

November 16, 2015

Jared Wheat, CEO  
Hi-Tech Pharmaceuticals  
6015-B Utility Drive  
Norcross, Georgia 30071

RE: Request for Opinion

Dear Jared:

We have been requested by Hi-Tech Pharmaceuticals, Inc., to provide an opinion regarding the legal status of 1-dehydroepiandrosterone (1-DHEA) and other DHEA derivatives under the Food, Drug & Cosmetic Act (“FDCA”) as amended by the Dietary Supplement Health and Education Act of 1994 (“DSHEA”). Hi-Tech has also requested a legal opinion as to whether the Designer Steroid Control Act of 2014 (“DSCA”) prohibits the sale and marketing of 1, 4, 5, and 19 DHEA compounds. The client has also requested an analysis of 3, 7 Keto DHEA a/k/a androsta 3, 5 diene 7, 17 dione – Alpha Isomer CAS # 1420-49-1 (“3, 7 Keto DHEA”). Based upon the following, it appears that 1-DHEA, 4-DHEA, 5-DHEA, 19-Nor-DHEA, Epiandrosterone, 7 $\alpha$  and 7 $\beta$  hydroxy DHEA, and 3, 7 Keto DHEA should qualify as a legal dietary supplements under DSHEA and also be exempted under DACA and, therefore, lawful and uncontrolled compounds.

**I. DSHEA & DSCA.**

Under DSHEA, dietary supplements are considered foods. 21 U.S.C. § 321(ff). In order to be considered a “dietary supplement,” a product must:

- (1) be intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of the foregoing ingredients;
- (2) (A) intended for ingestion in tablet, capsule, powder, softgel, gelcap or liquid form; (B) not represented for use as a conventional food or as a sole item of a meal or the diet; and (C) labeled as a dietary supplement; and
- (3) if it includes articles approved as new drugs under 21 U.S.C. § 355, then prior to its approval, the product must have been marketed as a dietary supplement or food, unless a regulation has been issued, after notice and comment, that the article when

used as a dietary supplement is unlawful under 21 U.S.C. § 342(f), but does not include articles approved as new drugs which prior to such approval were not marketed as dietary supplements unless a regulation has been issued, after notice and comment, finding the article is lawful under 21 U.S.C. § 342(f).

21 U.S.C. § 321(ff). In addition, it is important to recognize that a dietary supplement must not be intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. Such a use would place the product under the category of a “drug” as opposed to a dietary supplement. 21 U.S.C. § 321(g)(1)(B).

On January 3, 2014 Congress passed the Designer Steroid Control Act of 2014 (“DSCA”) and it was signed by the President on December 18, 2012.<sup>1</sup> The Act placed restrictions on the sale and marketing of products with substances that are substantially similar to anabolic steroids or similar supplements such as pro-hormones which were listed as controlled substances under previous legislation.

The DSCA listed 25 specific new compounds in sub-paragraph (A), and then provides that, “subject to certain exceptions as set forth in clause (ii) a drug or hormonal substance (other than estrogens, progestins, corticosteroids, and dehydroepiandrosterone) that is not listed in Sub-paragraph (A), and is derived from, or has a chemical structure substantially similar to 1 or more steroids listed in sub paragraph (A) shall be considered an anabolic steroid if it has been created or manufactured with the intent of producing another substance that either

- a) promotes muscle growth; or
- b) otherwise causes a pharmacological effect similar to that of testosterone.

However, any substance that is an estrogen, a progestin, a corticosteroid, or a dehydroepiandrosterone (DHEA) is not covered by this legislation and is specifically exempted.

## **II. DHEA.**

Dehydroepiandrosterone (DHEA) is a 19-carbon steroid that is naturally produced in the body in many forms. DHEA is an adrenal hormone that functions as a metabolic precursor for the production of testosterone, estrogen, and other hormones. DHEA qualifies as a dietary supplement under DSHEA because DHEA is produced naturally by the adrenal glands through a conversion of cholesterol. DHEA was first discovered as a urine metabolite in 1934 by Adolf Butenandt and Hans Dannenbaum from Germany, reaffirmed as a urinary metabolite in 1943 and isolated from

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<sup>1</sup> See <https://www.govtrack.us/congress/bills/113/hr4771>

serum in 1954. DHEA is subjected to extensive metabolism forming a multitude of metabolites including but not limited to androsterone, epiandrosterone and etiocholanolone. DHEA is the second most abundant circulating steroid in humans and serves as the substrate (precursor) for other androgens such as testosterone and dihydrotestosterone (DHT) as well as estrogens like Estrogen and 17 $\beta$ -Estradiol. DHEA is legal to sell in the United States as a dietary supplement. It is currently grandfathered in as an "Old Dietary Ingredient" being on sale prior to 1994.<sup>2</sup>

DHEA can turn into 7 $\alpha$ -hydroxyDHEA via an enzyme Oxysterol 7 $\alpha$ -hydroxylase (CYP3A4/5 has also been implicated), and this molecule can be converted into a beta form (7 $\beta$ -hydroxyDHEA) via 11 $\beta$ -HSD type 1. Conversion of DHEA into the 7 $\alpha$  and 7 $\beta$  oxygenated metabolites mentioned above is not limited to steroidogenic tissues (testes, ovaries) nor the adrenals, and can occur in brain, spleen, thymus, perianal skin, ventral skin, intestine, colon, coecum and muscle tissues. Both 7 $\alpha$  and 7 $\beta$  hydroxy DHEA can be further converted into 7-Oxo DHEA, which is sometimes referred to as 7-Keto (brand name) via the same 11 $\beta$ -HSD enzymes. Simply put, DHEA can be metabolized into derivatives via CYP7B1 and this is irreversible. The 7 $\alpha$  and 7 $\beta$  conjugates can convert to and from each other, using 7-Oxo (also known as 7-Keto) as an intermediate. These DHEA metabolites are more involved with the immunological and inflammation aspects of DHEA supplementation, and some neurological aspects.

5-DHEA is used as a supplement for a myriad of benefits. Epiandrosterone (EA) is the base molecule and the dehydro (DH) can be in many positions which all have benefits for health and longevity. These forms of DHEA provide similar benefits to traditional 5-DHEA without some of the negatives. 5-DHEA is often too active in tissues. Though the prefix "dehydro" in dehydroepiandrosterone implies that two hydrogen atoms have been removed and a double bond is located on the steroidal rings, 5-DHEA is the isomeric form of DHEA that is most often thought of and that is most commonly sold on the market.

4-DHEA is an isomer of 5-DHEA. It is different by 5-DHEA by the position of the double bond. 4-DHEA is metabolized similarly to 5-DHEA and is theorized to have similar effects; however, due to the repositioning of this double bond, studies show it is less active as a substrate

(compound to be metabolized) for the aromatase enzyme, therefore decreasing the estrogenic metabolites.

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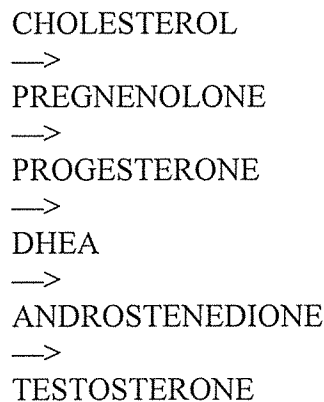
<sup>2</sup> The Intellectual Wellness, LLC patented compounds that have issued on several method claims for the use of DHEA Derivatives for enhancing physical performance including specifically, 1-androsten-3- $\alpha$ -17-one (commonly known as 1 Andro or 1 DHEA), and 4-androsten-3- $\alpha$ -17-one (commonly known as 4 Andro or 4 DHEA). These compounds are structurally dehydroepiandrosterone (DHEA) compounds (see attached analysis of Brian J. Shay, Ph.D. regarding the chemical support for what constitutes a DHEA compound) and are exempted from the Act as dehydroepiandrosterone (DHEA) compounds.

1-DHEA is dehydrogenated between C1 and C2 (double bond at the first position) and is consequently metabolized into 1-ene isomers (ene implies a double bond). 1-ene dehydrogenated steroids show no substrate activity for aromatase and consequently, 1-DHEA is not estrogenic.

Furthermore 1-ene variants act as an enzymatic inhibitor for 5 $\alpha$ -reductase which reduces the androgenicity of the compound and would be beneficial for people with prostate problems or hair loss due to androgenic alopecia.

19Nor-DHEA (both 4-ene and 5-ene isomers) is a demethylated derivative of DHEA where carbon-19 has been removed. 19Nor steroids show nearly zero estrogenicity, very low substrate activity for aromatization, and capability to bind directly to the androgen receptor. In addition, the enzyme, 5 $\alpha$ -reductase, metabolizes the compound to dehydro-nandralone derivatives which show anti-androgenic effects. 19Nor-DHEA is therefore beneficial for individuals who desire stronger anti-catabolic effects with little estrogenicity and anti-androgenic, 5 $\alpha$ -reduced metabolites. The aforementioned isomers and derivatives of DHEA are still considered safe due to the strong metabolic similarities; and in fact, the more targeted supplementation use enables the user to tailor the effects of DHEA to their physiological needs. 3 $\beta$ -Hydroxy-5-androstene-7,17-dione or 7-Oxodehydroepiandrosterone (7-Keto) is legal to sell in the United States as a dietary supplement. It currently has two premarket notifications with the FDA. Commercial sales of 7-Keto as a dietary ingredient began in June 1998.

By virtue of the Anabolic Steroid Control Act of 2004, the Controlled Substances Act (“CSA”) was amended to include in the definition of anabolic steroids, androstenedione (an anabolic steroid procurers) as well as several other similar steroid substances. Specifically, under the new definition, anabolic steroids now include “any drug or hormonal substance, chemically and pharmacologically related to testosterone (other than estrogens, progestins, corticosteroids and DHEA).” 21 U.S.C. § 802(41). Thus, through substantial industry efforts, DHEA was specifically excluded from the definition. However, as shown in the following flowchart, DHEA is a precursor to the currently prohibited steroids.



Nevertheless, at present, DHEA continues to be marketed as a dietary supplement in compliance with DSHEA. DHEA also continues to be excluded from the category of steroids prohibited as controlled substances. The term "dehydroepiandrosterone" is ambiguous chemically because it does not include the specific positions within epiandrosterone at which hydrogen atoms

are missing. DHEA has a number of naturally occurring isomers that may have similar pharmacological effects. Some isomers of DHEA are 1-DHEA and 4-DHEA. These isomers are also technically DHEA, since they are dehydroepiandrosterones in which hydrogens are removed from the epiandrosterone skeleton. This exemption for DHEA appears to provide a basis for finding that 1-DHEA should have similar treatment under DSHEA and the CSA.

### **III. 1-DHEA, 4-DHEA and 19-NorDHEA.**

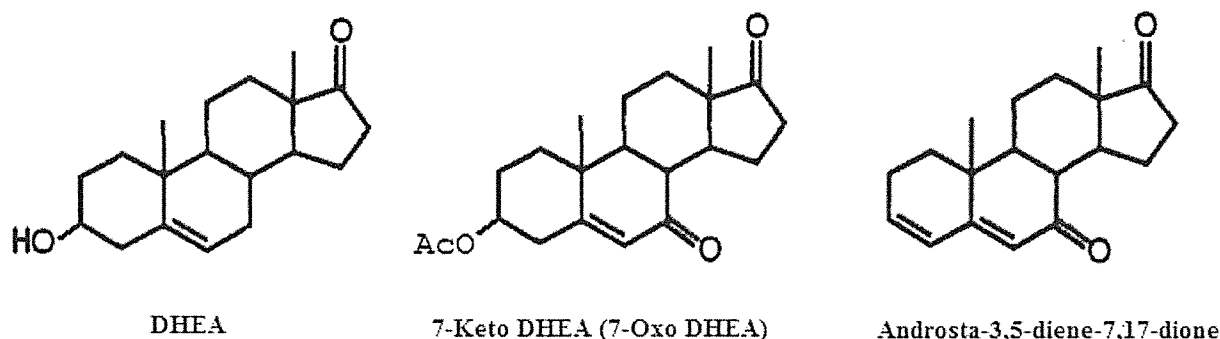
From a chemical perspective, it appears that 1-DHEA is a metabolite and isomer of DHEA. Furthermore, 1-DHEA is naturally occurring in pigs and boars. As stated above, metabolites and isomers of naturally occurring dietary ingredients are classified as dietary supplements for DSHEA purposes. 1-DHEA is dehydrogenated between C1 and C2 (double bond at the first position) and is consequently metabolized into 1-ene isomers (ene implies a double bond). 1-ene dehydrogenated steroids show no substrate activity for aromatase and consequently, 1-DHEA is not estrogenic. 4-DHEA is an isomer of 5-DHEA. It is different by 5-DHEA by the position of the double bond. 4-DHEA is metabolized similarly to 5-DHEA and is theorized to have similar effects; however, due to the repositioning of this double bond, studies show it is less active as a substrate (compound to be metabolized) for the aromatase enzyme, therefore decreasing the estrogenic metabolites. 19Nor-DHEA (both 4-ene and 5-ene isomers) is a demethylated derivative of DHEA where carbon-19 has been removed. 19Nor steroids show nearly zero estrogenicity, very low substrate activity for aromatization, and capability to bind directly to the androgen receptor. In addition, the enzyme, 5 $\alpha$ -reductase, metabolizes the compound to dehydro-nandralone derivatives which show anti-androgenic effects. 19Nor-DHEA is therefore beneficial for individuals who desire stronger anti-catabolic effects with little estrogenicity and anti-androgenic, 5 $\alpha$ -reduced metabolites. Accordingly, assuming such to be correct and assuming further that 1-DHEA is not intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animals such that the product would qualify as a drug under 21 U.S.C. § 321(g)(1)(B), then it would appear that 1-DHEA is presently entitled to classification as a dietary supplement under DSHEA.

### **IV. 3, 7 Keto DHEA.**

From a chemical perspective, it appears that 3, 7 Keto DHEA is a naturally occurring metabolite of DHEA. It is found in human urine. As stated above, metabolites and isomers of naturally occurring dietary ingredients are classified as dietary supplements for DSHEA purposes. Accordingly, assuming 3, 7 Keto DHEA is a naturally occurring isomer of DHEA and assuming

further that it is not intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals such that the product would qualify as a drug under 21 U.S.C. § 321(g)(1)(B), then it would appear that 3, 7 Keto DHEA would be presently classified as a dietary supplement under DSHEA.

This is a further metabolite of 7-Keto DHEA, and is the result when a single bond on the A ring between carbons 3 and 4 is turned into a double bond. This turns the *5-Androstene* designation into *3,5-dien*, as the *-en* refers to a double bond and the *di* refers to two. It is a natural metabolite found in the urine as this change from 7-Oxo (the addition of a double bond) appears to occur in the body somewhere perhaps in the liver. Sometimes this metabolite is also referred to as 3-desoxy-7-keto DHEA. Regardless of the colloquial name given, the elongated chemical name of this molecule is *(8R,9S,10R,13S,14S)-10,13-dimethyl-2,8,9,11,12,14,15,16-octahydro-1H-cyclopenta{a}phenanthrene-7,17-dione*.



*( Modified from: Numazawa M, et al. Synthesis of androst-5-en-7-ones and androsta-3,5-dien-7-ones and their related 7-deoxy analogs as conformational and catalytic probes for the active site of aromatase. J Med Chem. (1994) )*

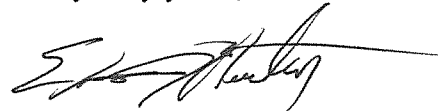
In addition, it should be noted that like 7 Keto DHEA, 3,7 Keto DHEA cannot convert to testosterone, estrogen or progesterone via enzymatic reaction. Therefore, it would appear that the 3,7 Keto DHEA compound would not fall within the definition of anabolic steroids. Under the Controlled Substances Act (“CSA”), as amended by the Anabolic Steroid Control Act of 2004, anabolic steroids are defined as “any drug or hormonal substance, chemically and pharmacologically related to testosterone (other than estrogens, progestins, corticosteroids and DHEA).” 21 U.S.C. § 802(41). (Emphasis added). Due to its inability to convert to testosterone, it would seem that 3, 7 Keto DHEA could not meet the definition of an anabolic steroid on its own even without the specific DHEA exclusion.

We have also reviewed the opinion letters from other attorneys on some of the same issues; i.e., Does DSHEA or the Designer Steroid Control Act of 2014 prohibit the sale and marketing of 1,4 and 5 DHEA compounds? It is the carefully reasoned opinion of this firm that all DHEA compounds are specifically exempted by the Designer Steroid Control Act of 2014 including but

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not limited to the 1,4, 5 and 19 DHEA compounds. This would also hold true for DHEA metabolites such as: 7 Keto DHEA, 3,7 Keto DHEA, 7 $\alpha$  and 7 $\beta$  hydroxy DHEA and Epiandrosterone. The inclusion of these DHEA compounds in dietary supplements would be legal under both the DSHEA and the Designer Steroid Control Act.

Very truly yours,



Edmund J. Novotny