



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Patrick J. Leahy
Chairman
Committee on the Judiciary
United States Senate
Washington, D.C. 20510-6275

The Honorable Arlen Specter
Chairman
Subcommittee on Crime and Drugs
Committee on the Judiciary
United States Senate
Washington, D.C. 20510-6275

NOV 05 2009

Dear Chairmen Leahy and Specter:

Thank you for providing the Food and Drug Administration (FDA or the Agency) the opportunity to testify at the September 29, 2009, hearing entitled, "Body Building Products and Hidden Steroids: Enforcement Barriers," before the Senate Committee on the Judiciary, Subcommittee on Crime and Drugs. Michael Levy, J.D., Director, Office of Compliance, Center for Drug Evaluation and Research, testified on behalf of the Agency.

We are responding to your letters of October 6, 2009, and October 7, 2009, that you sent in follow up to the hearing. We have included FDA's responses to the questions from each Member on the following, separate pages. Each question is restated in bold, followed by our responses.

Senator Arlen Specter

- 1. Did Mr. Travis Tygart in his testimony before the Senate Judiciary Subcommittee accurately describe the process of what it takes to get a dietary supplement on the market?***

In his written testimony, Mr. Tygart described the process of introducing a dietary supplement to market as follows:

"It is what this consumer does not know that is the reason we are all here today. What he or she does not know is that all it takes to cash in on the storefront steroid craze is a credit card to import raw products from China or India where most of the raw ingredients come from, the ability to pour powders into a bottle or a pill and a printer to create shiny, glossy labels."

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), a manufacturer or distributor does not need to obtain FDA approval of a dietary supplement before it is marketed. Therefore, as a generalization of the process for developing and marketing a dietary supplement,

*Denotes questions to which the Center for Food Safety and Applied Nutrition within FDA provided responsive information

**Denotes questions to which the Office of Criminal Investigation within FDA provided responsive information.

Mr. Tygart's description is correct; in most cases, a firm would only need to obtain raw material, manufacture and package the finished dietary supplement, and correctly label the package. There is no statutory requirement for the firm to get FDA approval of that product or its packaging before marketing it. However, for dietary supplements containing certain new dietary ingredients (NDI) not present in the food supply, the manufacturer or distributor would be required to submit

a premarket notification to FDA with the information, on the basis of which the firm has concluded that the dietary supplement will be reasonably expected to be safe.

2. Absent premarket clearance by the FDA for dietary supplements, are there effective ways for the FDA to deal with the problem of anabolic steroids being sold as body building dietary supplements?

FDA's ability to adequately address the enormous and expanding challenge of products that are marketed as dietary supplements but that contain active ingredients in FDA-approved drugs, analogs of approved drugs, and other compounds such as anabolic steroids that do not qualify as dietary ingredients, is limited. By merely labeling products as dietary supplements, unscrupulous firms can easily introduce into the marketplace products that contain ingredients that may pose risks to health, because 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 ingredient safety prior to marketing, unless the product contains an NDI that has not been part of the food supply as an article used for food (in a form in which the food has not been chemically altered).

FDA's regulation of these products is particularly challenging given the seemingly endless volume of potentially violative products and the painstaking process required to prove that a violation exists. By way of example only, a quick Internet search for "buy bodybuilding dietary supplements" yields close to 500,000 hits, indicating that a huge amount of resources would need to be dedicated to seek out all of the violative firms and products for this one category of products alone.

After identifying one of numerous potentially violative products, an in-depth analysis begins that includes examining labeling claims and ingredients. Because the law permits dietary supplements to bear truthful and nonmisleading claims about effects on the structure or function of the body ("structure/function claims"), determining whether a product is violative often must go beyond a superficial examination of a product's labeling. For example, some androgenic claims may be allowable structure/function claims if they are not false or misleading.

FDA often must also analyze the ingredients of a product to determine whether that specific product is violative. Although not the case with all body-building products, sometimes the active ingredient is undeclared on the labeling and FDA must conduct a laboratory analysis of the product. Even if the labeling of a particular dietary supplement identifies an ingredient we suspect renders the product violative, the process required to confirm a violation is in-depth and extremely time-consuming. With respect to steroids, there are not only many known steroids but also a variety of different names for each ingredient. In addition, manufacturers often misname an ingredient or use a nickname. FDA often must use a steroid expert to identify potentially dangerous ingredients.

When an ingredient that may render a product violative is adequately identified, FDA must then determine whether the ingredient is a dietary ingredient through an extensive search of the scientific literature. Once we determine whether the ingredient is a dietary ingredient, an examination of the product's other ingredients, labeling, and other promotional material is required to determine its proper regulatory status (e.g., unapproved new drug, adulterated dietary supplement).

Even if FDA concludes that regulatory action is warranted against a steroid product marketed as a dietary supplement, FDA must determine the location of the company marketing the violative product and the most responsible parties, before the Agency can proceed with a Warning Letter, civil enforcement action, or criminal investigation. This task is often difficult when a company is knowingly violating the law and does not want to be found. Further, taking regulatory or enforcement action against a firm does not necessarily prevent the firm from committing further violative acts; e.g., if FDA sends a firm a Warning Letter or even seizes product, the firm can easily market the same violative product under a different product name and labeling, or through a different distribution channel or Web site.

Thus, protecting the public from just one violative and dangerous product, much less an entire category of violative products is immensely challenging. The approach FDA must generally take— tackling products one by one—is unsustainable and ineffective in protecting the public from a growing problem.

3. How often have dietary supplement firms complied with the 75 day premarket requirement for filing substantiation reports for products which contain a new dietary ingredient?*

Under Section 413(c) of the FD&C Act (21 U.S.C. 350b(c)), the term “new dietary ingredient” means a dietary ingredient that was not marketed in the United States before October 15, 1994. A dietary supplement that contains a new dietary ingredient is deemed to be adulterated under section 402(f) of the Act unless it meets one of two requirements:

1. The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered, or
2. There is a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the firm submits to FDA the information which is the basis on which it has concluded that a dietary supplement containing an NDI is reasonably expected to be safe (21 U.S.C. 350b(a)(1)-(2)).

Since the enactment of the Dietary Supplement Health and Education Act of 1994 (DSHEA) (Pub. L. 103-417) in October 1994, FDA has received 600 NDI notifications submitted pursuant to 21 U.S.C. 350b(a)(2) and 21 *Code of Federal Regulations* (CFR) 190.6. The numbers of

submissions received vary from year to year; FDA received 55, 82, and 65 in FY 2009, 2008, and 2007, respectively.

FDA has not undertaken a systematic survey of the marketplace in order to attempt to determine the number of dietary supplement products on the market that contain NDIs for which a notification to FDA is required but for which no notification has been submitted. However, anecdotal observations of products marketed on the Internet, in conventional retail venues, or promoted at industry trade shows suggest that substantial numbers of such products are being marketed.

4. What are the penalties for ignoring this filing requirement and have these penalties been enforced? Please provide details of FDA's enforcement actions for ignoring this filing requirement.*

Under the Act, a dietary supplement containing an NDI for which a notification is required is adulterated if the required notification is not submitted at least 75 days prior to introduction or delivery for introduction into interstate commerce. FDA can initiate an injunction action or criminal prosecution against parties marketing violative products, or a seizure action against the products themselves.

FDA has not taken enforcement action against significant numbers of dietary supplements that contain NDIs for which notifications were not submitted. This circumstance derives primarily from the fact that FDA's limited enforcement resources have been directed to compliance activities that have a higher priority and involve an immediate public safety hazard, such as actions against dietary supplements that contain undeclared active pharmaceutical ingredients; e.g., sildenafil (Viagra) analogs or weight-loss drugs.

In 2004, FDA sent Warning Letters to 23 firms marketing dietary supplements containing the steroid androstenedione. The letters alleged that the products were adulterated because they contained an NDI for which a notification was required and no such notification had been submitted to FDA (copies of these Warning Letters can be found at <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/ComplianceEnforcement/ucm081774.htm>).

In cases involving dietary supplements containing only synthetic steroids as active ingredients, rather than allege that the products are adulterated because they contain an NDI for which a notification is required but was not submitted, FDA has generally charged that such products were unapproved drugs because they were intended to affect the structure or function of the body and could not be legally marketed as dietary supplements, because the synthetic steroids were not dietary ingredients (See Warning Letters at Tab A). To be a dietary supplement, a product must contain at least one dietary ingredient (See 21 U.S.C. 321(ff)(1)), and to the best of FDA's knowledge, no synthetic steroid currently being marketed is a dietary ingredient. In cases where the Agency does not have enough information to determine conclusively whether a steroid in a dietary supplement is a dietary ingredient (e.g., because the steroid may be a constituent of a plant rather than synthetically derived), FDA has generally alleged in the alternative that if the substance is a dietary ingredient, it is an NDI for which a notification is required (See LG Sciences seizure complaint and consent agreement at Tab B) and, accordingly, the dietary supplement containing the ingredient is adulterated.

5. Does the FDA have subpoena power to request a dietary supplement firm's substantiation files? Would having subpoena power to request those files be helpful?*

FDA does not have the authority to subpoena information that a firm may possess that substantiates the safety of its products or that substantiates any labeling claims about the products' purported benefits, safety, or other product attributes. FDA could only compel a firm to produce such information as part of the discovery process in a court proceeding.

At this time a determination has not been reached on whether having the ability to compel dietary supplement firms to disclose the types of information described above would be useful to FDA.

6. What are your top recommendations for tightening the regulations on dietary supplements without over burdening the manufacturers that manufacture and sell the good and safe products?

FDA's enforcement challenges are discovering the violation in a huge universe of dietary supplements, proving the violation, and effectively deterring future bad actors. After products enter the market, FDA must undertake intensive investigative and analytical processes to show that they are violative. Each enforcement action involves a collaborative effort by FDA chemists, laboratory staff, lawyers, physicians, and investigators that can span many months.

We cannot comment at this time on specific proposals for regulatory fixes. However, we would be happy to work with this Subcommittee and provide technical assistance if the Subcommittee wishes to make a formal legislative proposal.

7. Mr. Tygart, in his written statement, suggested some regulatory fixes for the problems addressed by this hearing. Which one, if any, do you support?

FDA agrees with Mr. Tygart that enforcement against illegal dietary supplements that contain steroids is very difficult, and would like to highlight key points of his testimony. FDA shares Mr. Tygart's concern in protecting populations, such as young athletes, law enforcement, fire department, and military personnel, particularly when these steroid supplement products are sold with false and misleading claims. As evidenced by Mr. Jareem Gunter's testimony at the hearing on September 29, these products can easily deceive young athletes with claims of being "legal" and "all-natural."

Mr. Tygart aptly characterizes the relative ease with which unscrupulous companies can enter the supplement marketplace. A violative steroid-containing, body-building product can be on a store shelf right next to a legitimate body-building product manufactured and distributed by a responsible, compliant supplement company. An average consumer has no way to distinguish between a responsible company and a bad actor. In his testimony, Mr. Tygart states that companies are "exploiting the lack of premarket regulation to sell magic powders and pills in a bottle, while using the reputation of the health food and vitamin industry to cloak themselves with the appearance of safety and respectability." This exploitation is detrimental to both consumers and to dietary supplement firms that invest in developing and marketing quality products.

We cannot comment at this time on Mr. Tygart's proposals for regulatory fixes. However, we would be happy to work with this Subcommittee and provide technical assistance, if the Subcommittee wishes to make a formal legislative proposal.

Senator Orrin G. Hatch

- 1. Has the FDA ever used the imminent hazard authority provided to the Agency through the DSHEA law? When we were writing this law back in 1994, we included this authority to make sure that the FDA's hands were not tied should a serious problem be discovered.***

Section 402(f)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) (21 U.S.C. 342(f)(1)(C)) states that a dietary supplement or dietary ingredient is adulterated if “the Secretary declares [it] to pose an imminent hazard to public health or safety, except that the authority to make such declaration shall not be delegated and the Secretary shall promptly after such a declaration initiate a proceeding in accordance with sections 554 and 556 of title 5, United States Code, to affirm or withdraw the declaration.”

FDA regulations define the term “imminent hazard” as follows:

(a) “Within the meaning of the Federal Food, Drug, and Cosmetic Act an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The *imminent hazard* may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an *imminent hazard* of such occurrence exists.”

(b) “In exercising his judgment on whether an *imminent hazard* exists, the Commissioner will consider the number of injuries anticipated and the nature, severity, and duration of the anticipated injury.” (21 CFR 2.5)

FDA has never made a recommendation to the Secretary to invoke the imminent hazard authority for dietary supplements.

- 2. In your testimony, you state that the FDA is very concerned with products containing synthetic steroid ingredients that are marketed as dietary supplements. Isn't it true that products containing synthetic steroid ingredients that are marketed as dietary supplements today are prohibited from being on the market through the DHSEA law? Doesn't the DEA have the authority, too, to remove that product if it contains anabolic steroids? The industry believes that products that contain anabolic steroid[s] marketed as dietary supplements should be removed from the market immediately. Isn't it true that DSHEA prohibits these products from being marketed?**

DSHEA does not specifically or necessarily prohibit dietary supplements from containing anabolic steroids. It is only in two situations that DSHEA would prohibit the marketing of a steroid-containing product as a dietary supplement. First, if an anabolic steroid was approved as a new drug or authorized for investigation as a new drug, for which substantial clinical investigations whose existence has been made public were instituted before the steroid was marketed as a dietary supplement or as a food, a product containing the steroid cannot legally be

marketed as a dietary supplement (See 21 *United States Code* (U.S.C.) 321(ff)(3)(B)). Second, if an anabolic steroid in a dietary supplement is not a dietary ingredient as defined in section 201(ff)(1) of the Act (21 U.S.C. 321(ff)(1)) and the product contains no other dietary ingredients, DSHEA prohibits the product from being a dietary supplement. However, some types of anabolic steroids (e.g., those made from plant material or animal tissue) may be dietary ingredients because they fit within one of the categories of dietary ingredients defined in section 201(ff)(1) of the Act.

Determining whether a steroid is a dietary ingredient is an arduous task. When FDA identifies a potential steroid ingredient, either because it was declared on the product's label as an ingredient or not declared but found as a result of laboratory testing, we must determine what the substance is.

In some cases, we cannot identify a substance that has been listed on a product label because it has been given a nickname or named incorrectly (either intentionally to confuse and mislead consumers or unintentionally because of a misunderstanding of steroid nomenclature), or because it is a novel steroid that has not been previously identified. In those cases, we must consult experts, either from within or outside FDA, to assist us in identifying the steroid ingredient. Once the steroid ingredient has been identified, FDA staff must do an extensive search of scientific literature to gather the information needed to determine whether it is a dietary ingredient.

Once FDA determines whether a steroid in a product is a dietary ingredient, an examination of the product's ingredients, labeling, and other promotional material is also required to determine the product's regulatory status and the violations that may apply to it. For products that contain a steroid that is not a dietary ingredient, depending on the product's other ingredients and the claims made for it, the product may be an unapproved new drug or it may be a dietary supplement that is adulterated under section 402(a)(2)(C) of the Act (21 U.S.C. 342(a)(2)(C)) because the steroid ingredient is an unapproved food additive. On the other hand, if FDA determines that the steroid in fact meets the definition of a "dietary ingredient," the Agency must also determine whether a premarket notification would be required for the dietary ingredient. If a premarket notification was required but not submitted at least 75 days before marketing, the product would be considered an adulterated dietary supplement (See 21 U.S.C. 342(f)(1)(B), 350b(a)).

If a product is an unapproved new drug or an adulterated dietary supplement, the product may not be marketed for consumption in the United States. However, DSHEA does not prohibit all products containing steroids from being marketed as dietary supplements, and determining whether a product that contains a steroid is being illegally marketed under the Act alone is a time-consuming task, even if the legality of the product under other statutes, such as the Controlled Substances Act, is not considered.

- 3. I would like to add that the action that your Agency took to protect the public from illegal steroids in dietary supplements was made possible through a law that Congress passed in 2006 to require serious adverse event reporting to the FDA. I was the sponsor of that legislation along with Senators Durbin, Enzi, Kennedy and Harkin. When the FDA issues its Warning Letters to companies illegally marketing products containing anabolic steroids, aren't these companies in violation of laws currently on the books? Could you please explain to me the specifics of current law for products containing these steroids? And why is the FDA's ability to solve problems associated with products**

containing illegal substances limited, especially since I have had four former FDA Commissioners tell me that the FDA has sufficient authority to regulate dietary supplements?

The law Congress passed in 2006 (the Dietary Supplement and Nonprescription Drug Consumer Protection Act) requires dietary supplement manufacturers and distributors to submit serious adverse event reports to FDA. We note that the action FDA took to protect the public from illegal steroid-containing products marketed as dietary supplements by American Cellular Laboratories was initiated as a result of voluntary adverse event reports FDA received from medical professionals. To date, American Cellular Laboratories has not submitted any adverse event reports to FDA.

When FDA issues Warning Letters to companies that are illegally marketing products containing anabolic steroids, these companies are indeed in violation of existing law. However, these violations are difficult to detect and prove, which makes it difficult for FDA to expeditiously address the enormous and expanding challenge of products marketed as dietary supplements that contain active ingredients in FDA-approved drugs or analogs of approved drugs. By merely labeling products as dietary supplements, unscrupulous firms can easily introduce into the marketplace products that contain ingredients that may pose risks to health, because 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 ingredient safety prior to marketing, unless the product contains an NDI that has not been part of the food supply as an article used for food (in a form in which the food has not been chemically altered).

FDA is in a reactive posture with respect to these types of products—a position that is particularly challenging, given the endless volume of potentially violative products and the painstaking process that is often required to prove that a violation exists. By way of example only, a quick Internet search for “buy bodybuilding dietary supplements” yields close to 500,000 hits, indicating that a huge amount of resources would need to be dedicated to seek out all the violative firms and products for this one category of products alone.

After identifying one of numerous potentially violative products, an in-depth analysis begins that includes examining labeling claims and ingredients. Because the law permits dietary supplements to bear claims about effects on the structure or function of the body (“structure/function claims”), determining whether a product is violative often must go beyond an examination of a product's labeling. For example, many androgenic, weight loss, and sexual enhancement claims are allowable structure/function claims.

Accordingly, FDA often must analyze the ingredients of a product to determine whether that specific product is violative. Although not the case with all products, sometimes the active ingredient is undeclared on the labeling and FDA must conduct a laboratory analysis of the product. Even if the labeling of a particular dietary supplement identifies an ingredient we suspect renders the product violative, the process required to confirm a violation is in-depth and time-consuming. Using the steroid example, there are not only many known steroids, but also a variety of different names for each ingredient. Also, manufacturers often misname an ingredient or use a nickname.

When an ingredient that may render a product violative is identified, FDA must then determine whether the ingredient is a dietary ingredient through an extensive search of the scientific literature. Once we determine whether the ingredient is a dietary ingredient, an examination of the product's other ingredients, labeling, and other promotional material is required to determine its proper regulatory status (e.g., unapproved new drug, adulterated dietary supplement).

If FDA concludes that regulatory action is warranted against a product marketed as a dietary supplement, FDA must first determine the location of the company marketing the violative product and the most responsible parties. This task is often difficult when a company is knowingly violating the law and does not want to be found. Further, taking regulatory or enforcement action against a firm does not necessarily prevent the firm from committing further violative acts. For example, if FDA sends a firm a Warning Letter or even seizes product, the firm can easily market the same violative product under a different product name and labeling, or a different distribution channel or Web site.

Thus, protecting the public from just one violative and dangerous product, much less an entire category of violative products is immensely challenging. The approach FDA must generally take— tackling products one by one—is unsustainable and ineffective in protecting the public from a growing problem.

- 4. Does the FDA and the DEA work together on these pressing issues associated with the illegal marketing of products containing anabolic steroids? It seems that there would be a lot of overlap between the two agencies. Is there coordination on these types of cases? And what type of outreach has the FDA pursued with the dietary supplement industry on this issue? Have there been any collaborations between the Agency and the industry? If so, will you take a few minutes to talk about those discussions?***

FDA's Office of Criminal Investigations (OCI) recognizes the need to coordinate with DEA on these types of investigations, particularly because some of these products contain controlled substances specifically listed in the Controlled Substances Act as anabolic steroids. OCI aggressively investigates the distribution of illegal dietary supplements containing synthetic "designer" steroids and recognizes the risks these products pose to consumers. OCI remains actively engaged with DEA to pursue these types of investigations. This strong partnership was highlighted during Operation Raw Deal (See DEA-issued press release, dated September 24, 2007, for additional information on this joint DEA-OCI operation (<http://www.usdoj.gov/dea/pubs/pressrel/pr092407.html>)).

The Agency has recently met with industry stakeholders, including the American Herbal Products Association, the Natural Products Association, the Consumer Healthcare Products Association, and the Council for Responsible Nutrition, on the use of steroids in dietary supplements. FDA has also issued many Warning Letters to companies marketing such products in the past five years. These letters are posted on FDA's Web site (<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm>) and are widely read by dietary supplement companies and the lawyers who advise them. In addition, in 2004, 2006, and 2009, the Agency issued press releases to publicize its enforcement activities concerning body-building products containing steroids and to inform consumers, industry, and health professionals about the risks of these products.

5. Could you walk me through the process of how the FDA considers a New Dietary Ingredient (NDI) for approval after it is submitted to the Agency by a dietary supplement manufacturer?*

FDA does not approve NDIs; however, FDA does review NDI notifications to determine whether there is a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. Upon receipt of incoming correspondence at FDA's Center for Food Safety and Applied Nutrition (CFSAN), an FDA Consumer Safety Officer (CSO) inspects the material to see if it is intended to be an NDI notification under 21 CFR 190.6. If so, the notification is filed for review, which starts the clock for the 75-day period during which the notifier may not market a dietary supplement containing the NDI.

Next, the CSO looks more carefully through the notification to see whether it complies with the administrative requirements of 21 CFR 190.6, the regulation implementing the NDI notification provision of the FD&C Act (21 U.S.C. 350b(a)(2)), which was enacted as part of DSHEA, and which gives FDA the authority to review the submission. Approximately 10 percent of submissions do not comply with 21 CFR 190.6. The most common reasons for noncompliance are notifications that include foreign language publications that have not been completely or accurately translated into English and notifications that make reference to published material but fail to provide reprints or photocopies of the published material. If the notification does not meet the requirements of 21 CFR 190.6, the Agency attempts to contact the notifier, by telephone if possible, to arrange for an amendment to complete the notification.

After review by the CSO, copies of the notification are distributed to employees with appropriate expertise to review the contents of the notification. The expertise needed for review varies somewhat based on the notification. Generally, a chemist and a toxicologist are assigned. Notifications with clinical studies may also be reviewed by a medical officer. Notifications for substances derived from plants are evaluated by botanists. Notifications with live microbial ingredients (e.g., probiotics) are evaluated by a microbiologist. Each member of the multi-disciplinary ad hoc team assigned to the notification provides a preliminary evaluation specific to his/her expertise. The evaluation is based on the material in the notification, publicly available information about the ingredient or similar ingredients identified through a literature search, and any relevant information from previous submissions from other notifiers for the same ingredient or for similar ingredients. At the conclusion of this preliminary review, the ad hoc team then comes together to provide a unified response based on the entire notification and any other relevant information that was uncovered during the preliminary review.

In parallel to its internal scientific review, CFSAN contacts FDA's Center for Drug Evaluation and Research (CDER) to see whether the ingredient might be excluded from use as a dietary supplement because the ingredient was approved as a new drug or authorized for investigation as a new drug for which substantial clinical investigations, whose existence has been made public, have been instituted. Under section 201(ff)(3)(B) of the FD&C Act, added by DSHEA, such articles may not be sold as dietary supplements unless the ingredient was marketed as a dietary supplement or food before it was approved or authorized for investigation as a new drug. Because there is no requirement that the holder of an effective investigational new drug application (IND) disclose the fact that clinical trials for which information is publicly available are in fact

authorized by FDA as investigations of new drugs, CFSAN must rely on confidential information from CDER to begin this analysis.

During review of a notification, FDA staff frequently have questions about the data and information that have been submitted. If these questions are significant enough to affect whether the NDI will reasonably be expected to be safe when used under the conditions described in the notification, FDA may present the questions to the notifier during the 75-day review period, usually during a telephone conference with FDA scientific staff to discuss the scientific issues raised during the FDA review. Administrative and other issues may also be discussed. Responses to these questions frequently arrive in the form of amendments to the notification. Simple responses generally do not affect the length of time it takes FDA to reach a conclusion regarding the information in the notification. However, sometimes responses that contain a substantial amount of new information are received. In order to have sufficient time to review this new information, FDA is authorized to reset the filing date of the notification when it receives a substantive amendment to an NDI notification (See 21 CFR 190.6(d)). Resetting the filing date starts a new 75-day review period.

On or before the 75th day after filing, FDA contacts the notifier to inform the notifier of the conclusions reached during the FDA review of the notification. This is done by letter, with a courtesy copy sent by fax, if fax contact information was provided. After receiving the response letter, some notifiers take advantage of the reminder in the letter to identify to the Agency material in the notification that the notifier considers to be confidential commercial information or trade secrets. On the 90th day after filing, the notification and the FDA response letter are forwarded to the CFSAN Freedom of Information Act (FOIA) staff, who review the material, redact any information that is protected from disclosure under FOIA, and forward a redacted copy to the FDA Division of Dockets Management. The Division of Dockets Management posts the redacted notification and response letter on Regulations.gov, where they are publicly available in docket FDA-1995-S-0039.

6. In your example of the products marketed by American Cellular Labs, Inc., you indicated that the company marketed that product by saying it was a potent anabolic and had low androgenic activity? Isn't such a product already illegal under current law?

The products listed in the American Cellular Labs, Inc. Warning Letter violate the FD&C Act but not solely, because they are marketed as being anabolic and having low androgenic activity. Unfortunately, FDA cannot always take an enforcement action against this type of product merely by looking at the product's marketing claims. For example, claims about enhancing muscle bulk may be allowable function structure claims as long as the claims are not false or misleading. The American Cellular Labs, Inc. body-building products were found to be violative because FDA analyzed each ingredient and determined that the products did not contain any dietary ingredients.

The enforcement challenge is not that these products do not violate the FD&C Act; rather, it is the way the FD&C Act must be enforced—discovering and proving the violation in a huge universe of dietary supplements. Because FDA generally does not receive information on these products prior to marketing, FDA usually cannot identify violative products before they enter the marketplace. After products enter the market, we must undertake intensive investigative and

analytical processes to show that they are violative. Each enforcement action involves a collaborative effort by FDA chemists, laboratory staff, lawyers, physicians, and investigators that can span many months. To find these potentially violative products, FDA staff must search the Internet, gyms, and retail stores. A quick Internet search for “buy bodybuilding dietary supplements” yields close to 500,000 hits, indicating that a huge amount of resources would need to be dedicated to seek out all the violative firms and products, even in this limited product category. Mr. Andrew Shao, Vice President for Science and Regulation at the Council for Responsible Nutrition, estimated that in 2007, \$2.8 billion was spent on products claiming to build muscle or enhance athletic performance. FDA’s arduous investigative and enforcement processes make it difficult for the Agency to monitor and control such a large industry.

After FDA finds a potentially violative body-building product, an in-depth analysis begins. FDA scientists must identify the potential steroid ingredient on the label. There is a vast array of known steroids (over 7,000), all variations of the same basic steroid chemical skeleton. There are also a variety of different names for each ingredient. For example, PubChem lists 60 known synonyms for the controlled substance androstenedione. Some of these include Androtex; Andro; 4-Androstenedione; 4-Androstene-3,17-dione; Fecundin; Androst-4-ene-3,17-dione; delta-4-Androstenedione; 17-Ketotestosterone; 3,17-Dioxoandrost-4-ene; Androstenedione (JAN); Androsten-3,17-dione; delta-4-Androsten-3,17-dione. Because of the multiplicity of steroids and steroid names, FDA must often use a steroid expert to sort through the labeled ingredients and identify potentially dangerous ingredients.

At times, the ingredient may not be listed on the labeling of the finished product, or the ingredient may be misnamed (e.g., parts of the chemical structure name are missing). When this occurs, FDA must send the products to one of our laboratories for analysis. FDA laboratories use scientific expertise and sophisticated instruments to identify the presence of synthetic steroids. Determining the molecular weight may be a useful first step to identifying a chemical compound; however, there could be 20 steroids with the same molecular weight, each representing a unique chemical compound. 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.

When the chemical is adequately identified, FDA must then determine whether the ingredient is a dietary ingredient through an extensive search of the scientific literature. Often, it is an entirely novel compound without any published scientific literature. Once we determine whether the steroid ingredient is a dietary ingredient, an examination of the product’s other ingredients, labeling, and other promotional material is also required to determine its proper regulatory status (e.g., unapproved new drug, adulterated dietary supplement).

If FDA concludes that regulatory action is warranted against a product, the Agency must first determine the location of the company and the most responsible parties. Often, there is no physical address listed for the company, only a post office box, phone number, or e-mail address. The companies are often not registered at their state’s secretary of state or have outdated registrations. FDA spends a significant amount of time tracking down the locations of these companies because many of them do not want to be found.

Only after this long process can FDA begin work on an enforcement action to protect the public from one firm's anabolic steroid or steroid-like products.

7a. How many serious adverse events were reported on an annual basis before the 2006 AER (adverse event reports) legislation was signed into law? Since the 2006 AER law has been implemented, has the FDA seen an increase in the number of serious adverse events?*

The number of serious adverse events reported to FDA markedly increased after the 2006 AER legislation (the Dietary Supplement and Nonprescription Drug Consumer Protection Act) became effective on December 22, 2007. The number of reports received went from 350 reports in calendar year 2007 to 1,107 reports in calendar year 2008.

Table 1 below lists the number of dietary supplement adverse event reports FDA received each year for the past five years. CFSAN staff searched the CFSAN Adverse Event Reporting System (CAERS) Oracle database for reports of adverse events associated with dietary supplements that were received during calendar years 2004 through 2008. Dietary supplement adverse event reports are stored in CAERS after they are received through FDA's MedWatch reporting program. Table 1 also shows the number of adverse events that were reported to FDA as serious each year and the corresponding percentage of serious adverse events for the year. The proportion of reporters to CAERS who characterized the adverse event(s) related to dietary supplement(s) as serious varied across the five years, with no specific trend observed. The highest year for proportion of reporters characterizing the adverse event as serious occurred in 2008, with 78.7 percent of reports characterized as serious.

There are several limitations of making inferences from passive surveillance systems such as CAERS, even with the advent of mandatory reporting. Among these limitations are that CAERS receives a small and unknown percentage of all adverse event reports, and that reported association of a product with an illness does not necessarily prove causation.

Table 1 Number of adverse event (AE) reports to CAERS about dietary supplements where reporter characterized AE(s) as serious By year: 2004-2008			
YEAR	<u>Total Number of Cases Per Year</u>	<u>Number of Cases Adverse Event Complaint (AEC) Serious as Reported</u>	<u>Percentage of Cases Where AEC Serious as Reported</u>
2004	657	483	73.5%
2005	491	364	74.1%
2006	317	213	67.2%
2007	350	213	60.9%
2008	1,107	871	78.7%

7b. If so, what is the protocol for the FDA to follow up with these companies once a serious AER [is received?]*

The medical reviewers in CFSAN's Division of Dietary Supplement Programs evaluate the adverse event reports for dietary supplements on a case-by-case basis and document their clinical reviews in FDA's CAERS database, where dietary supplement adverse event data are stored. FDA reviewers evaluate the seriousness of the adverse events and their relationship to the suspected dietary supplement. When the initial review indicates that the safety concern is serious enough and the data are strong, FDA then considers appropriate action to protect consumers or, if the information is not definitive enough to support regulatory action, initiates an in-depth analysis. If the level of concern is categorized as relatively low based on the professional judgment of FDA reviewers, FDA continues to monitor the safety signals generated by adverse event reports.

If the initial review indicates that a specific dietary supplement may present a health risk to consumers, FDA would initiate an in-depth review. This process includes, but is not limited to an intensive literature search and review; requesting additional information from academic institutions, individual experts, and industry; consulting experts inside FDA or, if necessary, outside FDA; and preparing a safety review.

The safety review informs Agency compliance and policy staff in considering what Agency action may be warranted. Depending on the seriousness of the injury, the certainty of the relationship to a particular dietary supplement or dietary ingredient, and other factors, a number of actions are available to FDA. These actions include issuing a Warning Letter, initiating a seizure or injunction action, requesting that a firm recall implicated product, issuing consumer alerts or other public warnings, working with state and local public health authorities to recall or embargo implicated products, or issuing a regulation to prevent the marketing of an unsafe dietary supplement or dietary ingredient. More than one of these tools may be used for any given situation.

7c. How does the relatively new adverse event reporting system for dietary supplements assist FDA's enforcement efforts against dangerous products?*

The serious adverse event reporting requirements of the Dietary Supplement and Nonprescription Drug Consumer Protection Act resulted in an increase in the number of adverse event reports about dietary supplements. The law also mandated that product labels accompany adverse event reports to FDA. These two new requirements have assisted FDA as follows: 1) the higher number of reports enables reviewers and statisticians to better detect unusual reporting patterns from clusters of adverse event reports, which can provide evidence to help FDA determine associations between products and adverse health effects; and 2) product labels allow for better characterization of the products and their ingredients than would result from voluntary consumer reports where the product may not be as clearly described. Better description and characterization of products associated with adverse events support FDA's investigation and enforcement efforts.

7d. What can be done, in your opinion, to encourage more people to report serious AERs?*

Increased outreach to health professionals, industry and consumers to aid in their awareness of where to report, how to report, and how FDA uses their reports could encourage more people to

report serious AERs. Product labels that provide information about where to report adverse health effects may also encourage more people to report serious adverse events.

8. What percentage of the FDA's annual budget is spent investigating the safety of dietary supplements?

FDA's FY 2010 budget for Dietary Supplement Safety is approximately 0.5 percent of our total annual budget, including user fees.

9a. What type of challenges does the FDA encounter when investigating products with synthetic substances?*

FDA cannot identify violative products before they enter the marketplace. The Agency must go through a detailed investigative and analytical process to show that products are violative after they enter the market; we face struggles to provide an effective criminal deterrent to persons who market these products with the intent to defraud or mislead, and we are unable to effectively prevent the import of all violative products.

Body-building products that contain synthetic steroids continue to be a challenging area for FDA. The marketing of most such 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. To find products with synthetic steroid ingredients, FDA staff must search the Internet, gyms, and retail stores. A quick Internet search for "buy bodybuilding dietary supplements" yields close to 500,000 hits, indicating that a huge amount of resources would need to be dedicated to seek out all of the violative firms and products in this category. Mr. Andrew Shao, Vice President for Science and Regulation at the Council for Responsible Nutrition, estimated that in 2007, \$2.8 billion was spent on products claiming to build muscle or enhance athletic performance. FDA's arduous investigative and enforcement processes make it difficult for the Agency to monitor and control such a large industry.

After FDA finds a potentially violative body-building product, an in-depth analysis begins. First, FDA scientists must identify the potential steroid ingredient on the label. There is a vast array of known steroids (over 7,000), all variations of the same basic steroid chemical skeleton. There are also a variety of different names for each ingredient. For example, PubChem lists 60 known synonyms for the controlled substance androstenedione. Some of these include Androtex; Andro; 4-Androstenedione; 4-Androstene-3,17-dione; Fecundin; Androst-4-ene-3,17-dione; delta-4-Androstenedione; 17-Ketotestosterone; 3,17-Dioxoandrost-4-ene; Androstenedione (JAN); Androsten-3,17-dione; delta-4-Androsten-3,17-dione. Because of the multiplicity of steroids and steroid names, FDA must often use a steroid expert to sort through the labeled ingredients and identify potentially dangerous ingredients.

At times, the ingredient may not be listed on the labeling or the ingredient may be misnamed (e.g., parts of the chemical structure name are missing). When this occurs, FDA must send the products to an FDA laboratory for analysis. FDA laboratories use scientific expertise and sophisticated instruments to identify the presence of synthetic steroids. Determining the molecular weight may be a useful first step to identifying a chemical compound; however, there could be 20 steroids with the same molecular weight, each representing a unique chemical compound. 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.

Lastly, in order to take regulatory action, FDA must determine the location of the company and the most responsible parties. Often, there is no physical address listed for the company, only a post office box, phone number, or e-mail address. The companies are often not registered at their state's secretary of state or have outdated registrations. FDA spends a significant amount of time tracking down the locations of these companies because many of them do not want to be found.

When firms selling violative products are identified, FDA uses both criminal and civil enforcement powers to address the problem of steroid products marketed as dietary supplements. FDA has used its civil enforcement authority through the issuance of Warning Letters to firms and by pursuing a seizure action, if warranted. However, these actions have a limited deterrent effect on unaffected firms and very often involve only one or two violative products. These factors limit the Agency's reach, given the size of the marketplace and the limited resources available.

Criminal investigations can present legal challenges to law enforcement because some dietary supplements contain novel synthetic steroids that are not specifically listed as anabolic steroids under CSA. 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 FD&C Act. If a dietary supplement contains a novel synthetic 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.

FDA also faces the challenge of determining the regulatory classification of steroid products marketed as body-building supplements. Although these steroid products are typically represented as dietary supplements, the products often do not meet the definition of dietary supplement under the Act. For example, if an anabolic steroid was approved as a new drug or authorized for investigation as a new drug, for which substantial clinical investigations whose existence has been made public were instituted before the steroid was marketed as a dietary supplement or as a food, a product containing the steroid cannot legally be marketed as a dietary supplement (See 21 U.S.C. 321(ff)(3)(B)). In addition, if an anabolic steroid in a dietary supplement is not a dietary ingredient, as defined in section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)) and the product contains no other dietary ingredients, the product does not meet the definition of a dietary supplement and may not be marketed as such. However, some types of anabolic steroids (e.g., those made from plant material or animal tissue) may be dietary ingredients because they fit within one of the categories of dietary ingredients defined in section 201(ff)(1) of the FD&C Act.

To be a dietary supplement, a product must contain at least one dietary ingredient (See 21 U.S.C. 321(ff)(1)). A dietary ingredient is defined as a vitamin, a mineral, an amino acid, an 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., the steroid is present in a food such as animal meat or organs used as food);
- a constituent of a plant or 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 for use 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 extracted and purified from the parent material. FDA believes that synthetic versions of otherwise eligible steroids are not dietary ingredients. 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 dietary ingredients. To the best of FDA’s knowledge, no synthetic steroid currently being marketed is a dietary ingredient.

FDA faces many challenges when it considers whether a particular steroid-containing dietary supplement violates the Act. Determining whether a product violates the Act is a time-consuming process that requires staff to search scientific literature. In cases where we cannot identify the steroid ingredient in a product marketed as a dietary supplement (e.g., because the ingredient is named incorrectly or is a novel steroid not previously identified in dietary supplements) or are unable to locate information in the scientific literature, we must consult an expert, either inside or outside FDA, to determine what it is.

Once FDA determines whether a steroid in a product is a dietary ingredient, an examination of the product’s other ingredients, labeling, and other promotional material is required to determine the product’s regulatory status and the violations that may apply to it. For products that contain a steroid that is not a dietary ingredient, depending on the product’s other ingredients and on the claims that are made for it, the product may be an unapproved new drug, or it may be a dietary supplement that is adulterated under section 402(a)(2)(C) of the FD&C Act (21 U.S.C. 342(a)(2)(C)) because the steroid ingredient is an unapproved food additive. On the other hand, if FDA determines that the steroid meets the definition of a dietary ingredient, the Agency must also determine whether a premarket notification would be required for the dietary ingredient. If premarket notification was required, but not submitted at least 75 days before marketing, the product would be considered an adulterated dietary supplement (See 21 U.S.C. 342(f)(1)(B), 350b(a)).

9b. When a product contains such a substance, isn’t it true that since it is adulterated or an unapproved drug, that it is illegal to market that product?*

In the great majority of cases, a product that contains a synthetic steroid is either an unapproved drug or an adulterated dietary supplement. It is a prohibited act under the FD&C Act to market an adulterated dietary supplement or unapproved drug. See previous response and response to Question #4 for the factors FDA considers in determining whether a product containing a synthetic steroid is an unapproved drug or an adulterated dietary supplement.

9c. When the FDA cannot identify a substance listed on the label, why wouldn't it contact the product manufacturer?*

There is no statutory bar to FDA's contacting a product manufacturer when a question is raised about an ingredient in one of the manufacturer's products. However, as a practical matter, FDA's experience has been that this approach is not useful in most situations because of legal limitations such as our inability to compel the firm to disclose information to FDA, and the fact that such contact provides advance notice to the firm of a possible enforcement action. Such advance notice may interfere with FDA's ability to collect evidence in subsequent inspections or searches.

10. Why did FDA take 13 years to issue the dietary supplement Good Manufacturing Practices regulations? Do you think they are helpful?*

In drafting the current Good Manufacturing Practice (cGMP) regulations for dietary supplements, FDA made an extensive effort to be thorough in its regulatory approach and attentive to the many possible impacts on such a varied commodity so frequently purchased by the American public. The aim of the regulations is to prevent inclusion of the wrong ingredients, too much or too little of a dietary ingredient, improper packaging and labeling, and contamination with substances such as natural toxins, bacteria, pesticides, glass, and heavy metals. The history of the rule shows that we carefully considered all comments and were inclusive in our outreach to ensure all stakeholders were able to participate in the process.

To minimize disruptions to small business operations, this rule has a three-year phase-in based on firm size. We are now in the second stage where firms of 20-500 employees are subject to the rule. By June 2010, firms of fewer than 20 employees will also have to comply with the cGMP regulations. Because of the phasing in of the rule's obligations based on firm size, most firms have only recently (June 2009) become subject to the regulations. Given that fact, we do not yet have sufficient inspection data to draw firm conclusions as to whether the cGMP regulations are having their expected impact by ensuring that dietary supplements are produced in a quality manner, do not contain contaminants or impurities, and are accurately labeled.

11a. Did the manufacturers of the products at issue here submit pre-market notifications, as required by current law? If not, aren't the products considered adulterated and FDA can take action under current law?*

FDA has not received NDI notifications for most steroid-containing products currently being marketed as dietary supplements. In many cases, this may be because the steroids are not dietary ingredients as defined in section 201(ff)(1) of the FD&C Act. If the steroids in some of these products are in fact dietary ingredients, however, FDA believes that most or all of them would be NDIs for which a notification is required. The fact that no such notification has been submitted to FDA would result in products containing such NDIs being adulterated dietary supplements whose

marketing would violate the FD&C Act. FDA could take enforcement action against such products if an investigation established evidence of the violations of law.

11b. Has FDA ever initiated an enforcement action because a dietary supplement failed to comply with the new dietary ingredient notification requirements?*

FDA has alleged that a dietary supplement is adulterated under section 402(f)(1)(B) of the FD&C Act (21 U.S.C. 342(f)(1)(B)) in three instances to date. In March 2004, FDA alleged in Warning Letters to 23 firms marketing androstenedione-containing supplements that, assuming that the firms had a basis to conclude that androstenedione was a dietary ingredient, it appeared to be an NDI for which a notification was required. The same charge was used in an August 19, 2009, Warning Letter to the firm EFT, Inc. for the products Perform Plus #3006, Cellprotect I, and Cellprotect II, because they contained either humic and fulvic acids or 4-androsten-3,17-dione. FDA also used this charge in a seizure action against two steroid-containing products marketed as dietary supplements by LG Sciences, LLC (See seizure complaint and consent decree at Tab B). The case ended in a consent decree that condemned the seized products and ordered their destruction.

12. In your testimony, you indicate that FDA is unable to prevent the importation of products that violate the Food Drug and Cosmetic Act. Doesn't this suggest that FDA needs to do a better job exercising its existing authorities before taking on new responsibilities?

Products containing steroids may be either produced domestically or imported. When made domestically, it has been our experience that investigations have determined that the bulk ingredients have been imported for encapsulation, bottling, labeling and distribution. FDA works closely with U.S. Customs and Border Protection to monitor imports. Under section 801(a) of the FD&C Act (21 U.S.C. 381), imported dietary supplements and drugs are subject to review by FDA at the time of entry through U.S. Customs. Products that do not appear to comply with FDA laws and regulations are subject to refusal of admission into the United States. Violative products must be brought into compliance (if feasible), destroyed, or re-exported. Shipments of violative dietary supplements and drugs, however, 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 limited resources, which prevent the Agency from performing a comprehensive evaluation of all incoming packages.

With regard to your question about new responsibilities, FDA is mindful of its obligation to use its existing authority well. Accordingly, the Agency will continue to use its available resources to detect imported steroid products and bulk ingredients that violate the FD&C Act and prevent them from being marketed to consumers in the United States.

13. Please go into more detail about the regulation of health claims for supplements on packaging and in advertising.*

Health claims are claims in the labeling of a dietary supplement or other food that expressly or by implication characterize the relationship of a food substance to a disease or health-related condition. An example of a health claim is "Adequate calcium throughout life, as part of a well-

balanced diet, may reduce the risk of osteoporosis" (See 21 CFR 101.72). FDA regulates health claims in supplement labeling; the Federal Trade Commission regulates such claims when they appear in supplement advertising. There are two ways by which FDA exercises its oversight in determining which health claims may be used in labeling for a dietary supplement:

1. **Health Claims Authorized by Regulation.** The FD&C Act provides for FDA to issue regulations authorizing health claims for dietary supplements and other foods based on an extensive review of the scientific literature, generally as a result of the submission of a health claim petition. The Agency uses the significant scientific agreement standard to determine whether the substance/disease relationship is well-established.
2. **Qualified Health Claims.** As a result of court decisions interpreting the First Amendment to the U.S. Constitution, FDA reviews qualified health claim petitions and issues a letter of enforcement discretion when the Agency's review of the scientific literature shows that there is credible scientific evidence supporting the claim, but the quality and strength of the scientific evidence fall below the standard for FDA to issue an authorizing regulation. Qualifying language is included with the claim to describe the limitations in the evidence supporting the claim and to convey any other information necessary to prevent the claim from misleading consumers.

14a. Could you please describe for the Committee in as much detail as possible how the Food and Drug Administration works with the Drug Enforcement Administration in investigating and addressing possible sale of illegal steroid and steroid precursor products? Do you have any formal interagency agreement in this area? If so, please provide a copy for the Committee.**

FDA's OCI continues to aggressively investigate the distribution of products containing synthetic steroids, and recognizes the risks these products pose to consumers. OCI remains actively engaged with DEA to pursue these types of investigations. This strong partnership was highlighted during Operation Raw Deal. See DEA-issued press release, dated September 24, 2007, for additional information on this joint DEA-OCI operation at <http://www.usdoj.gov/dea/pubs/pressrel/pr092407.html>. OCI recognizes the need to coordinate with DEA on these types of investigations, particularly because some of these products contain controlled substances specifically listed in the CSA as anabolic steroids.

FDA currently has two Memorandums of Understanding (MOUs) with DEA at Tab C. They are available at <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm116001.htm> and <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm116210.htm>.

The first MOU, which was signed in 1974, establishes a working arrangement for the operation and activities of a DEA/FDA Liaison Staff created to carry out the objectives of the CSA. The MOU states that the staff shall coordinate efforts to facilitate exchange of pertinent information necessary to controlled substances decisions. The second MOU, signed in 1976, is unrelated to the current topic of steroids in dietary supplements and pertains to narcotic treatment centers.

In addition, FDA is a member of the Interagency Committee on Drug Control (ICDC), established in the early 1970s as a forum to discuss problem areas in drug control that transcend the boundaries of individual Agency responsibilities. The purpose of the group is to help facilitate the exchange and coordination of information among agencies. The ICDC includes representations from the Office of National Drug Control Policy (ONDCP), DEA, FDA and National Institute on Drug Abuse (NIDA). Please find attached (Tab D) a copy of the charter.

14b. The Commissioner has stated that it is her priority to improve enforcement against illegal steroid products masquerading as dietary supplements. Please outline the steps your Agency is taking to follow through on this commitment.

In late July, FDA executed a search warrant on American Cellular Labs, Inc., and sent a Warning Letter to the firm for marketing and distributing body-building products containing synthetic steroid substances. This action was followed by the execution of a search warrant on Bodybuilding.com, a large online distributor of body-building products on the Internet. The Bodybuilding.com search warrant named over 60 products marketed as dietary supplements that contained one or more of five different steroids—"Madol," "Tren," "Superdrol," "Androstenedione," and "Turinabol."

In addition to these actions, FDA continues to use available resources to monitor the marketplace for potentially illegal products. FDA obtains information from inspections of dietary supplement manufacturers and distributors, the Internet, consumer and trade complaints, laboratory analyses of selected products, and adverse events that are reported to the Agency.

When a violative product is investigated, FDA must conduct scientific and labeling analyses of the ingredients, conduct a legal review, discover the firms' locations, and, when appropriate, take action. Because of the complexity of this process, it may take the Agency many months to complete an investigation and take an action against a violative firm.

If FDA thinks that there is a violative product that should be immediately removed from the market, the Agency must rely on the responsible firm to take such action. Recalls of dietary supplements and drugs are voluntary actions taken by manufacturers or distributors. FDA is not authorized to require recalls of dietary supplements or drugs. If the firm is willing to conduct a recall, FDA works with the firm on recall strategy and implementation. If the firm is not willing to remove dangerous products from the market and is unwilling to voluntarily cease distribution, FDA considers its enforcement tools, including seizure, injunction, and criminal sanctions.

FDA will continue to closely monitor the safety of steroid products marketed as dietary supplements. 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. While FDA has made it a priority to improve enforcement against bad actors, our resources are limited. We intend to focus on taking action against those products that pose the greatest health risk to the most vulnerable populations. We hope that industry will also continue to make it a priority to help consumers better distinguish bad actors from responsible supplement companies.

14c. How many possible illegal steroid or steroid precursor products have come to the attention of your Agency? How many of those have you acted on?

Because FDA generally does not receive information on these products prior to marketing, FDA generally cannot identify violative products before they enter the marketplace. However, based on consumer complaints, reported adverse events, and Internet searches, FDA believes that illegal steroid products are a widespread problem. In the search warrant executed on bodybuilding.com on September 25, 2009, FDA seized over 60 different steroid products. This involved one distributor and five different steroid compounds. In the recent American Cellular Laboratories case, FDA identified eight violative steroid products.

14d. If a person becomes aware of such a product, what is the best way to bring it to the attention of the FDA? Would the FDA investigate such a complaint?

FDA welcomes and encourages reports from consumers and health care professionals alerting the Agency to problems with products regulated by FDA. These reports help FDA ensure that products on the market are safe and properly manufactured, labeled and stored. In each case, the information is evaluated to determine how serious the problem is and what follow-up is needed. Top priority is given to products that have caused or may cause a serious illness, injury, or a life-threatening situation. Although FDA cannot respond to every complaint individually, the Agency will evaluate every complaint received.

A person can contact FDA through our Web site in a number of different ways: Report any criminal behavior to: <http://www.fda.gov/ICECI/CriminalInvestigations/ucm123025.htm> Report any safety issues or adverse events to FDA's MedWatch: <http://www.fda.gov/Safety/MedWatch/default.htm>. To report unlawful sales of medical products on the Internet, visit Reporting Unlawful Sales at: <http://www.fda.gov/Safety/ReportaProblem/ucm059315.htm>.

15. In a February 21, 2009 FDA Consumer Health Information notice, the FDA stated that since 2004, it has identified several products that claim to be dietary supplements for treating erectile dysfunction and enhancing sexual performance.

Some of these products were found to contain the active ingredient or a substance similar to the active ingredient in Viagra or Levitra. Both Viagra and Levitra were approved by the FDA, went through the premarket drug approval process and, today, may only be sold to consumers with a doctor's prescription.

However, this did not stop unscrupulous companies from marketing these products even though they were in clear violation of the Federal Food, Drug and Cosmetic Act. Similarly, products containing anabolic steroids that are marketed as dietary supplements are adulterated and misbranded. These anabolic steroid products are also in a clear violation of the law. Therefore, requiring the premarket approval of these products will not prevent unscrupulous companies from breaking the law. In my opinion, the better solution is to strengthen the enforcement activities of the FDA and DEA. Mr. Levy and Mr. Rannazzisi do you agree?

FDA will continue to closely monitor the safety of steroid products marketed as dietary supplements. 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. While FDA has made it a priority to improve enforcement against bad actors, our resources are limited. Therefore, we intend to focus on taking action against those products that pose the greatest health risk to the most vulnerable populations.

Generally, FDA's challenge in regulating these products, is in the way the law must be enforced—discovering the violation in a huge universe of dietary supplements, classifying and proving the violation, and effectively deterring future bad actors. After products enter the market, we must undertake intensive investigative and analytical processes to show that they are violative. Each enforcement action involves a collaborative effort by FDA chemists, laboratory staff, lawyers, physicians, and investigators that can span many months.

16. In his testimony, Mr. Tygart talks about a product called Superdrol. I have done a little research on this product and am having trouble understanding why it wouldn't be taken off the market through the laws currently on the books? The advertisements I have seen make muscle-building claims and tout it as an anabolic steroid.

Most products containing the ingredient known as "Superdrol," which is the synthetic steroid methasteron, violate the FD&C Act. However, these products do not violate the law solely because they are marketed with muscle-building claims and are touted as anabolic steroids. Unfortunately, looking at the marketing claims is only part of the analysis. Certain muscle-building claims can be claims that the ingredient affects the structure or function of the body. These types of claims are allowed for dietary supplements under the FD&C Act as long as they are not false or misleading. However, such claims are not allowed for drugs without FDA approval of a new drug application. Whether a product marketed as an anabolic steroid with muscle building claims will be regulated as a dietary supplement or a drug depends on whether the steroid ingredient is a dietary ingredient under 21 U.S.C. 321(ff)(1) and, if not, whether the product contains any other dietary ingredients. The Anabolic Xtreme Superdrol product that was the subject of FDA Warning Letters to the manufacturer and distributor in 2006 contained Superdrol, which is not a dietary ingredient. See <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm075812.htm>; <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm075813.htm>. The product contained no other dietary ingredients, and therefore it could not be a dietary supplement because a dietary supplement is defined as a product that, among other things, contains one or more dietary ingredients (See 21 U.S.C. 321(ff)(1)). Because Anabolic Xtreme Superdrol was intended to affect the structure and function of the body by building muscle, was not a dietary supplement and was not FDA-approved as a drug for building muscle, it was an unapproved new drug whose marketing violated the FD&C Act. However, because of the complex, fact-based nature of the legal analysis, FDA must evaluate each Superdrol-containing product individually to determine whether it violates the FD&C Act and, if so, under what provisions.

Because FDA generally does not receive information on steroid body-building products prior to marketing, FDA cannot identify violative products containing Superdrol before they enter the marketplace. After products enter the market, we must undertake intensive investigative and analytical processes to show that they are violative. Each enforcement action involves a

collaborative effort by FDA chemists, laboratory staff, lawyers, physicians, and investigators that can span many months.

- 17. As I reviewed the testimony of both the DEA and the FDA, both agencies argued that it takes a great deal of time to build a case against a product in order to take it off the market. In other words, the way I interpreted your statements – you are both saying that you cannot just pull a product off the market. But isn't it true that for the vast majority, if not all of these products, they would require an NDI (new dietary ingredient) notification to FDA? If they are marketing a supplement and haven't filed, FDA can take the product off the market because it is misbranded. If the company has filed an NDI, the FDA may still reject it, as the Agency has in over half of all NDI notifications.***

Based on FDA's experience to date with the steroids used in products marketed as dietary supplements, the Agency believes that the number of steroid ingredients that would require an NDI notification is very small because the great majority of such ingredients are synthetic steroids that do not meet the definition of a dietary ingredient. If a substance is not a dietary ingredient, by definition it is not an NDI (See 21 U.S.C. 350b(c)).

When FDA identifies a product being marketed as a dietary supplement that contains what appears to be a steroid, the Agency needs to seek information that will enable us to answer the following questions, among others:

1. Is the substance a dietary ingredient as defined in section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1))
2. If so, is it an NDI for which a notification is required?

Finding and evaluating information to answer these two questions takes time and resources. But, once that information is in hand, FDA has no regulatory tool that would enable us to compel a firm to remove its products from the market by administrative fiat. Rather, the tool available to us to remove a product if it contains a steroid that isn't a dietary ingredient (and that results in the product being an adulterated dietary supplement or unapproved new drug), or that is an NDI for which a notification was required but not submitted (meaning that the dietary supplement containing an NDI is adulterated) is to file a civil seizure or injunction case in federal court.

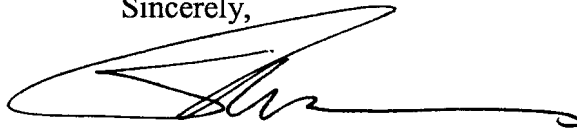
If a company submits an NDI notification to FDA, and FDA determines that the substance is not a dietary ingredient or FDA believes that the scientific evidence does not establish a reasonable expectation of safety, FDA's remedy to stop the marketing of a product containing the subject ingredient would be to file a seizure or injunction action in federal court. In most cases, this would happen after the product had been introduced into interstate commerce because FDA seldom knows whether or when a firm that has received an FDA letter objecting to an NDI notification intends to market its product.

It is important to note that NDI notifications are just that; they are not applications requiring FDA approval. A firm that submits a notification meeting the requirements of 21 CFR 190.6 may market its product 75 days later. At that point, the burden is on FDA to take action. If the Agency

concludes that there is no history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe, the Agency's only option to stop the marketing of the supplement is to initiate enforcement action and convince a court that the product violates the FD&C Act. This is because FDA's mere statement in a letter responding to a notification that the Agency believes a product is violative does not constitute a binding legal determination that the product is unlawful and may not be marketed. Rather, it is a statement of FDA's judgment of the information before it.

Thank you again for the opportunity to testify. Please let us know if there are further questions.

Sincerely,

A handwritten signature in black ink, appearing to be "Jeanne Ireland", written over a horizontal line.

For Jeanne Ireland
Assistant Commissioner
for Legislation

Enclosures