/or its metabolites was assessed for their ability to induce reverse mutations at the histidine locus in the genome of specific *Salmonella tyhimurium* tester strains and at the tryptophan locus in an *Escheichia coli* tester strain both in the presence and absence of exogenous metabolic activation system of mammalian microsomal enzymes (S-9) derived from Arochlor-induced rat liver. Doses of 7-keto-DHEA acetate ranged from 0.1 to 5.0 mg per plate. 7-keto-DHEA acetate did not cause a positive increase in the number of revertants per plate in any of the tester strains either in the presence or absence of S-9.

The acute toxicity of 7-keto-DHEA acetate, administered as single oral gavage doses, was assessed in five groups of CrI: CD (SD) BR VAF/Plus rats (five/sex/group) at dose levels of 0, 250, 500, 1000 or 2000 mg/kg. All animals survived to the scheduled day 15 sacrifice. There were no differences in body weight or body weight gain attributed to test material. 7-keto-DHEA acetate had no apparent effect on anatomical pathology results. Thus, the no-observable-adverse-effect level for 7-keto-DHEA acetate was greater than 2,000 mg/kg.

Safety was also addressed in rhesus monkeys in two separate studies. In one study, four monkeys (2/sex) received 7-keto-DHEA acetate by oral gavage at dose levels of 250, 500 and 1000 mg/kg on days 1, 3 and 5 respectively and 1000 mg/kg on days 7 through 11. Blood samples were collected for hematology and clinical chemistry tests on day 0, 7 and 12. Animals were anaesthetized, exsanguinated and necropsied on day 12. Administration of 7-keto-DHEA acetate at a level of 1000 mg/kg for five days had no apparent effects on clinical or anatomical pathology results.

In another rhesus monkey study, a total of 16 male monkeys, from 4 to 8 years old, were used in two experimental groups (Kernitz et al., 1997). First, 7-keto-DHEA was fed to groups of 2, 2 and 3 monkeys at doses of 7, 35 and 70 mg/kg daily, respectively. 7 and 35 mg/kg animals received compounds for one week while the high dose group received compound for two weeks. Liver biopsies

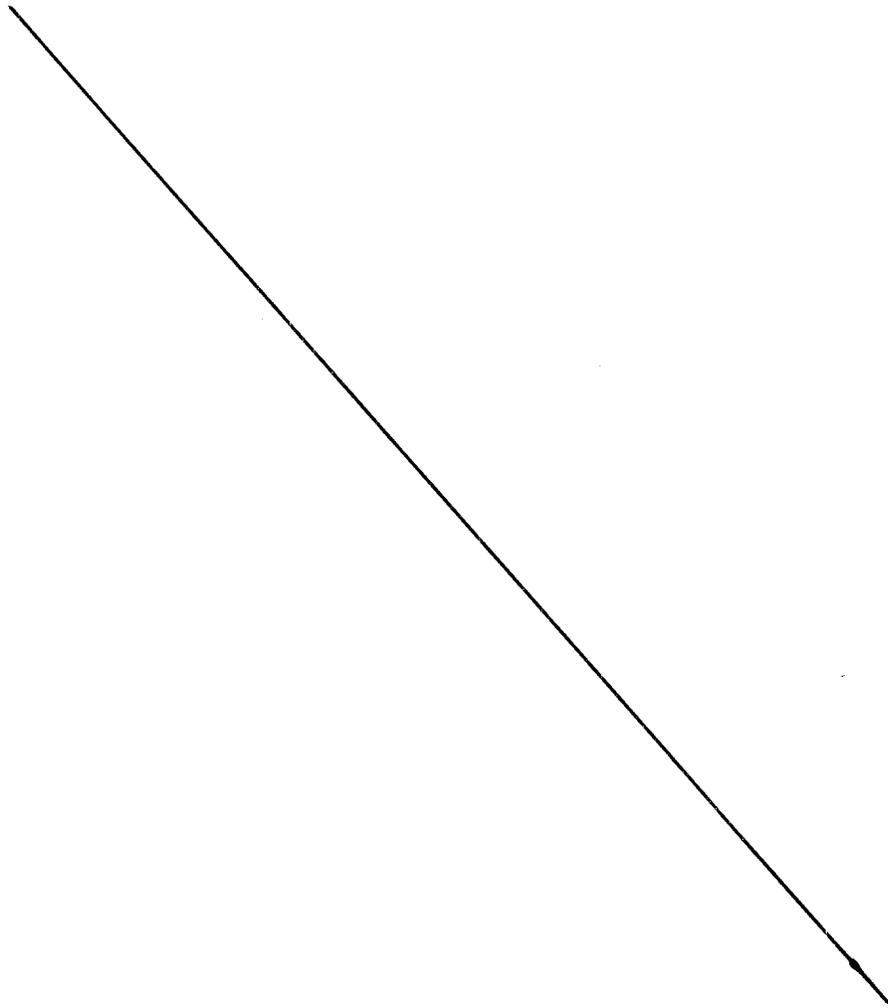
were obtained prior to dosing and on days 7 (or 14) and 28. In the additional experimental group, dosing was extended to 28 days. Groups of three monkeys received placebo, 25 ug thyroxin or 140 mg/kg 7-keto DHEA. Liver biopsies for histological examinations were taken before and at the end of the dosing period. In both experimental groups, fasting blood samples were drawn weekly. There were no effects on behavior or appearance. 7-keto-DHEA caused no detectable changes in blood chemistries, differential cell count, hemoglobin, hematocrit, mononuclear cell proliferation or liver histology. Body weights were not affected by 7-keto-DHEA.

Unlike DHEA, 7-keto-DHEA is not convertible to active androgens or estrogens. Sunde et al. (1982) reported that 7-alpha-hydroxytestosterone has no androgenic activity as measured by its lack of effect on maintenance of acid phosphatase in castrated rats. Lardy et al. (1995) further demonstrated that 7-hydroxytestosterone does not influence rat seminal vesicle weight nor does it induce thermogenic enzymes. Cedard et al. 1964 found that 7-keto androst-5-ene compounds are not aromatized and thus can not be converted to estrogens.

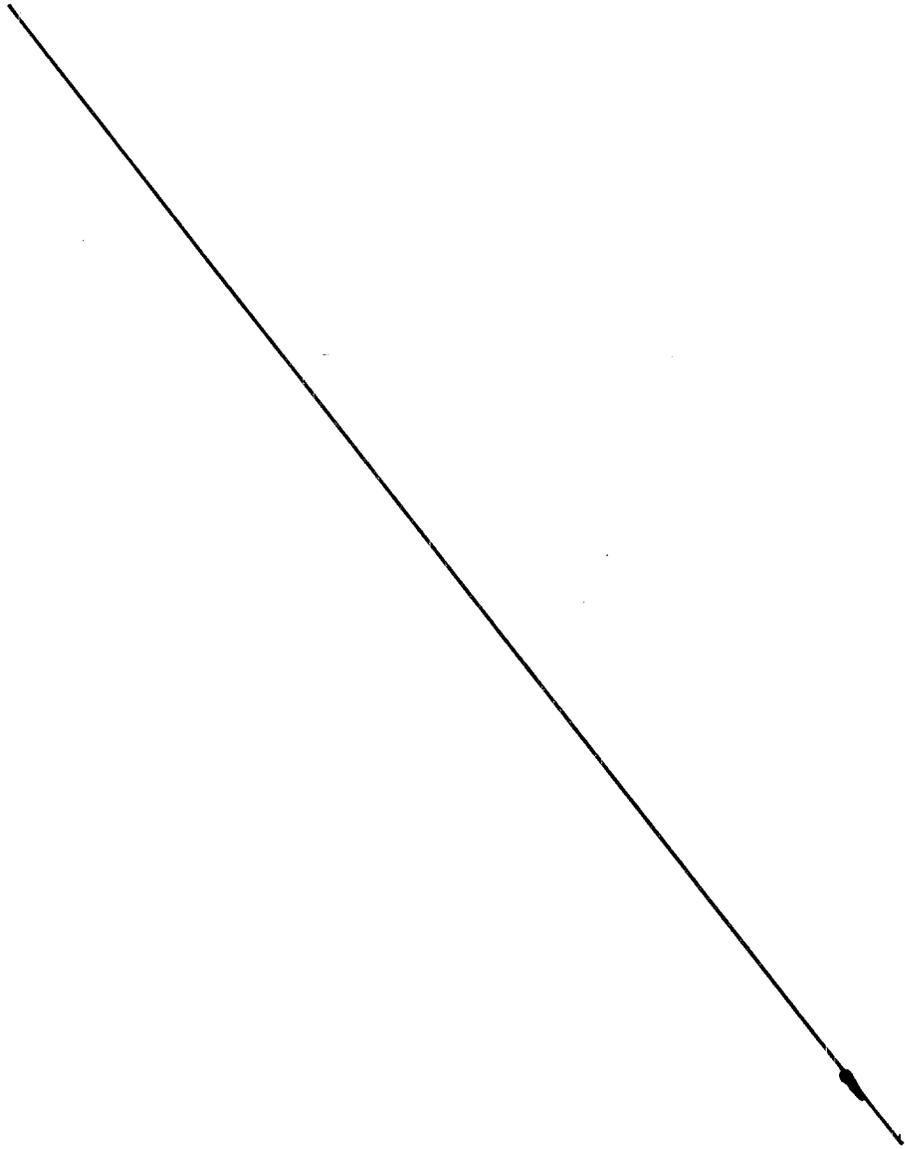
#### **Dose Considerations**

Selection of the dose of 7-keto-DHEA acetate for human consumption was determined from: 1) acute toxicity studies in rats and monkeys; 2) sub chronic exposure in monkeys; and 3) reference to well tolerated doses of DHEA, up to 750 mg TID for 16 weeks in human clinical trials (Dyner et al. 1993), on the rationale that DHEA is readily convertible to 7-keto-DHEA in humans. Based on acute oral safety results in rats (no deaths or untoward clinical signs at doses up to 2000 mg/kg), and rhesus monkey (no deaths, no changes in liver, blood or urine chemistries observed at doses up to 1000 mg/kg) as well the fact that no changes were observed in a 28 day study of 7-keto-DHEA in rhesus monkeys at doses of 140 mg/kg, it was determined that a dose of 25 mg 7-keto-DHEA up to two times daily would be well-tolerated in humans. This dose (50-75 mg/day) is about 1 mg/kg (in a 50-75 kg person) and is 1/2000 or 1/1000 the non lethal dose in rats and monkeys. Also 1 mg/kg 7-keto-DHEA acetate daily is 140-fold lower than the no effect dose given rhesus monkeys for 28 days.

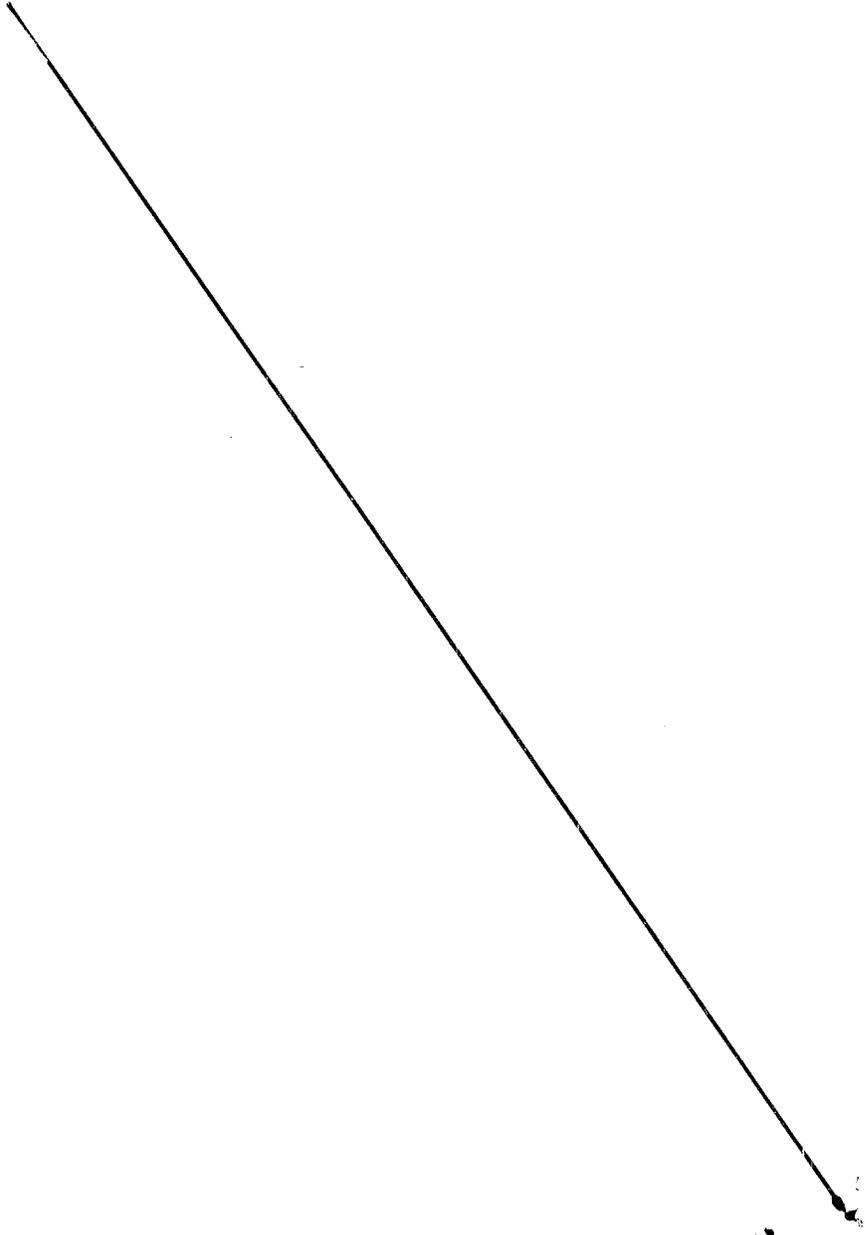
**ESCALATING DOSE ORAL GAVAGE  
TOXICITY STUDY IN RHESUS MONKEYS**



**ACUTE ORAL GAVAGE  
TOXICITY STUDY IN RATS**



**MUTAGENICITY TEST**



**LACK OF TOXICITY OF 7-KETO-DEHYDROEPIANDROSTERONE IN RHESUS MONKEYS**

