INTRODUCTION TO FOOD LAW AND REGULATION – DIETARY SUPPLEMENTS

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Introduction to Dietary Supplement Regulation

- Who regulates dietary supplements?
- What are dietary supplements?
- How do I label a dietary supplement product?
- What types of claims can be made about dietary supplement products?
- What ingredients can be used in dietary supplements?
- What happens if someone reports that they get sick from taking a dietary supplement product?
- Are there any standards that govern the manufacturing of dietary supplement products?
- What role do states play in dietary supplement regulation?

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Dietary Supplement Industry at a Glance

- Estimated $46 billion+ industry
- More than 170 million Americans take dietary supplements annually
- Many types of dietary supplements
  - Vitamins and minerals, botanicals
  - Sports nutrition supplements
  - Weight management products
  - Specialty supplement

Regulatory Oversight

Federal Regulatory Agencies

State Attorneys General

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Jurisdictional Issues

- Memorandum of Understanding
  - FDA has primary responsibility for the labeling of dietary supplements
  - FTC has primary responsibility for advertising of dietary supplements
- Not so black-and-white in application
  - FDA will look to advertising as evidence of "intended use"
  - FTC will look at whether claims are appropriate for product classification and coordinate with FDA
- FDA has exclusive jurisdiction over the safety of dietary supplements, including the manufacturing process

FDA Regulatory Authority

- Take action against dietary supplements that pose “a significant or unreasonable risk of illness or injury” or are unsanitary
- Stop the sale of dietary supplements that make false or unsubstantiated claims or make a claim that the products treat, cure, or prevent a disease
- Stop a new dietary ingredient from being marketed if the agency does not receive enough safety information in advance
- Require companies to report serious illness or injuries caused by a dietary supplement
- Require companies to register with the agency
- Require dietary supplements to meet strict manufacturing requirements (GMPs)
- Inspect certain records and require companies to maintain records for a certain period of time

DSHEA

- Before 1994, no official definition of dietary supplement
  - Dietary supplements were regulated as either food or drugs
- Dietary Supplement Health and Education Act (DSHEA)
  - Established regulatory framework for dietary supplements

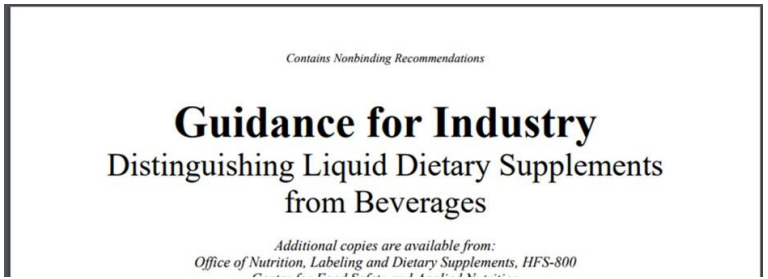
Dietary Supplements: Definition

- A product intended to supplement the diet that contains one or more of the following ingredients and is intended for ingestion in specified form:
  - A vitamin or mineral;
  - An herb or other botanical;
  - An amino acid;
  - A dietary substance used to supplement the diet by increasing total dietary intake; or
  - extracts, metabolites, concentrates, or combinations of the above

FD&C Act Sec. 201(ff)

Physical Form

- Intended for ingestion in tablet, capsule, softgel, gelcap, powder, liquid, or other ingestible form
  - Cannot be represented as a conventional food, for use as a conventional food, or as a sole item of a meal or the diet
  - Cannot be injected, administered sublingually, or transdermal



Contains Nonbinding Recommendations

Guidance for Industry

Distinguishing Liquid Dietary Supplements from Beverages

Additional copies are available from:
Office of Nutrition, Labeling and Dietary Supplements, HFS-800

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What is NOT a "Dietary Supplement"

- Definition excludes hormones, substances under investigation as a drug (i.e., IND), and drug or biologic substances

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IND Exclusion/Exception

- Excludes ingredients from the dietary supplement definition if:
  - The ingredient was subject to substantial clinical investigations;
  - The existence of these clinical investigations has been made public; and
  - The ingredient was not first marketed as a dietary supplement or food.

The Curious Case of CBD

THC and CBD in Food: 301(ll)

- CBD and THC cannot be added to foods under the FD&C Act regardless of whether the substances are hemp-derived.
  - Under section 301(ll) of the FD&C Act, it is prohibited to introduce or deliver for introduction into interstate commerce any food (including animal food or feed) to which has been added a substance which is an active ingredient in a drug product that has been approved under 21 U.S.C. § 355 (section 505 of the Act) or a drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public.
  - Exception: If article was marketed in food before the drug was approved or before the substantial clinical investigations involving the drug had been instituted or, in the case of animal feed, that the drug is a new animal drug approved for use in feed and used according to the approved labeling.
    - FDA has no evidence that this exception applies

Dietary Supplements for Animal Use

- FDA Interpretation of DSHEA
  - Not intended and does not apply to animal feed, including pet food
  - Products marketed as animal supplements are regulated as either foods or animal drugs, depending on intended use
  - FDA's Center for Veterinary Medicine may exercise enforcement discretion over supplements for companion animals provided there are no safety concerns, no therapeutic or disease claims are made, and other conditions are met

Drugs vs. Dietary Supplements – Key Differences and Similarities

Differences	Similarities
Pre-Market Approval	Adverse Event Reporting
Permissible Claims	Truthful and Non-Misleading Advertising
FTC/FDA Regulation of Advertising	FDA Regulation of Safety
Mandatory Labeling Requirements	
Current Good Manufacturing Practice Requirements	

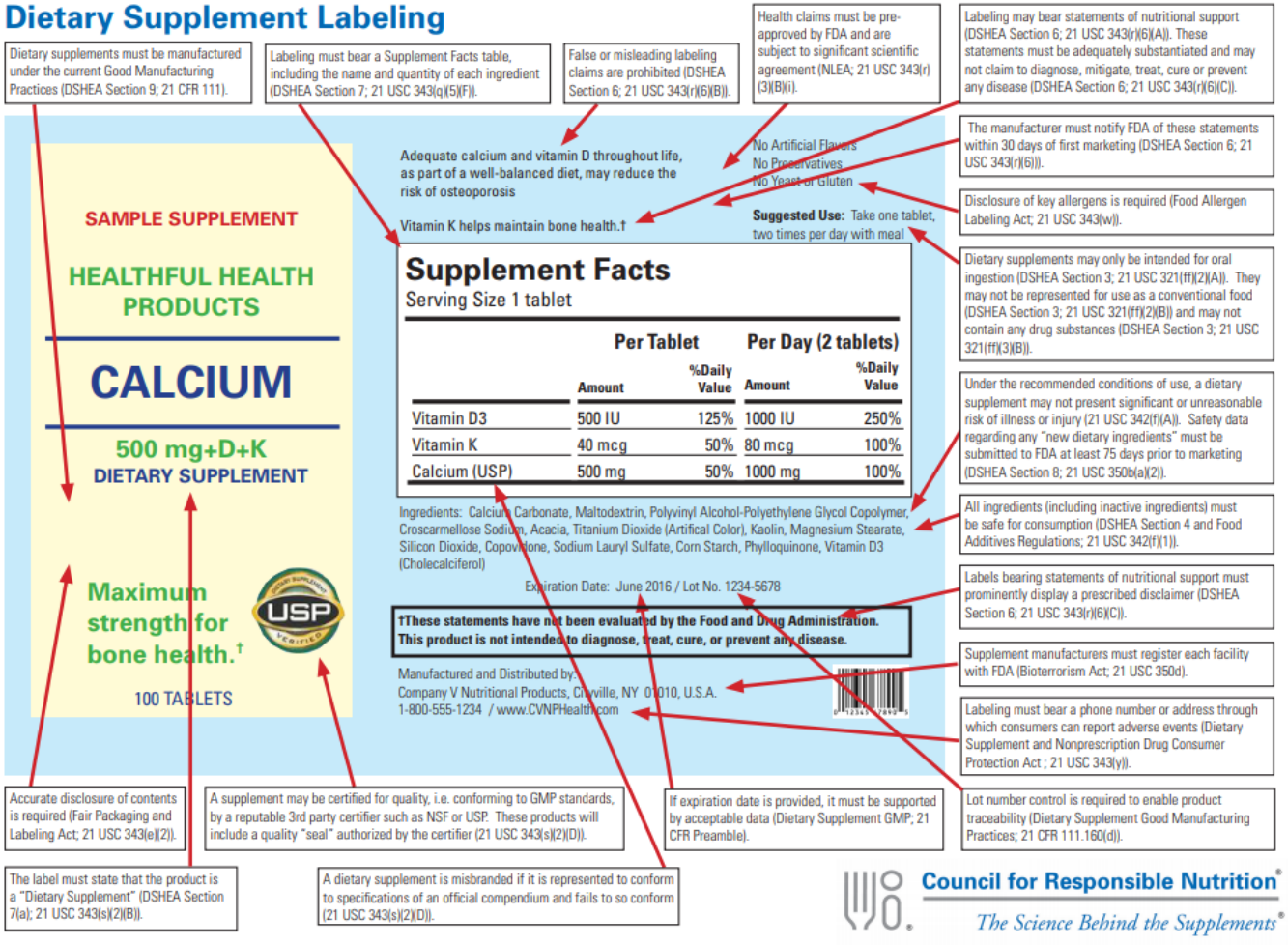
Labels and Claims

- A dietary supplement is misbranded if:
  - The labeling is false and misleading
  - The labeling fails to contain required information about the product (e.g., quantity of contents, "Supplement Facts", ingredients, name and place of business of the manufacturer, packer or distributor)

Labels: Required Elements

- Statement of Identity
  - Must include the word “supplement” (e.g., Vitamin D Dietary Supplement, Calcium Supplement)
- Net Quantity of Contents
- Nutrition Labeling
  - Supplement Facts Panel
- Ingredient List
- Name and Place of Business of the Manufacturer, Packer, or Distributor
- Contact information for adverse event reporting

Dietary Supplement Labeling



Council for Responsible Nutrition®
The Science Behind the Supplements®

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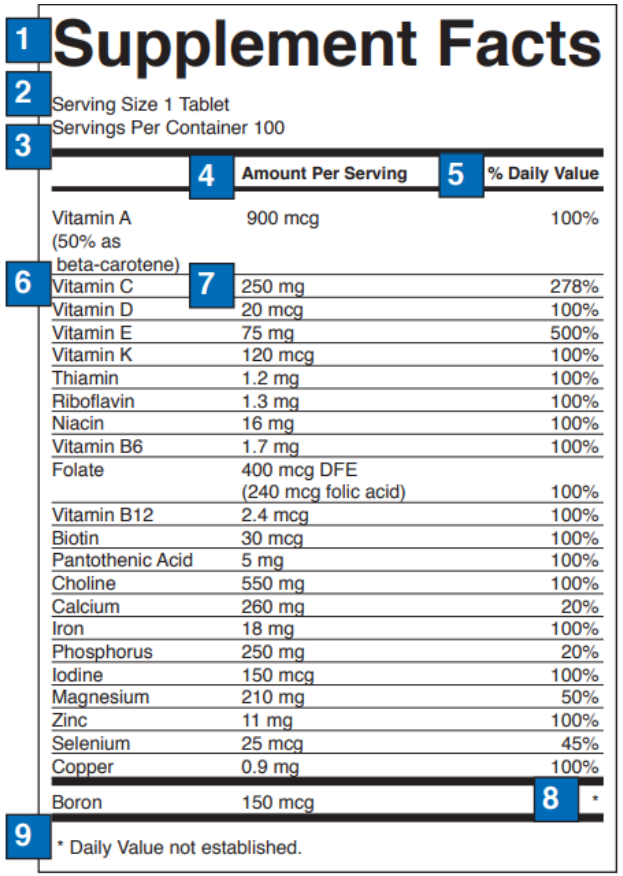

Supplement Facts

Serving Size 1 Tablet
Servings Per Container 100

	Amount Per Serving	% Daily Value
Vitamin A (50% as beta-carotene)	900 mcg	100%
Vitamin C	250 mg	278%
Vitamin D	20 mcg	100%
Vitamin E	75 mg	500%
Vitamin K	120 mcg	100%
Thiamin	1.2 mg	100%
Riboflavin	1.3 mg	100%
Niacin	16 mg	100%
Vitamin B6	1.7 mg	100%
Folate	400 mcg DFE (240 mcg folic acid)	100%
Vitamin B12	2.4 mcg	100%
Biotin	30 mcg	100%
Pantothenic Acid	5 mg	100%
Choline	550 mg	100%
Calcium	260 mg	20%
Iron	18 mg	100%
Phosphorus	250 mg	20%
Iodine	150 mcg	100%
Magnesium	210 mg	50%
Zinc	11 mg	100%
Selenium	25 mcg	45%
Copper	0.9 mg	100%
Boron	150 mcg	*

* Daily Value not established.

Other Ingredients: Choline bitartrate, calcium carbonate, ascorbic acid, dicalcium phosphate, magnesium oxide, microcrystalline cellulose, dl-alpha tocopherol acetate, ferrous fumarate, niacinamide, zinc oxide, magnesium stearate, d-calcium pantothenate, vitamin A acetate, pyridoxine hydrochloride, potassium iodide, boron citrate, phylloquinone, thiamin mononitrate, copper sulfate, d-biotin, sodium selenate, cholecalciferol, and cyanocobalamin.

Supplement Facts Example

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Claims

- Structure/Function Claims
- Nutrient Content Claims
- Health Claims
  - Qualified Health Claims

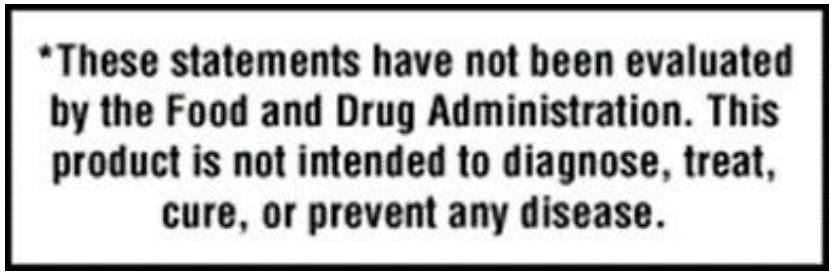
Structure/Function Claims

- Describe the role of a nutrient or dietary ingredient intended to affect normal structure or function in humans (*e.g.*, "calcium supports bone health")
- Characterize the action by which a nutrient or dietary ingredient maintains such structure or function (*e.g.*, "fiber helps maintain digestive regularity")
- Also includes claims about nutrient deficiency diseases (*e.g.*, vitamin C and scurvy), so long as the claim also discloses the prevalence of the disease in the U.S.

Structure/Function Claims: Notification

- Notification must be made to FDA within 30 days of making a structure/function claim on the label or labeling of a dietary supplement
- No official form for making the disclosure, but must include:
  - Name and address of manufacturer or distributor
  - Text of the claim
  - Name of the dietary ingredient or dietary supplement that is the subject of the claim; and
  - The name of the dietary supplement (including the brand name)

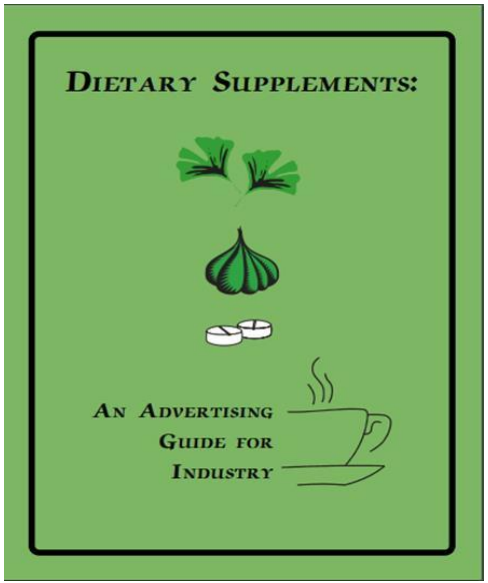
Structure/Function Claims: Disclaimers



- Must be made immediately adjacent to the claim or linked by a symbol (*e.g.*, an asterisk)

Structure/Function Claims: Substantiation

- FD&C Act requires that a company possess substantiation that a claim is truthful and not misleading
- FTC requires advertisers to have a reasonable basis to support all express and implied claims



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FTC Reasonable Basis Standard

- If no specific level of substantiation is claimed, what constitutes a reasonable basis is determined on a case-by-case basis by analyzing six factors:
  - The type of claim;
  - The benefits if the claim is true;
  - The consequences if the claim is false;
  - The ease and cost of developing substantiation for the claims;
  - The type of product; and
  - The level of substantiation experts in the field would agree is reasonable.

FTC Competent and Reliable Scientific Evidence Standard

- The FTC has typically applied a substantiation standard of "competent and reliable scientific evidence" to claims about the benefits and safety of dietary supplements and other health-related products.
- “Tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results.“
- FTC enforcement/litigation going beyond this standard?

Structure/Function Claims: Substantiation

- Important elements of both FTC and FDA standards:
  - Meaning of the claim(s) being made (express and implied)
  - Relationship of the evidence to the claim
  - Quality of the evidence
  - Totality of the evidence

Joint FTC-FDA Enforcement re: Opioid Cessation Products

- In January 2018, FDA & FTC posted warning letters to 11 marketers and distributors of opioid cessation products
- FD&C Act Violations – use of "drug" claims in labeling and marketing, including:
  - "For temporary relief of cravings, irritability, and inability to concentrate related to the use and over-use of. . . alcohol and narcotics";
  - "Support withdrawal relief, effective detox, and lasting recovery from addiction"; and
  - "Opiate withdrawal aid supplement."
- FTC Act violations – claims not supported by competent and reliable scientific evidence

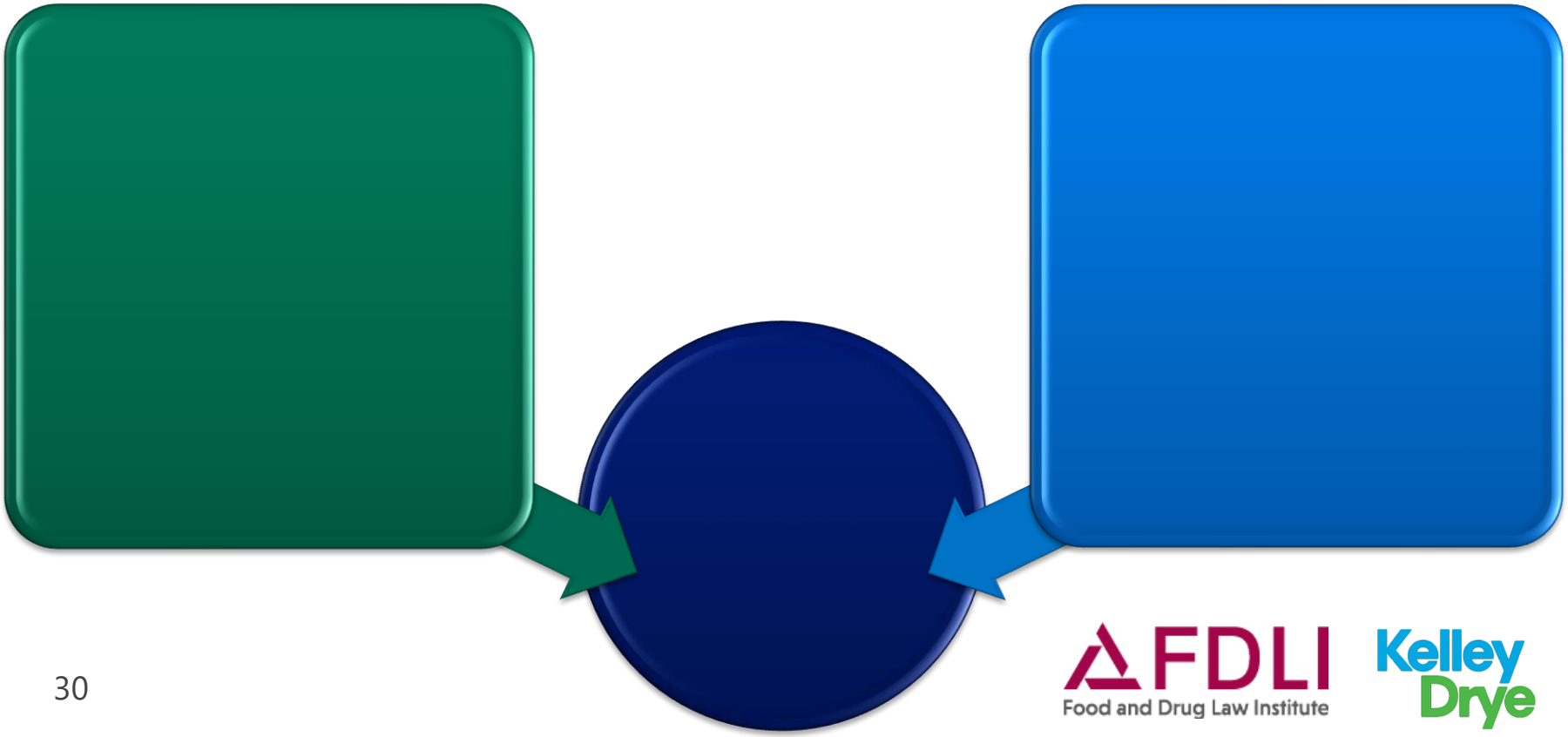
Joint FTC-FDA Enforcement on COVID-19

- FTC and FDA have sent 85 warning letters to manufacturers based on unapproved claims that a product treats or prevents the spread of COVID-19
  - "Organic antiviral against COVID-19 – to restore health & as prophylactic"
  - "Dr. Bob Melamede discusses how NAC and CBD Fight Viral Infections like Coronavirus. "
- FTC separately has sent over 200 additional warning letters
  - "according to the NIH, there is significant data showing that melatonin limits virus-related diseases and would also likely be beneficial in COVID-19 patients."
  - "HELPS FIGHT COVID-19 BUY NOW"

Nutrient Content Claims

- Characterize the level of a nutrient in the product
  - Ex: “High in antioxidant Vitamin C”; “Good source of calcium”, “High protein”
- Limited to those terms authorized by FDA regulation
  - Also generally limited to nutrients with an established daily value (DV)
  - May need to use disclosure statement re: fat, saturated fat, cholesterol or sodium content

Health Claims and Qualified Health Claims



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Claims Recap

Type of Claim	Description	Pre-approval
Nutrient Content Claim	Claims that describe the level of a nutrient in the product, using terms such as *free, high,* and *low*, or compare the level of a nutrient in a food to that of another food, using terms such as *more, reduced*, and *lite*.	Yes
Structure/ Function Claim	Describe an effect on the structure or function of the human body	No, but notification required
Health Claims	Describes the relationship between a substance and a disease or health-related condition and meets Significant Scientific Agreement standard; or based on authoritative statement of scientific bodies (currently only for conventional food)	Yes
Qualified Health Claim	Qualifying language where quality and strength of evidence falls below SSA standard	Yes - enforcement discretion

Ingredient Safety

- Adulteration
  - Any food, including supplements is adulterated if it is unsafe
    - "any poisonous or deleterious substance which may render it injurious to health" 21 U.S.C. 342(a)(1)
  - A dietary supplement is adulterated if:
    - It "presents a significant or unreasonable risk of illness or injury" under the recommended conditions of use
    - It contains a *new dietary ingredient* for which there is inadequate information to provide a reasonable assurance of safety
    - If the product poses "an imminent hazard to public health or safety"
  - Adulteration can lead to seizure, recalls, fines, and criminal prosecution

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Ingredient Safety: New vs Old

- Ingredients that were marketed before October 1994
  - Grandfathered or sometimes called “old dietary ingredients” (ODI)
  - May continue to be used without notification
- New Dietary Ingredient
  - DSHEA defined “new dietary ingredient” (NDI) as “a dietary ingredient that was not marketed in the United States *before October 15, 1994*
  - Must file an NDI notification with FDA, including safety information, at least 75 days before marketing

Ingredient Safety: New Dietary Ingredients

- 75-day premarket notification and summary on safety
- UNLESS the dietary ingredient has been “present in the food supply as an article used for food in a form in which the food has not been chemically altered”

Ingredient Safety: New Dietary Ingredients

- Information needed in a NDI Notification:
  - "… a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions suggested or recommended in the label of the dietary supplement ***will reasonably be expected to be safe***"
- FDA Guidance
- Comprehensive List
- FDA does not "approve" NDIs – will only "acknowledge" the NDI notification

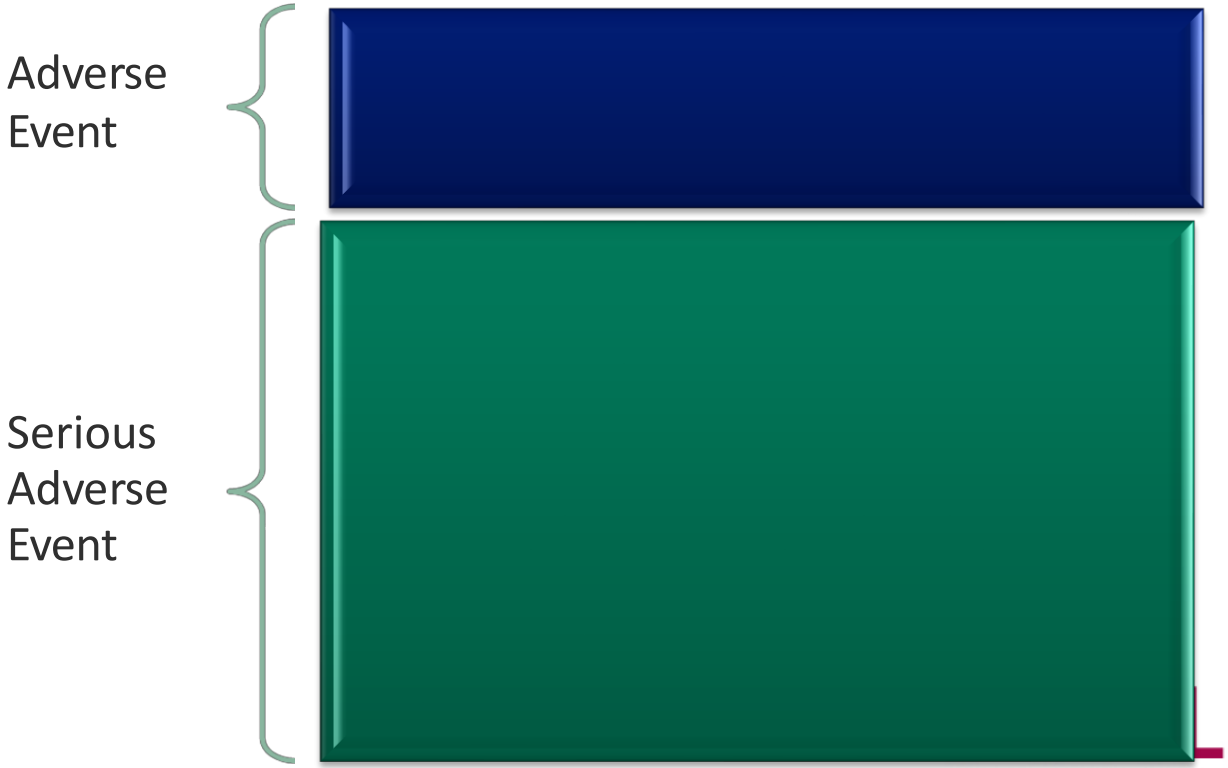
Ingredient Safety: NDI Enforcement

- Warning Letter – Driven Sports (4/4/14)
  - No information demonstrating that Dendrobex™ was lawfully marketed as a dietary ingredient in the U.S. before October 15, 1994, or that this ingredient was present in the food supply as an article used for food, and not chemically altered
  - Therefore, ingredient was subject to the NDI notification requirements
  - Because the required notification was not submitted FDA considers products containing Dendrobex™ to be adulterated
    - Subject to injunction and seizure

Post-Market Surveillance: Reporting Requirements

- Nonprescription Drug and Dietary Supplement Consumer Protection Act of 2006
  - Manufacturers must provide FDA with all reports they receive of ***serious*** adverse events associated with their dietary supplements within 15 days of receipt
  - Labeling must include an address or telephone number
  - Records of ***all*** adverse event reports they receive for 6 years must be saved
  - FDA has access to firm's records through inspection

Post-Market Surveillance: Important Definitions



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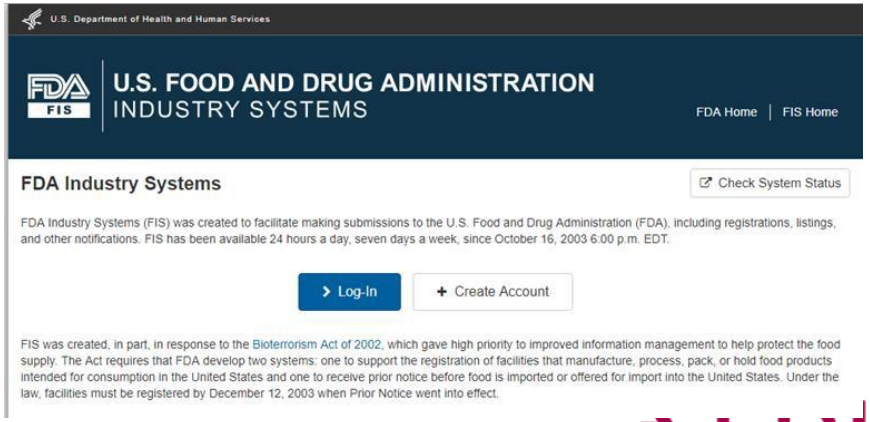
Value of Post-Market Surveillance

- Monitoring tool to identify potential public health issues that may be associated with the use of a particular product or ingredient already in the marketplace
- Serves as warning signals of possible problems, not as conclusions of causality
- Help identify concerns with ingredient safety, manufacturing issues, contamination (of either raw ingredients or finished products), tampering, and bio- terrorism

Manufacturing Dietary Supplements

- Facility Registration
  - Applies to both foreign and domestic entities
- Good Manufacturing Practices (GMPs)



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GMP Requirements

- DSHEA authorized FDA to prescribe good manufacturing practices for dietary supplements
- Applies to companies that manufacture, package, label, or hold dietary supplements
  - Both domestic and foreign facilities that import dietary supplements into the U.S.
  - Companies must comply with those provisions directly applicable to the operations a company performs
- The GMP rule (21 C.F.R. Part 111) requires supplement manufacturers to ensure the quality of the supplement and that it is packaged and labeled as specified in the master manufacturing record
  - Ensures that supplements are manufactured consistently as to identity, purity, strength, and composition
  - Provisions relate to many manufacturing activities, including facility maintenance, quality controls, cleaning, testing final product or incoming and in-process materials, handling consumer complaints, and maintaining records

GMP Requirements

1. **How is the DS CGMP rule organized?**

   The DS CGMP rule is organized as a series of "subparts," which each cover a different aspect of current good manufacturing practice. We list these subparts in Table 2.

Table 2
Subparts of the DS CGMP Rule

Subpart	Subject of Subpart
A	General Provisions (including coverage and definitions)
B	Personnel
C	Physical Plant and Grounds
D	Equipment and Utensils
E	Requirements to Establish a Production and Process Control System
F	Production and Process Control System: Requirements for Quality Control
G	Production and Process Control System: Requirements for Components, Packaging, Labels and for Product that You Receive for Packaging or Labeling as a Dietary Supplement
H	Production and Process Control System: Requirements for the Master Manufacturing Record
I	Production and Process Control System: Requirements for the Batch Production Record
J	Production and Process Control System: Requirements for Laboratory Operations
K	Production and Process Control System: Requirements for Manufacturing Operations
L	Production and Process Control System: Requirements for Packaging and Labeling Operations
M	Holding and Distributing
N	Returned Dietary Supplements
O	Product Complaints
P	Records and Recordkeeping

FDA Guidance for Industry: Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements; Small Entity Compliance Guide (December 2010)

GMPs and Laboratory Testing

- Testing required for both raw materials and finished product to confirm identity, purity, quality, strength, composition and limits of contamination
  - Responsibility of manufacturer to determine the appropriate test(s) or examination(s) needed
- Laboratory facilities "must be adequate to preform whatever tests and examinations are necessary"
  - Testing may be conducted in-house or by an outside contract lab

Testing and State AGs

- NY AG Investigation and DNA Barcoding
  - Investigation of private label dietary supplement distributors and the product manufacturers
  - Alleged that supplements did not contain herbal ingredients listed on the label
  - Allegations based solely on one type of testing – DNA barcoding

FDA GMP Enforcement

- Products that do not meet the GMP regulations, based on FDA's observations during a facility inspection are deemed adulterated under Section 402(g)(1) of the FD&C Act
  - Warning Letters: must respond with corrective action
  - Consent decrees, product seizures, injunctions in cases of continued GMP violations

FSMA and Dietary Supplements

- Subject to modified requirements
  - Maintain a list of foreign suppliers
  - Establish and follow written procedures for conducting foreign supplier verification activities
  - Conduct and document one or more of the following verification activities before using or distributing the dietary supplement and periodically thereafter to adequately verify that the foreign supplier is producing the dietary supplement in compliance with Part 111:
    - Periodic onsite audits of the foreign supplier (including a review of the foreign supplier's written food safety plan and its implementation of the plan for compliance with Part 111 requirements)
    - Periodic or lot-by-lot sampling and testing of the dietary supplement
    - Periodic review of the foreign supplier's food safety records; or
    - Other appropriate procedures
  - Importer must promptly review the results of the above verification activities
  - Importer not required to conduct a hazard analysis or "standard verification activities"

State Regulation

- State Attorneys General (AGs) enforce state statutes that prohibit deceptive advertising and trade practices, as well as govern the safety of dietary supplements
- Example: Oregon AG
  - Action alleged that dietary supplement products sold by Vitamin Shoppe contained substances that were not dietary ingredients
  - $545,000 settlement required Vitamin Shoppe to take steps to review status and safety of substances in products sold by the retailer
- State AGs may also jointly bring actions with federal regulators like the FTC

National Advertising Division (NAD)

- Council for Responsible Nutrition (CRN) and the NAD have partnered together since 2006 to monitor and promote truthful and accurate advertising for the dietary supplement industry
- More than 360 cases have been opened and closed regarding all sorts of claims, including:
  - Traditional claims for the industry, such as claims about weight loss, sports performance, heart disease, and cold and flu prevention
  - Less common claims about sun protection, breast feeding, sexual dysfunction, tinnitus, computer eye strain

Key Takeaways

- Dietary supplements are a subcategory of food
  - Be aware of unique requirements for each
- Claims and product positioning (*e.g.*, as a conventional food) can cause a product to violate the FDCA
- FDA adulteration and new dietary ingredient requirements govern safety of what is permitted in the dietary supplement
- GMPs help ensure production and distribution processes create a safe dietary supplement
- States play an important role in ensuring efficacy and safety

Questions?

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