

OSU Oregon State University

## Regulation and Toxicology of Dietary Supplements

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Pharmaceutical (drug)

Regulated by US FDA

Dietary Supplement

Regulated by US FDA

## Dietary Supplement

## Lecture Overview

- What is a dietary supplement?
- What are the distinctions between dietary supplements and drugs?
  - Regulatory perspective
  - Health perspective
    - Toxicology
- What are known and theoretical risks associated with dietary supplements
  - How is risk assessed?
  - Can risks be reduced? How?

## Review: What's In Our Food?

- Food as a complex mixture
  - Nutrients
  - Non-nutrient substances
    - Frequently vital for plant or organism survival
      - Plant hormones
      - Naturally occurring pesticides
    - Products of food preparation
      - Additives, coloring agents
    - Natural and unavoidable contaminants
      - Products of microbial contamination
    - Products of environmental pollution
    - Products of crop protection
    - Chemicals with pharmacological, toxicological properties in animals, humans

Food	Number of non-nutrient chemicals
Cheese	160
Bananas	325
Wine	475
Coffee	625
Beef	625

## Food Regulations: Federal Food, Drug and Cosmetic Act (FFDCA)

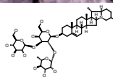
- Authorized federal government (US FDA) to ensure that all food involved in interstate commerce is safe
  - Reasonable certainty of no harm** standard of safety
    - A no-risk (risk averse) approach
    - Same standard of safety as FQPA (for pesticides)
  - Food bears a *presumption of safety* unless it was adulterated
    - Adulterated: defined as substances not **naturally** present in food, but contaminants or added ingredients.
  - Higher standards of safety for substances that were not natural components of food**
    - Require much more toxicology data for risk assessment

## Understanding FFDCA: Relevance to Dietary Supplements

- Natural components**
  - Nutritional components and other naturally occurring substances
    - Carry a **presumption of safety until proven otherwise**
- Substances intentionally added to food (food additives)**
  - Require extensive risk assessment
- Substances that can contaminate food**
  - role of action levels (legal limit)

## Natural Components of Food: An Example

- Solanaceous glycoalkaloids
  - Chemicals that are normally present in tomatoes, potatoes, eggplant
  - Naturally occurring insecticides
    - Similar mechanisms of toxicity as organophosphate, carbamate insecticides
- What are the risks?
  - Risk=Hazard x Exposure**
    - Depends on the dose and duration
      - Modern-day exposure is far below threshold for toxic effects
      - Epidemics of poisoning have been rarely reported throughout human history



Drug

Dietary Supplement

## Comparing Pharmaceuticals, Dietary Supplements

- | Role of Biotechnology   |   |
|---|---|
| <ul style="list-style-type: none"> <li><b>Pharmaceuticals</b> <ul style="list-style-type: none"> <li>FDA regulates as <b>drugs</b></li> <li>Chemical can be natural or synthetically derived</li> <li>Requires extensive regulatory (FDA) pre-market assessment of risk, efficacy                             <ul style="list-style-type: none"> <li>Post-marketing surveillance (for adverse reactions)</li> </ul> </li> <li>System is not perfect                             <ul style="list-style-type: none"> <li>Some risks not identified until after marketing</li> </ul> </li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li><b>Dietary Supplements</b> <ul style="list-style-type: none"> <li>FDA regulates as <b>foods</b> (<i>not</i> drugs)</li> <li>Chemical is derived from foods, microbes, animal tissues                             <ul style="list-style-type: none"> <li><i>Generally</i>, natural chemicals</li> </ul> </li> <li>Pre-market assessment of risk (by FDA) is limited                             <ul style="list-style-type: none"> <li>No assessment of efficacy</li> </ul> </li> <li>System is not perfect                             <ul style="list-style-type: none"> <li>Some risks not identified until after marketing</li> <li>Some risks differ from pharmaceuticals</li> </ul> </li> </ul> </li> </ul> |

## What is a Dietary Supplement?

- Defined by U.S. Congress in 1994
  - Dietary Supplement Health and Education Act (DSHEA) of 1994, amended Federal Food, Drug, Cosmetic Act
  - product taken *by mouth* that contains a "dietary ingredient" intended to supplement the diet
    - Includes nutrients *and* non-nutrients derived from foods
      - Vitamins, minerals, herbal or botanical extracts, enzymes, metabolites
  - DSHEA considers dietary supplements as **foods**, not drugs
    - Requires labeling to indicate it is a dietary supplement
- An industry generating \$billions/year in United States

## Dietary Supplement versus a Drug? Regulatory Distinctions

- Under DSHEA, it is the *intended use* of a product that distinguishes a drug from a dietary supplement
  - Drug:** Intended to diagnose, treat, prevent, or cure disease
  - Dietary supplement:** **Not** intended to diagnose, treat, prevent, or cure disease
    - Under DSHEA, product label must indicate this
    - DSHEA has other provisions which limit what may be claimed on the product label



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## DSHEA of 1994: Background and Provisions

- Prior to DSHEA, dietary supplements were not clearly defined under FFDCFA
- DSHEA amended FFDCFA, providing regulations specific for dietary supplements, including:
  - Dietary supplements are *not* considered food additives
    - Eliminated requirement for pre-market risk (toxicology) assessment
  - Dietary supplements are considered natural components of food**
    - Nutritional components and other naturally occurring substances
      - Carry a presumption of safety until proven otherwise

## DSHEA of 1994: Background and Provisions

- Burden of ensuring safety, efficacy placed upon manufacturers**
  - No requirements for toxicology data review by FDA
    - Contrast with FDA's regulatory role with food additives and drugs
- Manufacturers have no legal obligation under DSHEA to report data about safety and purported benefits of products
  - To FDA or to consumers
- Firms responsible for ensuring that label claims cannot be false, misleading
  - FDA is not required to approve labels prior to marketing

## Dietary Supplements: Distinctions from Food Additives

- Dietary supplements do not need approval from FDA before they are marketed
  - Carry a presumption of safety until proven otherwise**
    - Contrast with food additives
- Manufacturer is responsible for ensuring quality, purity of dietary supplements
  - Contrast with FFDCFA requirements for food additives, pharmaceutical drugs
    - Good Manufacturing Practices, Good Laboratory Practices

## Dietary Supplements and DSHEA (1994)

- There are no rules on serving size or amounts of ingredients in dietary supplements
  - Decision made by manufacturer, not subject to FDA approval
  - Contrast with pharmaceutical drugs
- Certain information must appear on label of dietary supplements
  - "Dietary Supplement"
  - manufacturer, packer, or distributor; a complete list of ingredients; and the net contents of the product
  - "Not intended to diagnose, treat, prevent, or cure disease"



## DSHEA of 1994: Labeling Claims on Dietary Supplements

- Three categories of health claims allowed on label:
  - **Nutrient content claims**
    - Product is a "good source of substance X"
  - **Health claims**
    - relationship between a substance and a disease or health-related condition
    - "diets high in \_\_\_\_\_ may increase/decrease....."
  - **Structure-function claims**
    - Benefits in context of physiological function
    - "calcium plays an important role in healthy bones"
- **Label cannot claim a supplement will treat, diagnose, or cure disease**
- Manufacturer (not FDA) responsible for confirming validity of the label claims



## Dietary Supplements under DSHEA (Summary)

- Considered foods (not drugs)
- Considered natural components of food
  - Presumed safe until proven otherwise
- Pre-market risk assessment is not required by FDA
- Manufacturer of supplement responsible for determining
  - Safety
  - Efficacy
  - Quality
  - Accuracy of label
  - Serving size

## DSHEA of 1994

- Under DSHEA, FDA has legal burden to determine a supplement is unsafe before it can restrict production, sale in U.S.
  - Needs to be proven harmful prior to legally restricting or prohibiting sale of the product
    - if it presents an "unreasonable risk of illness or injury"
  - Post-marketing surveillance for adverse events is under a voluntary reporting system in the United States
    - MedWatch <http://www.cfsan.fda.gov/~dms/ds-rept.html>

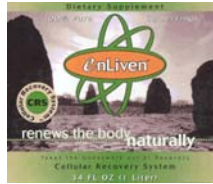
## Adverse Events Associated with Dietary Supplements: Examples

- Examples of supplements containing unwanted addition of undesirable contaminants
  - Digitalis poisoning resulting from plantain-derived dietary supplement contaminated by digitalis lantana
  - Kava kava (*Piper methysticum*) and liver failure
  - Studies have identified other environmental contaminants in dietary supplements
    - Aflatoxins, lead, mercury, DDT as examples



## Adverse Events and Dietary Supplements: GHB as Example

- Marketed as dietary supplement in 1990's
  - Active ingredient (GHB) occurs naturally in animal (and human) tissues
    - Sold at health food stores, fitness stores
    - Labeling emphasized "organic" derivation
- Purported euphoric, anabolic, "body building," other effects
- Became part of club scene
  - Sedative-hypnotic drug of abuse
  - Implicated in date rapes
- Now is a Schedule I Controlled Substance (DEA)



## Adverse Events Associated with Dietary Supplements: Examples

- Some dietary supplements may interact with effects of pharmaceutical drugs
- St John's Wort
  - Can induce as well as inhibit liver enzymes involved in the metabolism of drugs and other chemicals
    - Cyclosporin
    - Indinavir
    - Oral contraceptives
    - Antidepressants (prozac)
    - Benzodiazepenes (valium)



## Other Dietary Supplements of Current Concern

- Plant alkaloids containing ephedrine
  - Example of botanical: Ma Huang (*ephedra sinica*)
  - Contains mixture of mainly ephedrine, other stimulant alkaloids
    - Pseudoephedrine (common OTC decongestant)
- Widely marketed as dietary supplement
  - Weight loss, athletic enhancement
- Pharmacology, toxicology of ephedrine, related alkaloids
  - Increased heart rate, blood pressure (blood vessel constriction), bronchodilator effects
- Poor correlation between product labeling and actual dose of what appears in the product



## Dietary Supplements: Warnings and Safety Information

- FDA Webpage Reports Current and Emerging Issues, Warnings <http://www.cfsan.fda.gov/~dms/ds-warn.html>



### FDA Talk Paper

T05-25  
July 1, 2005

Media Inquiries:  
800-Stone-3031-4342  
Consumer Inquiries:  
800-INFO-FDA

#### FDA Issues Nationwide Alert for "Liqiang 4" Due to Potential Health Risk

The U.S. Food and Drug Administration (FDA) is warning consumers not to take Liqiang 4 Dietary Supplement Capsules because they contain glyburide – a drug that could have serious, life-threatening consequences in some people.

## Dietary Supplements: Observations and Challenges

- Components of dietary supplements can have pharmacological, toxicological effects on healthy individuals
  - What about individuals with disease?
  - Role of chemical interactions?
    - Dietary supplements with pharmaceutical drugs
  - What about other chemicals that may be present in the formulation?

## Dietary Supplements: Towards the Future

- Scientific community is becoming increasingly aware of risks
- Issues of public perception
  - "natural" is safer
  - Confusion (media, internet, advertising)
- Regulatory agencies (FDA) taking steps towards addressing known problems
- Many challenges lie ahead



## Dietary Supplements, 2008: Rulemaking (GMP's)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
21 CFR Part 111

[Docket No. 1996N-0417] (formerly Docket No. 96N-0417)  
RIN 0910-AB04

Current Good Manufacturing Practice in Manufacturing, Packaging,  
Labeling, or Holding Operations for Dietary Supplements

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.



**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule regarding current good manufacturing practice (CGMP) for dietary supplements. The final rule establishes the minimum CGMPs necessary for activities related to manufacturing, packaging, labeling, or holding dietary supplements to ensure the quality of the dietary supplement. The final rule is one of many actions related to dietary supplements that we are taking to promote and protect the public health.

## Questions for Discussion

- Are dietary supplements adequately regulated in the United States?
- Should the use of biotechnology in dietary supplements be regulated in the same way that Plant-Incorporated Protectants are?