Dietary Supplements

FDLI Introduction to Food Law and Regulation
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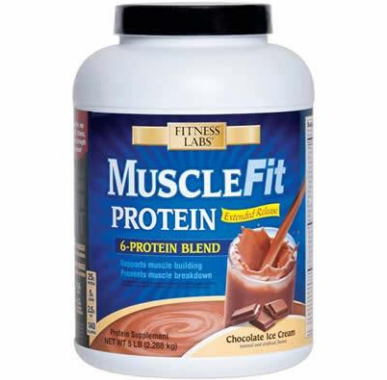
Agenda

1. What Is a **Dietary Supplement**?
2. What **Ingredients** Can It Contain?
3. What **Claims** Can It Bear?
4. What's the **Safety** Standard?
5. How Is **Manufacturing** Regulated?
6. Who are the **Enforcers**?
7. What's so Special About **CBD**?

What is a Dietary Supplement?



What is a Dietary Supplement?

Is it a "**Food**"? A "**Drug**"? Something Else?

- **"Food"** means "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article." FDCA § 201(f).

- **"Drug"** means, in relevant part, "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals." FDCA § 201(g)(1)(B).

What is a Dietary Supplement?

It's food. It's always been food.

- **DSHEA.** In October 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA), adding the term "dietary supplement" to the FDCA. Exempt from food additive requirement.

- **FDCA § 201(ff)**: "Except for the purposes of [two sections of the FDCA], a dietary supplement shall be deemed a food within the meaning of the Act."

FDCA to USC

- The Federal Food, Drug, and Cosmetic Act ("FDCA" or "FD&C" Act) is codified in Title 21 of the United State Code (USC).

- To convert from a section of the FDCA to a section of the USC, you can often drop the middle 0 and prefix a 3:

  Examples :

  FDCA § 201(ff) = 21 USC § 321(ff)
  FDCA § 402 = 21 USC § 342
  FDCA § 505(b) = 21 USC § 355(b)

- It works for FDCA § X0Y, *where* $X \leq 7$ *and* $Y \leq 5$.

What is a Dietary Supplement?

Legal Definition (Part 1 of 3), FDCA § 201(ff)(1):

- A product intended to supplement the diet that contains at least one of the following "dietary ingredients":
  - "(A) a vitamin;"
  - "(B) a mineral;"
  - "(C) an herb or other botanical;"
  - "(D) an amino acid;"
  - "(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or"
  - "(F) a concentrate, metabolite, constituent, extract, or combination" of any of the above.

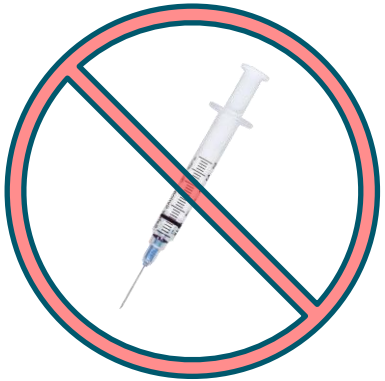
What is a Dietary Supplement?

Legal Definition (2 of 3), FDCA § 201(ff)(2):

- Intended for ingestion.
- Not represented as a conventional food or meal replacement.
- Labeled as a dietary supplement.

Intended for Ingestion

- ✖ Intended for Ingestion? Not if inhaled. 2012 FDA Warning to Breathable Foods, Inc., about inhalable caffeine.



- ✖ Cannot be injected, administered sublingually, or transdermal.

- ✓ May be in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders.

Not Represented as a Conventional Food

- Coffee energy drink is a beverage and a conventional food, not a dietary supplement.
- FDA 2012 Warning Letter to Rockstar
  - Labeling said “beverage”
  - Use of supplement facts doesn’t make it a dietary supplement

More Info: FDA Guidance for Industry: Distinguishing Liquid Dietary Supplements from Beverages (2014)

What is a Dietary Supplement?

Legal Definition (3 of 3), FDCA § 201(ff)(3):

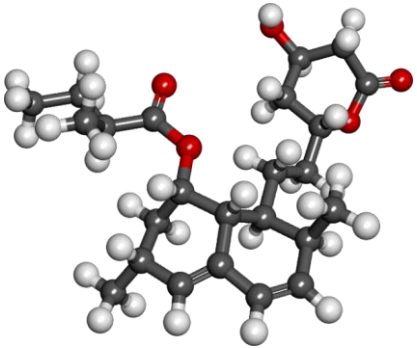
- Does not include an approved new drug, certified antibiotic, or licensed biologic.
- Does not include article authorized for investigation as a new drug for which substantial clinical investigations have been instituted and made public.

Unless marketed as a food or dietary supplement before it was approved or authorized for investigation as a drug.

Food Before Drug? The Saga of Red Yeast Rice

Red Yeast Rice

- ✓ Fermented rice, red from mold (red filamentous fungus).
- ✓ Color in Peking Duck.
- ✓ Dietary supplement? Yes.



Lovastatin

- ✓ Active ingredient in Mevacor
- ✓ Statin: lowers cholesterol.
- ✓ Constituent in red yeast rice.
- × Dietary supplement? No.

QUIZ: What Is Fish Oil?

A. A Conventional Food

B. A Dietary Supplement

C. A Prescription drug

D. All of the Above

QUIZ: What Ingredients Can A Dietary Supplement Contain?

A. Dietary Ingredients

B. GRAS Substances

C. Food Additives

D. Color Additives

D. All of the Above

Analysis of Dietary Ingredients

- **Step 1**: Determine Whether the Ingredient Is a "Dietary Ingredient."
- **Step 2**: Determine Whether an NDI Notification Must Be Submitted.

Step 1: Categories of Dietary Ingredients

A. "a vitamin"
B. "a mineral"
C. "an herb or other botanical"
D. "an amino acid"
E. "a dietary substance for use by man to supplement the diet by increasing the total dietary intake" or
F. "a concentrate, metabolite, constituent, extract, or combination" of any of the above

What is a “Dietary Substance”?

- “**Dietary Substance**” – commonly used as part of the usual diet, a substance used in human food or drink
  - Examples: fish oil, probiotics, synthetic caffeine

What Is a “Botanical”?

- “**Botanical**”:
  - A plant, algae, or fungus.
  - A part of a plant, algae, or fungus (e.g., bark, leaves, stems, roots, flowers, fruits, seeds, berries, or parts thereof);
  - An exudate (secretion) of a plant, algae, or fungus
- FDA does not recognize “synthetic botanicals” (but such a substance may qualify as a “dietary substance”)

Step 2. When Is an NDI Notification Required?

- An NDI notification is not required if an ingredient satisfies either of two exclusions:
  1. **The dietary ingredient is a "pre-DSHEA" dietary ingredient**.
  2. **The dietary ingredient is an "article used for food" which has not been "chemically altered."**
- Otherwise, submit an NDI notification to FDA at least 75 days before first using the ingredient in a dietary supplement.

What are new dietary ingredients (NDIs)?

- Old vs. New
  - **Pre-DSHEA dietary ingredient** (often called "old" or "grandfathered"):
    - Marketed in the United States before October 15, 1994.
    - Challenge is often verifying that the version in a product is the same as the version marketed pre-DSHEA.
  - **"New Dietary Ingredient"**: everything else.
- Legal Source:
  - FDCA § 413, codified at 21 U.S.C. § 350b
  - NDI draft guidance (2011, revised 2016)

What about “Other Ingredients”?

- FDA-approved food additives
- GRAS substance: substances that are “generally recognized as safe”
- FDA-approved color additives

“**Other ingredients**” 21 C.F.R. § 101.4(g) (“Ingredients in dietary supplements that are not dietary ingredients or that do not contain dietary ingredients, such as excipients, fillers, artificial colors, artificial sweeteners, flavors, or binders, shall be included in the ingredient list.”)

What Claims Can a Dietary Supplement Bear?

What Claims Can a Dietary Supplement Bear?

- **Nutrient Content Claims**
  - Characterize the level of nutrient (e.g., “low fat,” “high fiber,” “added vitamin D,” “excellent source of folate”).
  - Must be specifically authorized by FDA regulation, and only for nutrients with daily values (e.g., one cannot say “high in resveratrol” or “excellent source of omega-3s”)
- **Health Claims**
  - Claims about a nutrient/component and reduced risk of disease, e.g., “reduce the risk of osteoporosis.”
  - Must be specifically authorized by FDA.
- **Structure/Function Claims**

Analysis of Structure/Function Claims

- **Step 1**: Determine Whether the Claims Are Structure/Function Claims (e.g., not disease claims or another type of claims)
- **Step 2**: Determine Whether the Claims are Substantiated by scientific support.

Step 1: Is It a Structure/Function Claim?

Structure/Function Claims

- Claims a benefit related to a **classical nutrient deficiency disease**.
- Describe the **role of a nutrient or dietary ingredient** intended to affect the structure or function in humans.
- Characterize the **documented mechanism** by which a nutrient or dietary ingredient acts to maintain such structure or function.
- Describe the **general well-being from consumption** of a nutrient or dietary ingredient.

FDCA § 403(r)(6)

FDA policy – structure/function benefit of conventional foods must derive from the "nutritive value" of the food.

What's Not Allowed?

No drug claims for dietary supplements.

- *Cannot* suggest that the product intended to diagnose, cure, mitigate, treat, or prevent a disease. See definition of "drug."
- Drug claims can be explicit or implicit.
  - *Explicit*: "Treats arthritis"
  - *Implicit*: "Improves joint mobility and reduces inflammation" (rheumatoid arthritis)

Structure/Function v. Disease

Disease Claim	Associated Disease	Permissible Structure/Function Claim
“Protects against colds and coronaviruses”	FDA considers colds, flus, and coronaviruses to be diseases	“Helps support the immune system”
“Digestive (ulcerative colitis)”	Ulcerative colitis is a disease	“Helps support digestive health”
“Lowers blood sugar level”	Irregularities in the levels of blood sugar are associated with diabetes, a disease	“Helps to maintain blood sugar levels that are already within the normal range”
“Alzheimer’s prevention”	Alzheimer’s is a disease	“Improves absentmindedness”

Structure/Function Claims for Dietary Supplements

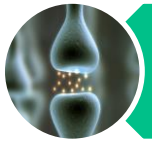
- 30-Day notification requirement:
  - Notification with the text of the claim to FDA no later than 30 days after first marketing.
  - FDA may respond with a “courtesy” letter.
- Labeling must include disclaimer:

> *These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

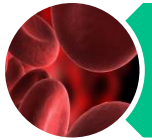
*These requirements to not apply to structure/function claims for conventional foods.

QUIZ: Structure/Function or Disease Claim?

supports healthy brain development



may reduce the risk of osteoporosis



supports healthy cholesterol levels

Substantiation and the Role of FTC

Substantiation

All claims must be substantiated in order to not be misleading

- FTC takes the lead
  - "**Competent and reliable scientific evidence**" in needed to support claims about the benefits and safety of dietary supplements and other health-related products.
  - FTC, Dietary Supplements: An Advertising Guide for Industry (April 2001).
- FDA has adopted a consistent approach.
  - FDA Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the FDCA (Dec. 2008)

FDA and FTC share jurisdiction over dietary supplement, food, and other non-drug product claims, pursuant to a long-standing MOU.

What is “Competent and Reliable Scientific Evidence”

- Flexible – what experts in field would consider adequate
  - NOT limited to placebo-controlled double-blind studies
  - Where specific level of support is stated/implied (e.g., “2 studies show“ and “lab tests prove”), substantiation must conform
- Quality is more important than quantity
- Typically need at least one human study (FTC: “Results obtained in animal and in vitro studies will also be examined, particularly where they are widely considered to be acceptable substitutes for human research or where human research is infeasible”)

What About Safety?

What About Safety?

- For some dietary ingredients, an NDI notification must be submitted containing information to show the NDI "will reasonably be expected to be safe."
- General food adulteration standard applies. FDCA § 402(a).
  - Prohibition against poisonous or deleterious substances.
  - Prohibition against contamination with insanitary or injurious substances.
- Special adulteration standards for dietary supplements.
  - Dietary ingredient must not present significant or unreasonable risk of illness or injury. FDCA § 402(f).
  - Must meet CGMPs. FDCA § 402(g).

Serious Adverse Event Reporting

- The manufacturer, packer, or distributor whose name appears on the label *must* report "**serious adverse events**" within 15 days of learning of event:
  - SAE is an adverse event that results in (or requires medical or surgical intervention to prevent):
    - Death;
    - A life-threatening experience;
    - Inpatient hospitalization;
    - A persistent or significant disability or incapacity; or
    - A congenital anomaly or birth defect.
- Must maintain for six years a record of each adverse event.

FDCA § 761, codified at 21 U.S.C. § 379aa-1

Dietary Supplement Current Good Manufacturing Practices

- **Finished dietary supplement** manufacturing governed by 21 C.F.R. Part 111.
  - Rather detailed.
  - Emphasis on supplier qualification, ingredient identification, master manufacturing record, batch record.
  - Using contract manufacturers does not absolve brand company of all responsibilities.
- **Dietary ingredient** manufacturing is under FSMA (dietary ingredients are food).
- FDA sends a lot of warning letters about GMP issues.

Types of Enforcement

- FDA Warning Letters
  - Threat of enforcement action if violation not remedied
- Seizure
- Injunction
- Civil and Criminal Penalties
  - Fines
  - Imprisonment
- FTC – fines, consent orders
- Non-FDA/FTC "enforcement"
  - State action (e.g., by attorneys general)
  - Consumer litigation

Trends in Litigation in the Dietary Supplement Industry

- State AG attention to the category
- Private class action litigation
  - Often following warning letter, state AG action, NAD challenge
  - Mostly claims-based (consumer fraud)
    - False/misleading
    - Unsubstantiated
  - Some personal injury actions
  - Litigation risk is major driver of compliance/consideration

CBD – The Current Legal Landscape

2018 Farm Bill: "Hemp" Not a Controlled Substance

- Defined "hemp" to mean:
  - the plant Cannabis sativa L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers . . . with a [THC] concentration of not more than 0.3 percent on a dry weight basis.
- Carved out "hemp" from the definition of marijuana
- So hemp, as defined, and CBD from hemp, is no longer a controlled substance as a matter of federal law

- But that is not the end of the story . . . .

FDA's Position on CBD

CBD (whether from marijuana or hemp) may not be sold as or in a dietary supplement or food in the United States

Under the FDCA, neither food nor dietary supplements can contain any article approved as a new drug or authorized for investigation for which "substantial clinical investigations have been instituted and for which the existence of such investigations has been made public," *unless* the article was first marketed as a dietary supplement or a food.

- FDA authorized substantial clinical investigations for CBD drugs, and approved Epidiolex.
- FDA believes CBD was not marketed as a dietary supplement or food first.

FDA can issue a regulation finding the article to be lawful in food or supplements.

CBD in cosmetic/topical products is not precluded by FDA's restrictions on CBD in dietary supplements or foods.

CBD in medical products would require pre-market review and approval.

Hemp vs. CBD

- On December 20, 2018, FDA had “no questions” about GRAS notices for three hemp seed ingredients: hulled hemp seeds, hemp seed protein, and hemp seed oil.
- On July 23, 2021, FDA objected to two NDI notifications for developers of hemp extracts, citing its finding that CBD is a drug. In its responses to both, FDA noted that the product had be developed to ensure “consistent levels of CBD” and are derived from material that provide “robust” levels of CBD.
- FDA continues to show interest in developing a pathway for cannabis and cannabis-derived products in food.

Questions?

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