DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT OF

MICHAEL LEVY, ESQ.

DIRECTOR, DIVISION OF NEW DRUGS AND LABELING COMPLIANCE

OFFICE OF COMPLIANCE

CENTER FOR DRUG EVALUATION AND RESEARCH

U.S. FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SENATE COMMITTEE ON THE JUDICIARY

SUBCOMMITTEE ON CRIME AND DRUGS

HEARING ON

"BODY BUILDING PRODUCTS AND HIDDEN STEROIDS: ENFORCEMENT BARRIERS"

SEPTEMBER 29, 2009

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Michael Levy, Esq., Director of the Division of New Drugs and Labeling Compliance, Office of Compliance, Center for Drug Evaluation and Research (CDER), at the Food and Drug Administration (FDA or the Agency), which is a part of the Department of Health and Human Services (HHS). Thank you for the opportunity to discuss FDA's perspective on the issue of steroids in products marketed as dietary supplements.

FDA is very concerned with products containing synthetic steroid ingredients that are marketed as dietary supplements. There is no requirement for the manufacturer of a dietary supplement to provide FDA with evidence of the product's effectiveness, and the manufacturer also need not provide FDA with evidence of product safety prior to marketing, unless the product contains a "new dietary ingredient" that has not been part of the food supply. By labeling steroid products as dietary supplements, unscrupulous firms can easily introduce into the marketplace products that contain ingredients that may pose risks to health. In some cases, the marketing of a steroid product as a dietary supplement is fraudulent because the product is actually an unapproved drug or an adulterated dietary supplement. Marketing a steroid product as a "dietary supplement" conveys to the consumer a false sense of safety and legitimacy for these potentially harmful products.

FDA has taken action to protect the public from illegal steroids in dietary supplements. In July 2009, for example, FDA issued a public health advisory warning consumers to stop using any body-building products that are represented to contain steroids or steroid-like substances. The public health advisory was issued in response to a cluster of serious adverse event reports

submitted to FDA associated with several products containing synthetic steroids and marketed as dietary supplements. Adverse events included serious liver injury, stroke, kidney failure, and pulmonary embolism (artery blockage in the lung). Although the body-building products containing these synthetic steroids were marketed as dietary supplements, they were not dietary supplements. Rather, they were unapproved and misbranded drugs that had not been reviewed by FDA for safety and effectiveness.

In the past five years, FDA has sent 28 Warning Letters to firms that were illegally marketing products containing steroids. These products were either unapproved new drugs or adulterated dietary supplements. Currently, FDA's civil and criminal enforcement offices are gathering and reviewing additional data about other products that are marketed for body building and that claim to contain steroids or steroid-like substances.

Despite these actions, FDA's ability to solve this problem is limited. Because FDA generally does not receive information on these products prior to marketing, FDA generally cannot identify violative products before they enter the marketplace. After products enter the market, we must undertake a painstaking investigative and analytical process to show that they are violative. Currently, the Agency struggles to provide effective civil and criminal deterrents to prevent unscrupulous firms from fraudulently marketing these products, and we are unable to effectively prevent the importation of many violative products. These gaps make it very challenging to interrupt the sale of these dangerous products.

STEROID PRODUCTS MARKETED AS DIETARY SUPPLEMENTS

As background, I would like to describe the substances addressed in this testimony. Chemically, steroids are a family of lipid molecules that include a large variety of substances

such as cholesterol, steroid hormones, bile salts, and many other substances. They occur not only in animals, but also in insects, plants, bacteria, and fungi. Many steroids occur naturally in foods or are used as food ingredients and present no significant regulatory issues. For example, phytosterols occur naturally in some foods, have a beneficial effect on heart health, and can legitimately be used as ingredients in dietary supplements and other foods. However, during this hearing, when I use the term "steroid," I am referring to the subgroup of steroids that have anabolic and/or androgenic effects in humans. This subgroup includes synthetic steroids. Body-building products marketed as dietary supplements are commonly found to contain these types of steroids.

The Dietary Supplement Health and Education Act (DSHEA) defines the term "dietary supplement" as a product that, among other things, is not represented for use as a conventional food or sole item in a meal or diet; is intended to supplement the diet; and contains at least one or more dietary ingredients. A "dietary ingredient" is defined as a vitamin, a mineral, an amino acid, a herb or other botanical, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any of the above dietary ingredients (section 201(ff)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act). Dietary supplements must be intended for ingestion and may be found in many forms such as tablets, capsules, powder, liquids, softgels, or gelcaps.

A dietary supplement may not contain an article approved as a new drug or an article authorized for investigation as a new drug for which substantial clinical investigations have been instituted and made public, unless the article was first marketed as a dietary supplement or conventional food. If a product marketed as a dietary supplement is excluded from the

dietary supplement category because it contains such an article, then a claim that the product is intended to affect the structure or function of the body causes the product to be a drug. Similarly, if a product marketed as a dietary supplement is not a dietary supplement because it contains no dietary ingredients, a claim that the product is intended to affect the structure or function of the body causes it to be a drug. Synthetic steroids are not dietary ingredients.

Claims that a steroid ingredient increases muscle mass or strength cause the product containing the steroid to be a drug. Some such products are specifically promoted to athletes to improve sports performance and to aid in recovery from training and competition. Many times they are marketed with claims that they are similar to an anabolic steroid listed in Schedule III under the Controlled Substances Act (CSA). The products can be found on the Internet, in gyms, and in retail stores. They are generally marketed with claims about the ability of the active ingredients to enhance or diminish androgen, estrogen, or progestin-like effects in the body.

Two recent examples of these synthetic steroid products are TREN Xtreme and MASS Xtreme, marketed as dietary supplements by American Cellular Labs, Inc. (ACL). These products were the subject of a recent FDA Warning Letter and search warrant. These two products included the ingredients 19-Norandrosta-4,9-diene-3,17 diene and 17α-methyl-etioallocholan-2-ene-17b-ol, which are the subject of a proposed rule published in the *Federal Register*, proposing to list these ingredients as Schedule III controlled substances. TREN Xtreme was marketed with claims that it was "[s]imilar to Trenbolone" and that it "binds to the androgen receptor 300% better than testosterone." MASS Xtreme was marketed with claims that it was "[s]imilar to Methyl Testosterone," "a potent anabolic," and

had "low androgenic activity." The firm also included misleading safety claims that the products were free from a number of dangerous side effects.

Safety Concerns

Adverse Event Reports. At the time that FDA issued the Warning Letter to ACL, FDA's MedWatch system contained 15 adverse event reports associated with body-building products. On further investigation, FDA determined that 13 of these 15 reports involved products that appeared to contain steroids and were marketed as dietary supplements. The product manufacturers identified in the MedWatch reports included ACL, which was cited in five MedWatch reports. For body-building products that were labeled as containing steroids or steroid-like substances, adverse events involved men (ages 22-55) and included cases of serious liver injury, stroke, kidney failure, and pulmonary embolism. All but one of the reports cited a temporal association with the use of the product(s) days or weeks prior to onset of the adverse event(s). As an example, one report involved a 37-year-old male patient with jaundice, fatigue, weight loss, nausea and vomiting after taking a 3-4 week course of TREN Xtreme, a synthetic progestin-containing product, and MASS Xtreme Size Promoter, a synthetic androgen-containing product. This patient was admitted to the hospital and subsequently diagnosed with renal failure and acute cholestatic liver injury. While it is difficult to establish a direct causal link between these synthetic steroid products and injury, there is at least a temporal association between the use of some of these body-building products and the development of acute liver injury.

FDA believes it is likely that adverse events for these products have been underreported. This may be because adverse events can occur many years after use of a product; because people who use such products may want to conceal their use; because resulting adverse

effects may be considered sensitive or embarrassing; and/or because people may not readily associate adverse events with this type of product.

Public Health Advisory. The July 2009 Public Health Advisory (PHA) was issued in response to the cluster of reports FDA received about serious adverse events associated with several products containing synthetic steroids and marketed as dietary supplements. Due to the potential serious health risks, FDA recommended that consumers immediately stop using body-building products marketed as containing steroids or steroid-like substances and report any adverse events associated with them to FDA. In addition, FDA suggested that consumers consult their health care professionals if they experience symptoms possibly associated with these products, particularly nausea, weakness or fatigue, fever, abdominal pain, chest pain, shortness of breath, yellowing of the skin or whites of the eyes, or brown/discolored urine.

Adverse Effects of Anabolic Steroid Use. Acute liver injury is known to be a possible harmful effect of using anabolic steroid-containing products. Anabolic steroids may also cause other serious long-term health consequences in men, women, and children. These include shrinkage of the testes and male infertility, masculinization of women, breast enlargement in males, short stature in children, adverse effects on blood lipid levels, and increased risk of heart attack and stroke. Anabolic steroid use can also induce psychological effects such as aggression, increased feelings of hostility, psychological dependence, and addiction. Upon abrupt termination of long-term anabolic steroid use, users may experience withdrawal symptoms, including severe depression.

FDA Enforcement and Challenges

In general, products that are marketed as dietary supplements but that contain active ingredients in FDA-approved drugs, analogs of approved drugs, and other compounds that do not qualify as dietary ingredients, present an emerging and expanding challenge. Specifically, body-building products that contain synthetic steroids or steroid-like substances, and are marketed as dietary supplements, continue to be a challenging area for FDA. In addition to the Agency's concerns that many of these products have not been clinically studied or demonstrated to be safe, the products are often sold with misleading labeling and are frequently manufactured without quality controls.

Enforcement Authority. At the core of FDA's dietary supplement enforcement efforts is the Agency's commitment to protect the public health by removing unsafe products from the market. The marketing of unsafe or otherwise violative products as dietary supplements places FDA in a position where it must identify the products and the firms that market them after the products have already been introduced into the marketplace. FDA scours online and retail marketplaces in search of illegal supplement products, conducts scientific and legal analyses of the ingredients, discovers the manufacturers' locations, and, when appropriate, takes action. Because of the complexity of this process, it often takes the Agency many months to complete an investigation and take an action against a violative firm.

When violative firms are identified, FDA has a variety of enforcement tools, including both criminal and civil enforcement powers, that it can use to address the problem of steroids in dietary supplements. In the July 2009 action against ACL, FDA both executed a criminal search warrant and issued a Warning Letter regarding the illegal manufacture of various body-building supplements that contain synthetic steroids. This is not the first time FDA has taken action against steroid-containing products marketed as dietary supplements. In 2004,

as part of the HHS crackdown on companies that manufacture, market and distribute products containing androstenedione, or "andro," FDA sent Warning Letters to 23 companies asking them to cease distributing androstenedione-containing products sold as dietary supplements, and warning them that they could face enforcement action if they did not take appropriate action. Androstenedione was subsequently added to the list of Schedule III controlled substances in January 2006. In March 2006, FDA sent Warning Letters to four more manufacturers and distributors of synthetic steroid-containing products illegally marketed as dietary supplements. One of these companies, LG Sciences (formerly Legal Gear), was the subject of an FDA seizure in April 2008 of nearly $1.3 million worth (23,300 bottles) of illegal synthetic steroid-containing body-building products labeled as dietary supplements.

When criminal sanctions may be warranted, FDA's Office of Criminal Investigations (OCI) will become involved. OCI is the entity within the Agency responsible for the conduct and coordination of criminal investigations and, as such, maintains liaison and cooperative investigative efforts with other federal, state, local, and international law enforcement agencies. OCI is instrumental in implementing FDA criminal investigation policy, training, and coordination. OCI uses all customary and legal criminal investigative techniques, interfaces directly with federal and local prosecutorial offices, and participates in grand jury proceedings and judicial actions as required.

FDA's OCI continues to aggressively investigate distributors and manufacturers of dietary supplements containing synthetic steroids and recognizes the risks that these products pose to consumers. However, these investigations can present legal challenges to law enforcement because many of these dietary supplements contain new steroids that are not specifically

listed as anabolic steroids under the CSA. These new steroids are sometimes called "designer steroids." In such cases, proving that the "designer steroid" meets the definition of an anabolic steroid at 21 U.S.C. 802(41)(A), because it is a substance "chemically and pharmacologically related to testosterone (other than estrogens, progestins, corticosteroids, and dehydroepiandrosterone)," can be a complicated and time-consuming task. In such cases, only misdemeanor violations of the FD&C Act may apply, unless there is evidence of intent to defraud or mislead, a requirement for establishing a felony violation of the Act. If a dietary supplement contains a steroid that is not a controlled substance under the CSA and the product is accurately labeled, it may be difficult to establish a felony violation of the Act. Nevertheless, OCI is actively engaged with its law enforcement partners, such as the Drug Enforcement Administration (DEA), to target these products more effectively. FDA and DEA are constantly encountering new steroids as firms attempt to stay one step ahead of the law.

Challenge of Distinguishing Legal and Illegal Steroids in Dietary Supplements. Although some steroid-containing products are represented as dietary supplements, the products generally do not meet the definition of a dietary supplement under the Act. To be a lawful dietary ingredient in a dietary supplement, a steroid must fit within one of the categories of "dietary ingredients" defined in section 201(ff)(1) of the FD&C Act – that is, a vitamin, mineral, amino acid, herb or other botanical, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any of the above dietary ingredients.

Some types of steroids may be dietary ingredients because they are either:

- a dietary substance for use by man because the substance has a history of use as a food or food ingredient;

- a constituent of a 'dietary substance' (e.g., a component of a food such as an animal meat or organs used as food);
- a constituent of a plant or other botanical (e.g., plant-derived ecdysteroids, phytosterols, saponins, etc.); or
- a metabolite of a substance that is a dietary ingredient.

Therefore, these steroids could be extracted and purified and used as dietary ingredients. However, steroids that are dietary ingredients because they are a constituent of another dietary ingredient are only dietary ingredients if they are in fact extracted and purified from the parent material (e.g., a botanical extract made from a plant). FDA believes that synthetic versions of otherwise eligible steroids are not dietary ingredients unless the synthetic version itself is a dietary substance because it has a history of use as a food or food ingredient. This conclusion results directly from the language of the dietary ingredient definition; that is, a synthetic substance that was never a part of a dietary ingredient cannot be understood to be a "constituent" of that dietary ingredient; rather, it is a synthetic copy of the constituent. Because we believe that most steroids that are being marketed as dietary supplements are synthetically produced, most are not eligible dietary ingredients. Depending on whether the product contains another active ingredient that falls into one of the dietary ingredient categories (e.g., a vitamin or mineral) and whether it is marketed to affect the structure or function of the body (e.g., with body-building claims), a steroid-containing product may be an adulterated dietary supplement, an unapproved new drug, or both.

FDA faces several challenges when it considers whether a particular steroid-containing dietary supplement violates the Act. When the Agency finds a potential steroid ingredient listed on a label, we must determine what the substance is and whether it is present in any article used as food. This is a time-consuming process that requires staff to search the scientific literature. In cases where we cannot identify the substance (because the ingredient

is named incorrectly or is a novel steroid that we have not previously encountered), or when we are unable to locate information about it in the scientific literature, we must consult FDA's experts—or, sometimes, experts outside the agency—to determine what it is.

If FDA determines that the substance is a steroid, there are several possible enforcement outcomes, depending on the product's ingredients and marketing. First, if the steroid is the only active ingredient and the product is intended to affect the structure or function of the body, the product is an unapproved new drug. Second, if the product contains the steroid, in addition to one or more legitimate dietary ingredients (for example, herbal ingredients), the product would be an adulterated dietary supplement because it contains an unsafe food additive. Third, in rare instances, it may be determined that the steroid meets the definition of a dietary ingredient. In those instances, if the steroid is a new dietary ingredient for which a premarket notification is required, the product would still be an adulterated dietary supplement unless the manufacturer or distributor submitted a new dietary ingredient premarket notification to FDA at least 75 days before marketing.

Analytical Challenges. Analyzing the steroid ingredients requires FDA laboratories to use scientific expertise and sophisticated instruments to identify the presence of synthetic steroids. Each steroid ingredient can have numerous different synonyms, many of which are obscure, alternative chemical names. Some may be nicknames given to the compound by the manufacturer or the body-building community. Furthermore, these products are frequently mislabeled, either intentionally to confuse and mislead consumers or unintentionally because of a misunderstanding of steroid nomenclature. If FDA cannot determine what ingredient is in the product based on the labeling alone, FDA sends the product to the lab for ingredient analysis.

From the laboratory perspective, the steroid analysis is complicated due to the vast array of known steroids (over 7,000), which are all variations of the same basic steroid chemical "skeleton." These variations are caused by the locations and numbers of substituent and double bonds. As a result, while determining the molecular weight may be a useful first step toward identifying a chemical compound, there could be twenty steroids with the same molecular weight, each representing a unique chemical compound. Differences in stereochemistry further complicate the challenges faced by the laboratory. There are so many different steroid compounds that in many instances reference standards, which are needed for the laboratory to conclusively identify the chemical, are not available. In these situations the laboratory's only option is to have the compound custom-made at a cost that is frequently prohibitive.

Importation Challenges. The firms that manufacture and distribute these fraudulently marketed dietary supplements typically do not import them through legal means. It has been our experience that most of the raw steroid ingredient powders and final dosage forms are imported in ways that intentionally evade FDA's review or make such review difficult. For instance, products being imported typically are flagged for FDA review based on, among other things, information provided by the importer and product labeling. However, large commercial-size shipments of raw ingredient and finished product are frequently mislabeled or otherwise improperly identified, including being identified as products not subject to FDA review. In addition, shipments of fraudulently marketed dietary supplements frequently enter the United States through the international mail facilities and courier services. Such shipments can be extraordinarily difficult to effectively address and prevent because of their sheer volume and FDA's inability to perform a comprehensive evaluation of all packages.

Scheduling of Controlled Substances. Although anabolic steroids have been included in Schedule III of the CSA since 1990, the Anabolic Steroid Control Act (ASCA) of 2004 amended the legal definition of anabolic steroid, and expressly listed androstenedione (an anabolic steroid precursor) and a number of other similar steroid substances as anabolic steroids. Specifically, the ASCA amended the CSA to redefine anabolic steroids as "any drug or hormonal substance, chemically and pharmacologically related to testosterone (other than estrogens, progestins, corticosteroids, and dehydroepiandrosterone)." There are currently 59 Schedule III anabolic steroids specifically listed in the regulations. In April 2008, DEA published a proposed rule to add three more compounds to the nonexclusive list of Schedule III anabolic steroids.

DEA has the primary role in classifying these anabolic steroids as controlled substances. However, the administrative procedure that DEA must follow to schedule new anabolic steroids is extremely time-consuming. In order to be classified as an anabolic steroid and meet the legal definition of anabolic steroid under the CSA, the drug must be shown to be chemically and pharmacologically related to testosterone. By the time DEA determines the chemistry and pharmacology of the steroid and shows that it meets the definition of "anabolic steroid" under the CSA, the manufacturer may have changed or redesigned the steroid used in the product—in which case DEA must start over and evaluate the chemistry and pharmacology of the new steroid ingredient. Unfortunately, while scheduling new anabolic substances temporarily removes certain ingredients from the market, FDA and DEA may always be a step behind the next novel anabolic steroid compound.

CONCLUSION

Despite FDA's efforts, and those of other agencies, to identify and remove illegal steroid products from the legitimate dietary supplement marketplace, we face significant regulatory challenges. FDA will continue to closely monitor the safety of steroid products marketed as dietary supplements by addressing those products that pose the greatest health risk to the most vulnerable populations. This is an important public health issue that can only be addressed by collaborative efforts with DEA, other federal agencies, regulated industry, health care professionals, and consumers. As a public health agency, we are committed to doing everything we can to protect the American public, not only through regulation and enforcement, but also through education, outreach, and collaboration with entities outside FDA. FDA's Web site (*www.fda.gov*) contains extensive information for consumers about drug importation, buying drugs online, counterfeit drugs, enforcement activities, and potential public health threats, as well as resources to report problems with FDA-regulated products or Web sites that could be selling fraudulent, adulterated, or harmful products.

Thank you for the opportunity to discuss FDA's activities with regard to steroids marketed as dietary supplements. FDA looks forward to working with Congress on this important public health issue. I would be happy to answer any questions.