



Anabolic Steroids: Dietary Supplements in Disguise

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It's really a simple issue: Dietary supplements are legal products used by millions of people every year to enhance their health and well-being, and anabolic steroids are controlled drug substances that are illegal without a prescription and punishable by up to seven years in prison. The clarity of this distinction, however, becomes blurred when the competitive desire of athletes to increase muscle size, strength, and endurance fuels the business opportunity for entrepreneurs to make millions of dollars in the lucrative market of anabolic steroids, and when legislators ease the restrictions around their use.

In October 1994, the Dietary Supplement Health and Education Act (DSHEA) was signed into law by President Clinton, giving the US Food and Drug Administration (FDA) responsibility for regulating the safety and labeling of dietary supplements. The new law also restricted the FDA's authority over supplements, provided that manufacturers make no claims about their products treating, preventing, or curing disease. Unlike new drugs that require years of research in animals and completion of extensive clinical trials in humans to demonstrate safety and efficacy prior to commercialization, dietary supplements do not need approval from FDA before they are marketed. Under DSHEA, the "firm" has responsibility for determining the safety of its own dietary supplements, and any representations or claims must be substantiated by adequate evidence to show that they are not false or misleading.

Manufacturers may make three types of claims for their dietary supplement products: health claims, structure and/or function claims, and nutrient content claims. While nutrient content claims are self-explanatory, health claims describe a relationship between a food substance and a disease or health-related condition, such as "diets high in calcium may reduce the risk of osteoporosis." Structure function claims state the role of a nutrient intended to affect a structure or function of the body, such as "calcium builds strong bones," "glucosamine helps support healthy joints," or "the hormone melatonin helps establish normal sleep patterns." Advertising claims such as a "pro-anabolic," "bulking," and "gain lean muscle," are also consistent with structure function claims typically accepted by FDA when presented in concert with appropriate disclaimers stating that they do not intend to diagnose, treat, cure,

or prevent any disease. When a manufacturer makes a structure or function claim on a dietary supplement label, the following statement or disclaimer must appear: *"This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."*

Manufacturers and distributors of marketed dietary supplements must record, investigate, and forward to FDA any reports they receive of serious adverse events associated with the use of their products that are reported to them directly. A reasonable interpretation of this statement is that the distributors are not required to periodically scan the literature or the Internet for adverse health effects of their products, but rather, just to report any serious adverse health effects to the FDA that are reported to them directly. This interpretation is supported by the fact that the FDA gives themselves the responsibility to show that a dietary supplement is unsafe. Under DSHEA, once the product is marketed, FDA has the responsibility for showing that a dietary supplement is "unsafe," before it can take action to restrict the product's use or remove it from the marketplace.

So the die is cast. The desire to be stronger, better, and faster is driving the market for the manufacture and distribution of anabolic substances, and the market, like the muscle mass, is huge. Adverse effects experienced by some anabolic steroid users precipitate wrongful-injury litigation, but where does the responsibility fall?

The Technical Approach

Anabolic steroids were added to the 1990 Controlled Substances Act (CSA) in 2004, a bill known as the Anabolic Steroid Control Act of 2004. This bill listed a number of specific steroids by chemical name using current IUPAC steroid nomenclature, presumably representing those specific anabolic steroids that were known at the time. Whether by design or through steroid nomenclature illiteracy, many manufacturers

have used steroid nomenclature dating back to World War II in the listing of their ingredients. For example, Methasterone or Superdrol has the IUPAC chemical name $2\alpha, 17\alpha$ -dimethyl- 5α -androstan-3-one- 17α -ol, but can also be named $2\alpha, 17\alpha$ -dimethyl-etioallocholan-3-one- 17α -ol using outdated steroid nomenclature. Compounds identified using outdated steroid nomenclature will typically escape identification using typical Internet search engines. If not specifically listed or recalled by the FDA, the marketing and distribution of these substances continues as the synthesis of similar molecules continues to outpace regulations, recalls, and the law. A fundamental understanding of steroid chemistry is crucial to determine whether a substance is present on the FDA's list or to ensure that it is not.

Determining that adverse health effects result from anabolic steroid use is not as simple as one might imagine. The literature on side effects of anabolic steroids is primarily anecdotal and taken from case reports. When researching the health effects of anabolic steroids, attention is required for confounding that may occur secondary to consumption of prescription drugs, recreational drugs, or other performance-enhancing products co-administered with the anabolic steroid. While the overall prevalence of adverse hepatic effects among long-term anabolic steroid users is low, cases of acute effects of jaundice have been reported since the 1960s. Adverse effects of anabolic steroid use in some individuals are dose- and structure-related and include elevated liver enzymes, cholestasis (cholestatic jaundice), peliosis hepatitis (blood-filled sacs within the liver) and various neoplastic lesions. Typically, as dose increases the number and severity of adverse effects increases. Hepatic effects are most commonly associated with the use of 17β -alkylated steroids, because this chemical modification protects the 17β -hydroxyl group, enhancing bioavailability after oral administration. The subsequent 17β -conjugates of these substances (which are produced as the body attempts to break these substances down and eliminate them) resemble bile acids, which compete for binding to bile transporter receptor sites and reduce bile transport out

of the liver, resulting in excess bile in the bloodstream (i.e., jaundice). Cholestatic jaundice and pruritis (itching due to the build-up of bile acids in the skin) occur occasionally with steroid use; symptoms typically resolve within 3 months of discontinuing the substances.

The Adverse Event Reporting System (AERS) has been described as “a computerized information database designed to support the FDA’s post-marketing safety surveillance program for all approved drug and therapeutic biologic products.” It is used by the FDA to monitor for adverse events and medication errors that might occur with marketed products. Information for the database comes from health-care professionals and consumers. However, there is no certainty that the FDA receives all adverse-event reports associated with a product, and there is “no certainty that the reported adverse event was actually due to the product.” AERS is, however, a useful tool for the FDA in looking for new safety concerns that might be associated with a marketed product.

As of January 4, 2010, manufacture, import, export, distribution, or sale of anabolic steroids, including boldione, desoxymethyltestosterone, and 19-nor-4,9(10)-androstadienedione, except by DEA registrants, is a violation of the Anabolic Steroid Control Act of 2004 that may result in imprisonment and fines (21 U.S.C. 841 and 960; Federal Register. 2009 Dec 4;74(232):63603-10). Of course, anabolic steroids can continue to be prescribed by physicians. There is intense interest within the pharmaceutical industry in developing safer anabolic steroids by designing new anabolic molecules that lack pronounced androgenic effects. Anabolic steroids are prescribed for the treatment of wasting syndrome secondary to cancer chemotherapy and to combat the effects of muscle loss with aging. From a policy and legal perspective, the manufacturing, marketing, sale, and use of dietary supplements containing anabolic steroids remains problematic. Current regulatory characterization and control of the products and their constituents is not well adapted to address families of anabolic steroids,

which makes it difficult to enforce the current regulations concerning chemical-specific steroids. Particularly problematic are variability in the level of sophistication among manufacturers and distributors, and the legal implications and imputation of knowledge of what is known or should be known of potential adverse health outcomes. The characterization of adverse health risks from the use of these dietary supplements is constrained by the limited numbers of well-designed epidemiologic cohort or case-control investigations.



Exponent's Expertise

Exponent provide regulatory, toxicological, and epidemiologic expertise in dietary supplement cases.

Dr. Kelce is a toxicologist and pharmaceutical development health scientist with over 29 years of training and experience in the areas of physiology, toxicology, and drug development. He is a Fellow of the Academy of Toxicological Sciences. As a consultant, he has served on numerous government, industry, and academic committees, workshops, and task forces regarding environmental hormone disruptors, and he serves on editorial review boards for three scientific journals: *Toxicology and Applied Pharmacology*, *Birth Defects Research*, and *Environmental Health Perspectives*. He also reviews pharmaceutical development programs for their robustness and adherence to appropriate regulatory guidelines and provides strategic guidance on the pharmaceutical development strategy. Dr. Kelce has studied steroidogenesis and mechanism of androgen action for more than 25 years and has written 96 original manuscripts, book chapters, and scientific abstracts in this field. He holds an adjunct academic appointment at the University of North Carolina–Chapel Hill, School of Medicine, Department of Pediatrics, and the Labs for Reproductive Biology.

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