REGULATION OF DIETARY SUPPLEMENTS

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LEARNING OBJECTIVES

- Define how dietary supplements are regulated
- Develop an understanding of dietary supplement regulations
- List GMP requirements and adverse event reporting requirements
- Identify upcoming issues
THE U.S. MARKET

- Over half of American adults use dietary supplements
- Doctors, dietitians, nurses, pharmacy students, and other health professionals also use supplements
WHY USE SUPPLEMENTS?

- Science shows benefits
- People make the “diet-disease” connection
- Increasing acceptance of alternative medicine
- Aging baby boomers are seeking wellness
Do you personally use dietary supplements, including multivitamins or herbal preparations?

- YES
- NO
TOP VITAMINS/MINERALS

- Multivitamins
- Vitamin C
- Vitamin E
- Calcium
TOP BOTANICALS

- Echinacea
- Ginseng
- Ginkgo Biloba
- Garlic
- St. John’s Wort
- Golden Seal
- Saw Palmetto
POLLING QUESTION

- We often hear in the media that dietary supplements are unregulated. Is this true? Are dietary supplements regulated or unregulated?

- Regulated
- Not regulated
Under the Food, Drug and Cosmetic Act, dietary supplements are regulated as a category of foods, and have been since at least 1938.
REGULATION

- Critics of dietary supplements who claim they are “unregulated” usually mean they are not subject to premarket approval and the kind of stringent regulation that applies to drugs.
- Being regulated as a category of foods is definitely not the same as being “unregulated.”
REGULATION

- Foods, including supplements, are adulterated if they are unsafe.
- Foods, including supplements, are misbranded if their labeling is false or misleading in any respect.
FOOD LABELING

- Common or usual name
- Name of manufacturer/distributor
- Net contents
- Ingredient list
- Nutrition labeling
NUTRITION LABELING

- Conventional foods “Nutrition Facts”
- 21 CFR Part 101.9
- Dietary supplements “Supplement Facts”
- 21 CFR Part 101.36
- Foods can list only certain nutrients
- Supplements list all relevant substances
DSHEA

- Dietary Supplement Health and Education Act of 1994
- Assured access to wide variety of products
- Increased consumer information about products
DSHEA DEFINITION

- Dietary supplements may contain:
  - Vitamins or minerals
  - Botanicals
  - Amino acids
  - Other dietary substances
  - Extracts or combinations of these
INGREDIENTS

- Ingredients are not “food additives”
- “Grandfathered” ingredients—Old ingredients, on the U.S. market before Oct. 15, 1994—can be used without further notification
- “New dietary ingredients”—Require a notification to FDA, with a summary of safety information, at least 75 days before marketing
SAFETY

- Ingredient is adulterated if it “presents a significant or unreasonable risk of illness or injury”
- FDA relied on this provision in banning the herb ephedra in 2004, after a decade of controversy and many reports of adverse events
The Nutrition Labeling and Education Act of 1990 for the first time permitted health claims in food labeling, provided they were supported by “significant scientific agreement” and authorized by FDA.

A health claim describes the association between a food substance and a disease or health-related condition.
APPROVED HEALTH CLAIMS

- Calcium reduces risk of osteoporosis
- Folic acid (a B vitamin) reduces risk of having a baby with a neural tube birth defect
- Psyllium and other specific fiber sources reduce the risk of heart disease
HEALTH CLAIMS

- What if a FDA disapproves a health claim?
- Courts ruled that the claim cannot be completely banned if it is truthful, even if not supported by “significant scientific agreement.”
- FDA must consider whether language can be developed (“qualified language”) that truthfully describes the state of the evidence.
QUALIFIED HEALTH CLAIMS

- Contain qualifying language explaining that the scientific evidence is not conclusive.
- “Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease.”
Permitted by DSHEA for dietary supplements
Company must notify FDA within 30 days that the claim is being made, and must have substantiation for the claim
May not claim to prevent or treat disease
Label must bear a “disclaimer”
Disclaimer has two purposes.

(1) To distinguish structure/function claims from health claims, which are evaluated by FDA.

(2) To distinguish structure/function claims from drug claims, which do refer to preventing or treating disease.
This statement has not been evaluated by FDA. This product is not intended to diagnose, treat, cure or prevent any disease.
STRUCTURE/FUNCTION CLAIMS

- More than 10,000 letters of notification have been submitted to FDA, since DSHEA passed in 1994
- Structure/function claims are widely utilized and are useful in helping consumers understand intended uses of many dietary supplements
STRUCTURE/FUNCTION CLAIMS

- Calcium builds strong bones and teeth.
- Omega-3 fatty acids (EPA and DHA) support a healthy heart.
- Lutein helps maintain good vision.
- Echinacea promotes a healthy immune system.
ENFORCEMENT

- FDA takes regulatory action against label claims that are false or misleading, and against products making unapproved drug claims.
- The Federal Trade Commission (FTC) takes enforcement action against advertising claims that are false or misleading.
GOOD MANUFACTURING PRACTICES (GMPs)

- Describe currently acceptable practices in the manufacturing of specific product categories
- Provide industry guidance
- Provide a basis for inspection of manufacturing plants by FDA or by state food and drug agencies
FOOD GMPs: 21 CFR 110

Describe GMPs that must be observed in manufacturing, packing, or holding human food.
DRUG GMPs, 21 CFR 211

- Extensive quality control procedures to ensure quality and content of pharmaceutical products
DSHEA, 1994

- Recognized concerns about quality of dietary supplements
- Authorized FDA to establish separate dietary supplement GMPs “modeled after current good manufacturing practice regulations for food.”
INDUSTRY INITIATIVE

- Industry concerned about quality of some products
- Approached FDA and offered assistance in drafting GMPs
- Industry draft submitted to FDA, 1995
- Published as an ANPR by FDA, for public comment, 1997
- Proposed rule in 2003
FINAL RULE ON GMPs

- Final rule on GMPs for dietary supplements published June 2007
- Becomes effective for large companies in June 2008
- Smaller companies have another year to comply
- Smallest companies have another 2 years to comply
DIETARY SUPPLEMENT GMPs: 21 CFR 111, OVERVIEW

- A snapshot of how dietary supplements are made and what controls are required by the new GMP regulations
GOAL OF GMPs

- Ensure that consumers are provided with dietary supplements that have the expected identity and quality
OVERALL APPROACH

- Final rule emphasizes effective control over ingredients and all stages of the production process
- Recognizes importance of requiring written procedures for key operations
- Recognizes that control of ingredients and processes can justify reduced testing burden at the end
COMPANIES SUBJECT TO NEW GMPs (Subpart A)

- Manufacturers, labelers, and distributors of finished dietary supplements must comply with new GMPs.
- Applies to imports as well as products manufactured domestically.
- Ingredient suppliers will continue to be covered by food GMPs.
COMPLIANCE PERIOD

- One year for large companies (June 25, 2008)
- Two years for small companies (less than 500 employees)
- Three years for very small companies (less than 20 employees)
WRITTEN PROCEDURES

- Calibration of instruments and controls
- Cleaning/maintaining equipment and utensils and contact surfaces
- Quality control operations
- Laboratory operations and testing
- Manufacturing operations
- Handling of product complaints
PERSONNEL (Subpart B)

- Health, cleanliness, gloves, hair covers, no rings
- Adequate training, education or experience (training must be documented)
- Qualified supervision
- Must designate personnel responsible for QC function
PHYSICAL PLANT AND GROUNDS (Subpart C)

- Must be designed to facilitate cleaning and maintenance
- Separate areas for receiving, manufacturing, packaging, labs
PHYSICAL PLANT AND GROUNDS (Subpart C)

- Cleaning procedures, pest control, water supply, plumbing, drainage, bathrooms, trash disposal
- Ventilation, temperature control, lighting
EQUIPMENT (Subpart D)

- Equipment adequate to its purpose; designed to facilitate cleaning and maintenance, while avoiding contamination of product with lubricants, metal, glass, corrosion
- Calibration of equipment, including automated equipment
PROCESS CONTROLS (Subpart E)

- Must have a system of production and process controls covering all stages of the operation
QUALITY CONTROL
(Subpart F)

- QC personnel must approve or reject all materials, processes, labels, and finished products, based on testing and established specifications.
- QC personnel must make a decision about disposition of products that do not meet specifications.
- Review and approve all written procedures and documentation.
RECEIVING MATERIALS (Subpart G)

- Must quarantine materials received until samples are collected and QC personnel approve the materials for use.
- Must keep records that allow tracing all materials to their suppliers and to the product in which it is used.
MASTER MANUFACTURING RECORD (Subpart H)

- Must prepare and follow a master manufacturing record for each batch size of each product manufactured.
- Master record must specify ingredients, quantities, intentional overage, controls and procedures, packaging and labels to be used for each product.
Batch production record must be prepared for each batch of product manufactured, based on master record.

- Each batch must have a control number.
- Initials required to document date and time of performance of each step in the process.
BATCH RECORD
(Subpart I)

- Weight or measure of each component, and its lot number
- Identity of processing equipment used
- Results of tests performed during processing (or reference to results)
- Documentation that product specifications were met
- Yield calculations
- Copy of (or reference to) labels used
LABORATORY OPERATIONS (Subpart J)

- Must test or examine components, in-process materials and finished products to determine compliance with specifications.
- Tests must be “scientifically valid”.
- May use sound sampling plan.
MANUFACTURING
(Subpart K)

- Must design operations to ensure that product specifications are consistently met
- Must protect against microbial or chemical contamination
- Must use filters, traps, metal detectors or other controls to avoid inclusion of metal fragments or other foreign materials
PACKAGING AND LABELING (Subpart L)

- Packaging and labeling must meet specifications and be kept in a secure location.
- Must ensure that correct packages and labels are used.
- Must be able to follow labeled product throughout distribution.
HOLDING AND DISTRIBUTION (Subpart M)

- Must hold components, products, and packaging under conditions that do not adversely affect them and that do not lead to mixups
- Considerations include temperature, humidity, and light
RETURNED PRODUCTS
(Subpart N)

- QC personnel must conduct a material review and make a disposition decision
- Returns must be destroyed, unless disposition decision permits salvage or reprocessing
- Reprocessed product must meet specifications
PRODUCT COMPLAINTS
(Subpart O)

- Product complaints must be reviewed by a qualified person.
- Complaint possibly related to failure to meet GMP specifications must be investigated and must extend to related batches.
RECORDS (Subpart P)

- Records must be retained and available for inspection by FDA, when requested, for a period of 2 years past the date of distribution or 1 year past the shelf life.
BOTTOM LINE

- Industry was very pro-active in supporting GMPs throughout the process, and FDA was very responsive to comments in preparing the Final Rule.
- Final GMPs should benefit industry and consumers by establishing a level playing field and ensuring product quality.
EVERYBODY WINS

- The new GMPs will raise the bar for quality of dietary supplements and help ensure product safety and benefits for consumers.
MANDATORY REPORTING OF SERIOUS ADVERSE EVENTS

- Adverse events sometimes occur, despite the best efforts of even the most sophisticated drug manufacturers to ensure safe use
- Drug manufacturers marketing products under a New Drug Application must promptly notify FDA of any serious adverse event that comes to their attention
REPORTING OF ADVERSE EVENTS

- There is no requirement for food manufacturers to report adverse events to FDA
- Until recently there was no requirement for dietary supplement manufacturers to report adverse event to FDA
- Same was true of manufacturers of OTC drugs marketed according to FDA monographs (not NDAs)
CALL FOR MANDATORY REPORTING

- After numerous adverse events, including deaths, were reported in association with ephedra-containing dietary supplements, there was a call for companies to be required to report such events to FDA.
- Federal and state legislation was proposed but not passed.
Industry associations worked with Congress to draft strong legislation requiring mandatory reporting of serious adverse events by manufacturers of dietary supplements and OTC drugs.

Legislation passed in December 2006 and became effective in December 2007.
SERIOUS ADVERSE EVENTS

- Death or life-threatening experience
- Inpatient hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Events that require medical or surgical intervention to prevent above outcomes
MANDATORY REPORTING

- Reports of serious adverse events that come to the attention of a manufacturer must be reported to FDA within 15 business days, using the MEDWATCH form and reporting system.
UPCOMING ISSUES

- Continuing concern over safety and quality of imported ingredients and products, requiring companies and FDA to step up oversight efforts.
- Increasing focus on consumer responsibility for health, including selection of healthful foods and dietary supplements as part of a wellness lifestyle.
UPCOMING ISSUES

- Continuing flow of new scientific findings.
- Need for health professionals, including pharmacists, to help consumers evaluate new findings and put them in the context of the full body of scientific information.
Dietary supplements are a category of foods, and have been defined as such since 1938.

DSHEA grandfathers “old” ingredients and requires submission of safety data on “new” dietary ingredients.

Truthful health claims and structure/function claims are permitted.
SUMMARY

- New rules on Good Manufacturing Practices for dietary supplements will raise the bar for quality, help ensure a level playing field in the industry, and increase consumer confidence.
SUMMARY

- New requirements for mandatory reporting of serious adverse events will provide FDA with prompt information about any potential safety issues that require further evaluation.
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