Foods

Emil Wang

Outline

- Resources
- Food Safety
- Food Additives
- Dietary Supplements
- Cosmetics

Resources

- CRS Report, The Federal Food Safety System: A Primer
- CRS Report, The FDA Food Safety Modernization Act
- Starting From Scratch?: Reinventing the Food Additive Approval Process, 78 B.U. L Rev 329
- Rethinking the Applicability and Usefulness of the GRAS Concept, 46 Food Drug Cosm LJ 553
- CRS Report, Dietary Supplements: Legislative and Regulatory Status

Federal Food Safety

- Overview
  - ✓ Americans spend > $1T on food every year
  - ✓ As many as 15 federal agencies collectively administer at least 30 laws related to food safety – fragmented food safety system
  - ✓ Federal laws give food manufacturers, distributors, and retailers basic responsibility for assuring foods are safe, wholesome, and handled under sanitary conditions
  - ✓ Federal agencies, in cooperation with state, local, and international entities regulate food quality and safety
  - ✓ Challenges in organization, coordination, resources, and consistency of law implementation and enforcement
  - ✓ Volume and Burden:
    - > 70,000 domestic establishments registered
    - > 200,000 foreign establishments registered
    - FDA inspects about 6,000 high-risk facilities annually, ~ 56% food facilities are not inspected during 5-year period
    - Approximately 9M lines of human and animal foods imported in FY 2011, FDA inspects ~ 1% food imported

Federal Food Safety

- Food and Drug Administration (FDA), see http://www.fda.gov/Food/default.htm
  - ✓ Regulates 80-90% of all foods
  - ✓ Responsible for ensuring that all domestic and imported food products (includes produce, dairy products, seafood, processed foods, meats not regulated by USDA), except for most meats and poultry, are safe, nutritious, wholesome, and accurately labeled
  - ✓ Primary statutory authority are Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and the Egg Products Inspection Act
  - ✓ FDA Food Safety Modernization Act (2011) – most sweeping reform of FDA's food safety authority since 1930s, see http://www.fda.gov/Food/FoodSafety/FSMA/default.htm
  - ✓ Office of Foods: oversees Center for Food Safety and Applied Nutrition (CFSAN) and Center for Veterinary Medicine (CVM)
  - ✓ See FDA Foods and Veterinary Medicine Strategic Plan 2012 – 2016, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofFoods/ucm273269.htm

Federal Food Safety

- US Department of Agriculture (USDA), Food Safety and Inspection Service (FSIS), see http://www.fsis.usda.gov/
  - ✓ Regulates 10-20% food supply – most domestic and imported meat and poultry and some egg products to ensure that products are safe, wholesome, and correctly labeled and packaged for human consumption
  - ✓ Primary statutory authority are Federal Meat Inspection Act, Poultry Products Inspection Act, Egg Products Inspection Act, Humane Methods of Livestock Slaughter
  - ✓ FSIS inspectors inspect all meat and poultry at slaughter on a continuous basis and are on site daily to monitor plant's adherence to standards for sanitary conditions, ingredient levels, packaging, and to conduct statistical sampling and testing of products
  - ✓ FSIS certifies that foreign meat and poultry plants operate under an inspection system equivalent to US system before they can export products to US
  - ✓ See FSIS Strategic Plan 2008 – 2012, http://www.fsis.usda.gov/PDF/Strategic_Plan_2008-2013.pdf

Federal Food Safety

Table 1. Major Federal Food Safety Agencies

Agency	Major Responsibilities and Activities	Primary Authorities
Department of Health and Human Services		
Food and Drug Administration[a]	Ensuring that all domestic and imported foods, except processed egg products and major types of meat and poultry, are safe, wholesome, and properly labeled, by setting safety and sanitation standards, periodically inspecting manufacturing facilities, reviewing records of and spot-checking imports. Also overseeing the safety of animal drugs and feeds including those used in food-producing animals	As may be amended by the FDA Food Safety Modernization Act (FSMA): Federal Food, Drug, and Cosmetic Act (FFDCA; 21 U.S.C. 301), Public Health Service Act (42 U.S.C. 201), Egg Products Inspection Act (21 U.S.C. 1031), Public Health Security and Bioterrorism Preparedness and Response Act (21 U.S.C. 341), others
Centers for Disease Control and Prevention	Monitoring, identifying, and investigating foodborne diseases; developing and evaluating improved epidemiological and laboratory methods	Public Health Service Act (42 U.S.C. 201)
Department of Agriculture		
Food Safety Inspection Service[a]	Regulating the safety, wholesomeness and proper labeling of most commercial types of both domestic and imported meat and poultry, catfish products, and processed egg products, by approving establishment designs, safety plans; inspecting every animal and carcass in slaughtering plants and daily inspecting all meat and poultry processing plants; determining the equivalency of importing countries' meat and poultry safety systems	Federal Meat Inspection Act (21 U.S.C. 601), Poultry Products Inspection Act (21 U.S.C. 451), Egg Products Inspection Act
Animal and Plant Health Inspection Service	Overseeing animal and plant health, including the prevention of foreign diseases and pests, eradication and containment of such problems domestically (including those that threaten public health)	Animal Health Protection Act (7 U.S.C. 8301), Plant Health Protection Act (7 U.S.C. 7701)
Agricultural Marketing Service	Establishing quality and marketing grades and standards for dairy products, fruits and vegetables, livestock, meat, poultry, seafoods, and shell eggs; certifying quality programs; conducting quality grading services, generally user fee-funded	Agricultural Marketing Act of 1946 (7 U.S.C. 1621), Egg Products Inspection Act (21 U.S.C. 1031), Agricultural Marketing Agreement Act (7 U.S.C. 601)
Food and Nutrition Service	Encouraging and coordinating efforts to ensure the safety of foods in school lunch and other domestic programs	Program subsidies authorized by Richard B. Russell National School Lunch Act (42 U.S.C. 1751),Child Nutrition Act (42 U.S.C. 1771).
Grain Inspection, Packers and Stockyards Administration	Setting quality standards for, and testing, grains and related commodities, primarily for marketing purposes	U.S. Grain Standards Act (7 U.S.C. 71), Agricultural Marketing Act of 1946

Federal Food Safety

Agency	Major Responsibilities and Activities	Primary Authorities
Agricultural Research Service	Conducts in-house USDA research on agricultural and food topics, of which food safety is one of many	Numerous laws dating to the Department of Agriculture Organic Act of 1862 (7 U.S.C. 2201 note), up through and including recent omnibus farm laws
Cooperative State Research, Education, and Extension Service	Coordinates and administers federal funding of land grant and other institutions to conduct agricultural and food research, education and extension activities; food safety is one of many subject areas	Numerous laws dating to the Department of Agriculture Organic Act of 1862, up through and including recent omnibus farm laws
Department of Commerce		
National Oceanic and Atmospheric Administration	Offering a variety of voluntary seafood safety and quality inspection services on a fee-for-service basis	Agricultural Marketing Act of 1946, Fish and Wildlife Act of 1956 (16 U.S.C. 742)
Environmental Protection Agency	Regulating pesticide products; setting maximum allowable tolerances for residue levels on food commodities and animal feeds	Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136), FFDCA
Federal Trade Commission	Enforcing federal prohibitions against unfair or deceptive acts or practices in trade, including consumer deception regarding foods	Federal Trade Commission Act (15 U.S.C. 41)
Department of the Treasury		
Alcohol and Tobacco Tax and Trade Bureau	Administering and enforcing laws on the production, safety, distribution and use of alcoholic beverages	Federal Alcohol Administration Act (27 U.S.C. 201), Internal Revenue Code (26 U.S.C. Ch. 51)
Department of Homeland Security		
U.S. Customs and Border Protection	Coordinating many food security activities, including at the border; now conducting agricultural border inspection activities formerly done by APHIS	Homeland Security Act (6 U.S.C. 101)

Food – Jurisdiction

- Food, Section 201(f) FDCA
  - ✓The term “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
- Raw, unprocessed food substances – may or may not be food
- “Food” includes food-contact articles i.e., containers, cutting surfaces

Food Safety

- Adulteration, Section 402 FDCA
- Poisonous or Deleterious Substances, Section 402(a)(1) FDCA:
  - ✓ If it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health
  - ✓ "May Render Injurious to Health"
    - *U.S. v. Lexington Mill & Elevator Co.*, 232 U.S. 399 (1914)
    - *U.S. v. Anderson Seafoods*, 622 F.2d 157 (5th Cir. 1980)
  - ✓ "Ordinarily Render Injurious to Health"

Food Safety

- Unavoidable Contaminants, Section 402(a)(2) FDCA:
  - ✓ If it bears or contains any added poisonous or added deleterious substance ... that is unsafe within the meaning of section 406
  - ✓ Section 406 FDCA: any poisonous or deleterious substance added to any food, except when such substance is required in the production thereof or cannot be avoided by good manufacturing practice, shall be deemed to be unsafe and, dust, adulterated within the meaning of section 402(a)(2)(A)
  - ✓ FDA can set 406 tolerances for "unavoidable contaminants" or tolerances necessary for the protection of public health – legally enforceable limit
  - ✓ FDA can set "action levels" – represents level that food is considered adulterated under section 402(a)(1). FDA must prove "may render injurious to health" standard

Food Safety

- Filthy, Putrid, Decomposed Substances, Section 402(a)(3) FDCA:
  - ✓ If it consists in whole or in any part of any filthy, putrid, or decomposed substance.
    - *U.S. v. Tomato Paste*, 22 F.Supp. 515 (E.D. Pa 1938)
    - *U.S. v. Canned Tomato Paste*, 236 F.2d 208 (7th Cir. 1956)
  - ✓ Defect Action Levels for filth published in Compliance Policy Guides Manual – set at tolerances that can be achieved by applying GMPs
- "Unfit" Food, Section 402(a)(3) FDCA
  - ✓ If it is otherwise unfit for food
  - ✓ Aesthetic quality of food
    - *U.S. v. 24 Cases, More or Less*, 87 F.Supp. 826 (1949)
    - *U.S. v. Herring Roe*, 87 F.Supp. 826 (D.Me. 1949)
  - ✓ Present a safety hazard

Food Safety

- Pesticide Residues, Section 408 FDCA:
  - ✓ Pesticide residues are deemed to adulterate food unless a tolerance or tolerance exemption for the residues is promulgated
  - ✓ “pesticide chemical” includes any substance that is a pesticide within the meaning of FIFRA, section 201(q)(1) FDCA.
  - ✓ “pesticide residue” - residue in or on a raw agricultural commodity or processed food of the pesticide chemical, or any other added substance that is primarily the result of the metabolism or other degradation of a pesticide chemical, section 201(q)(2)
  - ✓ Tolerance is set at levels "necessary to protect the public health"

Food Safety

- Good Manufacturing Practices, Section 402(a)(4) FDCA:
  - ✓If it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health
  - ✓GMPs represent general standards of food processing and handling deemed necessary to avoid contamination of food with poisonous or deleterious substances, filth, or potentially harmful microorganisms

Food Safety

- Hazard Analysis Critical Control Point (HACCP)
  - ✓"conditions" that may render a food injurious to health, section 404(a)(4) FDCA, 701(a) FDCA, record maintenance and record access
  - ✓HACCP System – hazard analysis and establishment of critical control points – for identifying and monitoring potential specific foodborne hazards to ensure safety of food
  - ✓Seafood HACCP, 21 CFR Part 123
  - ✓Juice HACCP, 21 CFR Part 120

Food Safety

- Food Safety Modernization Act (FSMA) – Prevention-Based Controls and Standards
  - ✓ Prevention – Science-based preventive controls across food supply, section 418 FDCA
    - Science-based minimum standards for safe production and harvesting of produce, section 418(n) FDCA
    - Performance standards, section 104 FSMA
    - Standards for Produce Safety, section 419 FDCA
  - ✓ Inspections and Compliance
    - High-Risk Facilities, section 421 FDCA
    - Enhancing Tracking and Tracing of Food and Recordkeeping, section 204 FSMA
    - Access to records, section 414 FDCA
    - Protection Against Intentional Adulteration, section 420 FDCA

Food Safety

- Food Safety Modernization Act (FSMA) – Prevention-Based Controls and Standards (cont'd)
  - ✓ Regulatory Response
    - Mandatory recall authority, section 423 FDCA
    - Administrative Detention, section 304(h)(a)(A) FDCA
    - Suspension of food facility's registration, section 415 FDCA
  - ✓ Imported Food and Food Ingredients
    - Foreign supplier verification program, section 805 FDCA
    - Importer certification for high-risk foods, section 801(a) FDCA
    - Inspection of foreign food facilities, section 421 FDCA
  - ✓ Governmental Collaboration

Food Safety

- Low-Acid Canned Food Regulations, 21 CFR Part 113
  - ✓If it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health, Section 404(a)(4) FDCA
  - ✓FDA can require a manufacturer to obtain and comply with terms of an "emergency permit" to remain in operation in order to prevent the distribution of food that may be injurious due to contamination by microorganisms, Section 404 FDCA

Regulation of Food Ingredients

- Food Additives
  - ✓ Food Additive Amendment of 1958
  - ✓ … means any substance will the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate it safety, as having been adequately shown through scientific procedures (or, in a case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use. Section 201(s) FDCA

Regulation of Food Ingredients

- Food Additive Approval Process, Section 409 FDCA
  - ✓ Any food that bears or contains any unsafe food additive (i.e., unapproved or used outside approval parameters) is considered adulterated and subject to regulatory action
  - ✓ Food Additive Petition, Section 409(b) FDCA, 21 CFR Part 171 – "safe for its intended use"
    - Name of substance
    - Chemical identity and composition
    - Proposed conditions of use
    - Proposed labeling
    - Physical effects data
    - Technical effects (and levels) data
    - Information on manufacturing process, facilities, and controls
    - Methods of detecting and determining quantity of food additive in finished food
    - Results of safety investigations
    - Environmental assessment
  - ✓ FDA review – 180 days
  - ✓ Clearance is granted on issuance of regulation upon finding that food additive is safe

Regulation of Food Ingredients

- Determining Safety of Food Additives
  - ✓ Two-part safety standard
    - "general safety clause" – reasonable certainty in the minds of competent scientists that a substance is not harmful under its intended conditions of use
      - Redbook – toxicological testing requirements
      - Calculate acceptable daily intake (ADI) derived from toxicological effects data and determination of "no observable adverse effect level" to which appropriate safety factor (1/100) is applied
    - Delaney Clause – "[n]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal. Section 409(c)(3)(a) FDCA

Regulation of Food Ingredients

- Food Ingredients and Substances that are not Food Additives
  - ✓ Traditional Foods as Ingredients
  - ✓ Prior-Sanctioned Substances – "Any substance used in accordance with a sanction or approval granted prior to enactment [of Food Additive Amendment - September 6, 1958]"
  - ✓ Generally Recognized as Safe (GRAS) Substances – GRAS determination: general safety clause + determination that terms for GRAS status are satisfied
    - Traditional "Unlisted GRAS" Ingredients, 23 Fed. Reg. 9512 (1958) and 24 Fed. Reg. 9368 (1959)
      - For example, salt, pepper, sugar, vinegar, baking powder, and monosodium glutamate
    - "Old GRAS List," 21 CFR Part 182
      - For example, hydrofluoric acid, caffeine, sodium tripolyphosphate, tricalcium silicate, the preservatives BHA and BHT, and the artificial sweeteners cyclamate and saccharin

Regulation of Food Ingredients

- Food Ingredients and Substances that are not Food Additives
  - ✓ Generally Recognized as Safe (GRAS) Substances (cont'd)
    - GRAS Affirmation Petition, 21 CFR Part 184
    - "Self"-Affirmed GRAS Substances, 21 CFR Part 186
    - GRAS determination process: safety is evaluated within context of its intended use
      - GRAS status established through safety data collected by "scientific procedures" ("those human, animal, analytical, and other scientific studies, whether published or unpublished, appropriate to establish the safety of a substance")
      - GRAS eligibility regulation – general recognition of safety through scientific procedures "shall require the same quantity and quality of evidence" as is required to obtain food additive approval and "shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information," 21 CFR Part 170
      - GRAS Notification Proposal, 62 Fed. Reg. 18,938 (Apr. 17, 1997)

Regulation of Food Ingredients

- Classifications Related to Food Additive Status
  - ✓ Interim Food Additives – intermediate step for substances where a substantial question of safety has been raised but there remains reasonable certainty that the substance will not cause harm
  - ✓ "Threshold" Indirect Additives – process for determining when likelihood or extent of migration to food of a substance used in a food contact article is so trivial as not to require food additive approval
    - Monsanto v. Kennedy,613 F.2d 947 (D.C. Cir. 1979)
    - "Threshold of regulation" – Exempts from food additive regulation non-carcinogenic substances in food contact articles that result in dietary concentration of 0.5 ppb or less. Regulated direct food additives are also exempted when used in food contact articles that result in dietary exposure of 1% of less ADI. 21 CFR 170.39.
  - ✓ "Food Contact Substance" – any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding of food if such use is not intended to have any technical affect in such food
    - Food Contact Substance Notification, section 409(h) FDCA: filed 120 days before introduction into interstate commerce and becomes effective unless FDA concludes that safety is not established and food additive petition required.

Food Labeling

- Statutory Authorities
  - ✓ Federal Food, Drug, and Cosmetic Act (FDCA) – applies information on label to outside container or wrapper of retail package
  - ✓ Fair Packaging and Labeling Act (FPLA) – requirements only apply to outside container or wrapper of retail package
- "Label" – "display of written, printed or graphic matter on the immediate container of any article, section 201(k) FDCA
- "Labeling" – "[includes] all labels and other written, printed or graphic matter on any article or any of its containers or wrappers, or accompanying such article," section 201(m) FDCA
- Misbranding, Section 403 FDCA – violations of labels and labeling
  - ✓ False or misleading, section 403(a) FDCA
  - ✓ If food is offered for sale under name of another food, section 403(b) FDCA
  - ✓ Standard of identity (imitation food), section 403(c) FDCA
  - ✓ If container is so made, formed, or filled as to be misleading, section 403(d) FDCA

Food Labeling – Basic Components

- 21 CFR Part 101, Subpart A
  - ✓ Required information on Principal Display Panel (PDP) and Information Panel (IP)
- Product Name/Statement of Identity, section 403(g) FDCA, 21 CFR Parts 131 – 169
- Quantity of Contents/Net Quantity of Contents Statement, section 403(e)(2) FDCA, 21 CFR 101.105(a)
- Responsibility Statement/Name and Place of Business of Manufacturer, Packer or Distributor, section 403(e)(1) FDCA, 21 CFR 101.5(a)
- Ingredient Statement/Listing of Ingredients, sections 403(i), (k) FDCA, 21 CFR 101.22
- Nutrition Labeling, section 403(q)(1 FDCA, 21 CFR 101.9

Food Labeling – Basic Components

- 21 CFR Part 101, Subpart A
  - ✓ Required information on Principal Display Panel (PDP) and Information Panel (IP)
- Product Name/Statement of Identity, section 403(g) FDCA, 21 CFR Parts 131 – 169
- Quantity of Contents/Net Quantity of Contents Statement, section 403(e)(2) FDCA, 21 CFR 101.105(a)
- Responsibility Statement/Name and Place of Business of Manufacturer, Packer or Distributor, section 403(e)(1) FDCA, 21 CFR 101.5(a)
- Ingredient Statement/Listing of Ingredients, sections 403(i), (k) FDCA, 21 CFR 101.22
- Nutrition Labeling, section 403(q)(1 FDCA, 21 CFR 101.9
- Country of Origin, 19 CFR Part 134

Dual Column Format

Nutrition Facts

2 servings per container

Serving size 1 cup (255g)

	Per 1 cup		Per container	
Calories	**220**		**440**	
	% DV*		**% DV***	
Total Fat	**8%**	5g	**15%**	10g
Saturated Fat	**10%**	2g	**20%**	4g
Trans Fat		0g		0g
Cholesterol	**5%**	15mg	**10%**	30mg
Sodium	**10%**	240mg	**21%**	480mg
Total Carbs	**12%**	35g	**23%**	70g
Dietary Fiber	**21%**	6g	**43%**	12g
Sugars		7g		14g
Added Sugars		4g		8g
Protein		9g		18g
Vitamin D	25%	5mcg	50%	10mcg
Calcium	15%	200mg	30%	400mg
Iron	6%	1mg	10%	2mg
Potassium	10%	470mg	20%	940mg

* Footnote on Daily Values (DV) and calories reference to be inserted here.

Food Labeling - Claims

- Nutrient Content Claims – any claim in the label or labeling of a food "which expressly or by implication … characterizes the level of any nutrient which is of the type required … to be [in nutrition labeling]" may be made only if the characterization of the level made in the claim uses terms [required by FDA in regulation," section 403(r)(1)(A) FDCA
  - ✓ Absolute Claims – describes level of nutrient in a serving of product
  - ✓ Relative Claims – compare level of nutrient per serving to reference product
- Health Claims – a statement that expressly or by implication characterizes the relationship of any nutrients which is of the type required … to be [in nutrition labeling] to a disease or health-related condition," section 403(r)(1)(B) FDCA, 21 CFR 101.14
  - ✓ May be authorized if FDA determines, based on totality of publicly available scientific evidence, there a "significant scientific agreement" (SSA) … that claim is supported
  - ✓ Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999)
- Structure-Function Claims also permitted for conventional foods if derived from "nutritive value," 21 CFR 101.14(a)(3)

Color Additives

- Color Additive, section 201(t) FDCA – any material that, when added to food, is capable of imparting color, except those that the Secretary of Health and Human Services, by regulation, determines are used "solely for a purpose or purposes other than coloring."
  - ✓Section 721 FDCA – provides framework for listing and certification color additives ≈ food additive premarket approval process
  - ✓Color additives may be subject to precise specifications and batch certification
  - ✓Includes Delaney Clause
  - ✓No exclusion for GRAS or prior sanctioned colors

Infant Formulas

- "Infant formula" means "a food which purports to be or is represented for special dietary use solely as a food for infants for reason of its simulation of human milk or its suitability as a complete or partial substitute for human note." Section 201(z) FDCA
  - ✓ Special requirements for infant formula, section 412 FDCA
    - Infant formula deemed adulterated if it does not provide specific nutrients, or
    - Not produced in compliance with applicable cGMPs
    - Record retention requirements
    - Labeling, i.e., nutrient content, directions for preparation and use, "use by" date
    - Consumer complaints
  - ✓ Registration for new infant formulas at least 90 days before marketing - includes quantitative formulation of new infant formula or description of any reformulation or change in processing of formula

Dietary Supplements

- Dietary Supplement Health and Education Act (DSHEA) 1994
  - ✓ Product is "dietary supplement" under section 201(ff) FDCA only if it meets criteria governing
    - Ingredients: 1) vitamin, 2) mineral, 3) herb or botanical, 4) amino acid, 5) dietary substance for use by man to supplement the diet by increasing total dietary intake, or 6) concentrate, metabolite, constituent, extract of combination of any ingredients listed above
    - Formulation: intended for ingestion. Dietary supplement may not be represented as conventional food or for use as a sole item of meal or diet
      - *U.S. v. Ten Cartons Ener-B Nasal Gel*, 888 F.Supp. 381 (E.D.N.Y.)
    - Intended use: dietary supplement may not be intended for use as a drug (intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease)
    - Relationship to drugs and biologics: article marketed as a dietary supplement before being approved as a new drug is eligible for dietary supplement status
      - *Pharmanex Inc. v. Shalala*, 35 F.Supp.2d 1341 (D.Utah 1999)

Dietary Supplements – Safety

- All dietary supplements must be safe (i.e., not adulterated)
- Dietary supplement deemed adulterated if it, or any dietary ingredient contained in it:
  - ✓ “presents a significant or unreasonable risk of illness or injury" under conditions of use recommended or suggested in labeling (or if no conditions of use or suggested or recommended in the labeling, under "ordinary" conditions of use), section 402(f) FDCA
  - ✓ bears or contains any poisonous or deleterious substance that may render it injurious to health, section 402(a) FDCA
- Exact scope of data needed to support safety for dietary supplements has not been defined
- Standard for FDA to deem dietary supplement (or dietary ingredient) adulterated, section 402(f) FDCA
  - ✓ FDA bears burden of proof to show that dietary supplement is adulterated
  - ✓ Manufacturer has opportunity to present its views to FDA
  - ✓ Nutraceutical Corp. . Von Eschenbach, 459 F.3d 1033

Dietary Supplements – New Dietary Ingredients

- New dietary ingredient, section 413 FDCA
  - ✓ Manufacturer's responsibility to determine – any dietary ingredient not marketed in US in a dietary supplement before October 15, 1994, section 413(c) FDCA
- Additional safety requirements:
  - ✓ If dietary supplement contains a "new dietary ingredient" with in adequate information to provide reasonable assurance that ingredient does not present a significant or unreasonable risk of illness or injury, when used under the condition recommended or suggested in the labeling then the product is considered adulterated, section 402(f)(1)(B) FDCA
- Information to be reported to FDA – reportable NDI: ingredient has not been present in food supply or if its form has been chemically altered
  - ✓ History of use or other information that dietary ingredient will reasonably be expected to be safe
  - ✓ 75-day Notification: information and data that forms basis that dietary ingredient will reasonably be expected to be safe
- Dietary ingredient deemed adulterated if conditions for reportable NDI not met, section 402(f)(1)(B) FDCA

Dietary Supplements – Requirements

- Facility Registration
  - ✓ Public Health Security and Bioterrorism Preparedness and Response Act 2002 requires domestic and foreign facilities that manufacture, process, pack, or hold food, including dietary supplements, to register with FDA
- Current Good Manufacturing Practices (cGMPs)
  - ✓ Dietary supplement is adulterated If it has been prepared, packed or held under conditions that do not meet current Good Manufacturing Practice (cGMP), section 402(g) FDCA, 21 CFR Part 111.
- Postmarketing Surveillance
  - ✓ Dietary Supplement and Nonprescription Drug Consumer Protection Act 2006 requires dietary supplement manufacturers, packers, or distributors to report serious adverse event to FDA and recordkeeping

Dietary Supplements – Labeling

- Required Labeling Components, 21 CFR 101, Subpart A
  - ✓ Statement of identity
  - ✓ Ingredient statement
  - ✓ Nutrition information
  - ✓ Name and place of business of manufacturer, packer, or distributor
  - ✓ Accurate statement of quantity of contents
- Nutrition Labeling, 21 CFR 101.36
- Ingredient Labeling, 21 CFR 101.4(g), (h), and 101.36(d)

Supplement Facts

Serving Size 1 Tablet

	Amount Per Serving	% Daily Value
Vitamin A (as retinyl acetate and 50% as beta-carotene)	5000 IU	100%
Vitamin C (as ascorbic acid)	60 mg	100%
Vitamin D (as cholecalciferol)	400 IU	100%
Vitamin E (as dl-alpha tocopheryl acetate)	30 IU	100%
Thiamin (as thiamin mononitrate)	1.5 mg	100%
Riboflavin	1.7 mg	100%
Niacin (as niacinamide)	20 mg	100%
Vitamin B_6 (as pyridoxine hydrochloride)	2.0 mg	100%
Folate (as folic acid)	400 mcg	100%
Vitamin B_{12} (as cyanocobalamin)	6 mcg	100%
Biotin	30 mcg	10%
Pantothenic Acid (as calcium pantothenate)	10 mg	100%

Other ingredients: Gelatin, lactose, magnesium stearate, microcrystalline cellulose, FD&C Yellow No. 6, propylene glycol, propylparaben, and sodium benzoate.

Dietary Supplements – Labeling Claims

- Structure-Function Claims, section 403(r)(6) FDCA
  - ✓ Permissible claims:
    - Claims benefit related to classical nutrient deficiency disease
    - Describes role of nutrient or dietary ingredient intended to affect structure of function
    - Characterizes documented mechanism by which nutrient or dietary ingredient acts to maintain structure or function
    - Describes general well-being from consumption of nutrient or dietary ingredient
  - ✓ Conditions:
    - Substantiation that claim is truthful and not misleading
    - FDA Notification within 30 days, 21 CFR 101.93
    - Disclaimer: "**This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, cure, or prevent any disease**." 21 CFR 101.93.
  - ✓ Structure-Function Claims v. "Disease" Claims (states or implies that dietary supplement treats, cures, mitigates, or prevents disease) , 21 CFR 101.93(f), (g)

Dietary Supplements – Labeling Claims

- Health Claims, 21 CFR 101.14
  - ✓ Expressly or by implication characterize the relationship of a conventional food or dietary supplement to a disease or health-related condition
  - ✓ Generally not permitted unless FDA has issued regulation stating conditions for use of such claim, including specific permissible language of claim
  - ✓ "Qualified" health claims may be made as process for formal regulatory approval is evolving, provided disclaimer is stated
- Nutrient Content Claims, 21 CFR 101.13 and Subpart D
  - ✓ Highlights specific nutritional attributes of products through uniform framework of reference
  - ✓ Specific language defined in regulations must be used
  - ✓ 120-Day Notice must be submitted to FDA that authoritative statement is supported is supported by scientific body of U.S. government