

# Dietary Supplements & Functional Foods

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## Overview: Dietary Supplements & Functional Foods

- The Markets
- The Definitions
- The Regulations
- The Challenges



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## A Few Facts

- Sales in the global "nutraceutical" industry are projected to reach \$187 billion by 2010 (2007)
- Includes:
  - ◆ Dietary Supplements
  - ◆ "Functional" Foods
  - ◆ Medical foods



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## A Few Facts

- Dietary Supplements
  - ◆ US adults who report taking dietary supplements
    - Council of Responsible Nutrition (CRN) → 68%
    - National Health Interview Survey → 51%
  - ◆ US health care professionals
    - 79% of physicians and 82% of nurses recommend dietary supplements to clients/patients (CRN)



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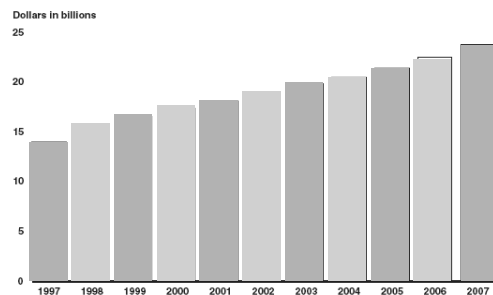
## A Few Facts

- Functional foods (IFIC 2007)
  - ◆ 80+% say they consumed, or are interested in consuming, functional foods/beverages
  - ◆ Average \$90/year pp



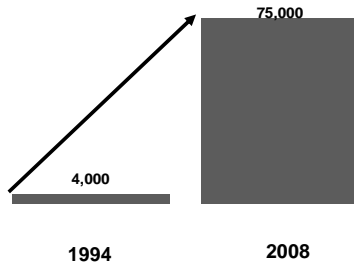
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## USA Dietary Supplement Sales



Source: Nutrition Business Journal

## Dietary Supplements: Products on the US Market



Source: GAO

## The New York Times

### As Economy Is Down, Vitamin Sales Are Up

By ALEX WILLIAMS  
Published: April 4, 2009

For the 3-months ending Dec. 28, sales of vitamins rose nearly 8 percent compared with the same period in 2007, according to Information Resources Inc., a market research company in Chicago.

## So What Is This Stuff?

- Lines are sometimes blurred
  - ◆ Conventional Food ?
  - ◆ Functional Food ?
  - ◆ Dietary Supplement ?
  - ◆ Drug?



## Definitions

- FDA has precise definitions for:
  - ◆ Food
  - ◆ Dietary Supplement
  - ◆ Medical Food
    - Orphan Drug Act (21 CFR 360ee (b) (3))
  - ◆ Foods for Special Dietary Use
    - 21 CFR 411(c)(3) i.e., infant formula
  - ◆ Medicine (OTC and Prescription)



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## Dietary Supplement DSHEA (1994)

- Intended to supplement the diet and contains one or more:
  - ◆ Vitamins
  - ◆ Minerals
  - ◆ Herbs or other botanicals
  - ◆ Amino acids
- To supplement the diet by increasing total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these
- Intended for ingestion in pill, capsule, tablet, or liquid form
- Not represented as a conventional food or as the sole item of a meal or diet
- Labeled as a "dietary supplement"

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## Dietary Supplement DSHEA (1994)

- No pre-market approval unless product contains a New Dietary Ingredient (NDI)
- Notification 75 days prior to market
- No NDI formal guidance from FDA
  - ◆ safety profiles ?
    - Creatine
    - Synephrine



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## Definitions

- FDA has NO definitions for:
  - ◆ Functional Food
    - Foods for Specific Health Use (Japan, 1991)
  - ◆ Nutraceutical
  - ◆ Superfood
  - ◆ Muscle food
  - ◆ Energy drink, etc.



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## Determined by Intended Use: Labeling

### Nutrition Facts

Serving Size: 1 fl oz (31g)	
Amount Per Serving	
	% Daily Value*
Calories 11	Calories from Fat: 0
Total Fat 0 g	0%
Saturated Fat 0 g	0%
Trans Fat 0 g	0%
Cholesterol 0 mg	0%
Sodium 6.43 mg	0%
Potassium 5.81 mg	0%
Total Carbohydrate 2.7 g	3%
Dietary Fiber 0 g	0%
Sugars 2.66 g	
Sugar Alcohols	
Protein 0 g	
Vitamin A	
Vitamin C	
Calcium 0.31 mg	0%
Iron 0 mg	0%

### SUPPLEMENT FACTS

Standard Serving Size: 17 grams (1 ounce)	
Amount per Standard Serving	% DV
Sorbitol	22
Calcium Hydroxide	0
Saturated Fat	0
Sodium	30 mg 1%
Potassium	490 mg 14%
Total Carbohydrate	2.4
Dietary Fiber	1.8
Sugars	1.6
Protein	1.1 g 1%
Vitamin C	100%
Vitamin B6	100%
Vitamin B12	100%
Proprietary Blend	4.450 mg 1
* % Daily Value based on a 2,000 Calorie diet	

Other Ingredients: Maltodextrin, Crystalline Fructose, Potassium Citrate, Citric Acid, Sodium Citrate, Hydroxybenzoic Acid, Cinnamic Acid, Natural & Artificial Flavor



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## Functional Foods

- American Dietetic Association
  - ◆ Foods that... "move beyond necessity to provide additional health benefits that may reduce disease risk and/or promote optimal health."
- IFT
  - ◆ Foods that... "provide a health benefit beyond basic nutrition (for the intended population). These substances provide essential nutrients often beyond quantities necessary for normal maintenance, growth, and development, and/or other biologically active components that impart health benefits or desirable physiological effects."



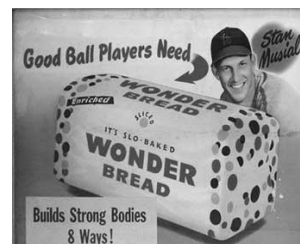
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## Examples



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## 1930s to 1950s



- "Wonder Bread helps build strong bodies 8 ways"
- "Wonder Bread helps build strong bodies 12 ways"



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## Year 2000



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- Helps build strong bodies 13 ways ?
- "Neurons in your brain need calcium to transmit signals. Without it they can be, well, a little slow."



## Eggland's Best: 1994

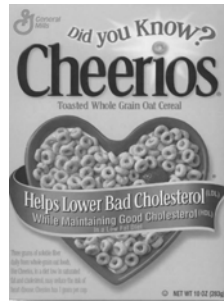
- "Eggland's Best. Eggs that won't increase your serum cholesterol"
- "In clinical tests in a low-fat diet even twelve a week caused no increase in serum cholesterol. ... Eggland's Best. Now, you can eat real eggs again"



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## Qualified Health Claim: Example

- 21 CFR 101.18
- "Diets that low in saturated fats and cholesterol and that include soluble fiber from whole oat foods like Cheerios in a diet low in saturated fat and cholesterol may reduce the risk of coronary heart disease." (1997)
- "Three grams of soluble fiber daily from whole grain oat foods like Cheerios in a diet low in saturated fat and cholesterol may reduce the risk of heart disease. Cheerios has 1 gram per cup."



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## St. Petersburg Times Kellogg slapped for claims that Frosted Mini-Wheats improve attentiveness

By Ivan Penn, Times Staff Writer  
In Print: Wednesday, April 22, 2009

- "...clinically shown to improve kids' attentiveness by nearly 20 percent"
- FTC → "...claims were false and violated federal law."



- Structure/Function Claims
  - ◆ The digestive system provides a barrier against potentially harmful substances and microorganisms.
  - ◆ Intestinal transit is an important part of your overall digestive system health.

## Dietary Supplement Regulations

- FD&C Act, as amended by:
  - ◆ Dietary Supplement Health and Education Act of 1994 (DSHEA)
  - ◆ Dietary Supplement and Nonprescription Drug Consumer Protection Act (2006)
  - ◆ FD&C Section 402(g) enables 21 CFR Part 111, Current Good Manufacturing Practice regulations (2007)
- Public Health Security and Bioterrorism Preparedness and Response Act of 2002
- Federal Trade Commission (Title 16)



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## Functional Food Regulations

- Regulated as conventional foods including cGMPs in 21 CFR Part 110:
  - ◆ Foods with added dietary ingredients ...the ingredient must either be generally recognized as safe (GRAS)
  - ◆ No prior FDA notification required before market
    - unsupported or incorrect GRAS determination
      - Kava or Echinacea in juice
      - Ginkgo or ginseng in cereals (warnings)
- FDA does not track functional foods separately from other foods, but does track dietary supplements



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## Functional Food Regulations

- 2006: FDA Public hearing → comment period
- GMA → "...current statutory and regulatory frameworks provide the necessary requirements and guidance to address all foods."
- ADA → "...a reasoned review of existing law and regulation to develop modifications that truly address enduring consumer needs over those of market trends."



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## Banning Unsafe Dietary Supplements

- FDA may remove a dietary supplement from the market if it presents a significant or unreasonable risk of illness or injury when used according to its labeling or under ordinary conditions of use
- In 2004, FDA made such a finding for dietary supplements containing ephedrine alkaloids
- Burden of proof on FDA 21 U.S.C. 342 (f)(1)



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## Actionable by FDA

If a dietary supplement:

- Is toxic or unsanitary → Section 402(a)
- Makes false or unsubstantiated claims → Section 403(r)(6)
- Claims to cure, treat, mitigate, a disease → Section 201(g)
- Is a new dietary ingredient without premarket approval (safety data) → Section 413
- Fails to be made according to food cGMP → Section 402(g)
- Not labeled properly, fails to meet label claim



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## Hydroxycut Recall

- 9 million+ units of 14 separate Hydroxycut products were sold in 2008 the USA
- Primary ingredients
  - ◆ Calcium/potassium salt of 60% HCA extract from *Garcinia cambogia*
  - ◆ Niacin-bound chromium
  - ◆ *Gymnema Sylvestre* Extract
  - ◆ Green tea
  - ◆ Caffeine



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## Actionable by FDA

- Section 505 → unapproved drug
- Section 502 → misbranded drug
- Section 403 → misbranded food
- Section 402 → adulterated food
- Section 409 → unapproved food additive
- Section 510 → unregistered drug facility
- Section 801 → import/export
- Section 408 → pesticide
- Section 503 → prescription drug



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## Allowable Claims: Dietary Supplements

- Substantiation that claims are truthful and not misleading
- Required labeling
  - ◆ *"This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."*
- Must notify FDA within 30 days after first marketing of the dietary supplement with health claim that is being made



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## Disallowed Claims: Dietary Supplements

- Any claims to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases
- Even if truthful and well substantiated
  - ◆ Cholesterol-lowering claims
  - ◆ Insomnia claims



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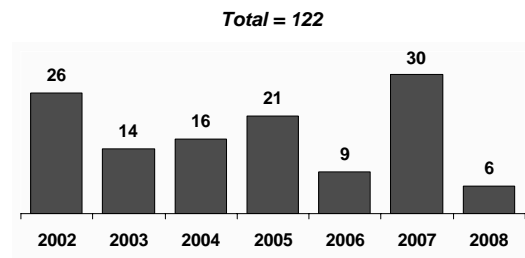
## Disciplinary Stages

- FDA holds regulatory meeting with the firm
- Issues firm a warning
  - ◆ 293 warning letters 2002 to 2007
  - ◆ 41 warning letters in 2008 after review of websites
- Reasons:
  - ◆ Cancer cure or diabetes, heart disease, cold/flu
  - ◆ 70% involved unapproved drugs or misbranded drugs
- Issue consumer alerts
  - ◆ 12 consumer alerts 1999 to 2008
- Issue advisory to industry



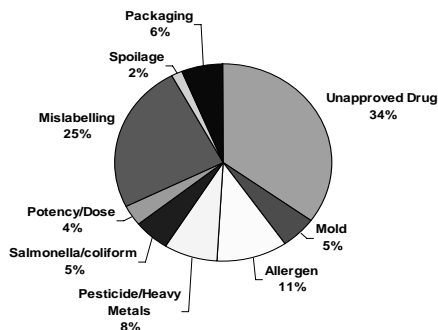
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## Dietary Supplements: Voluntary Recalls 2002-2008



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## Dietary Supplements: Reasons for Recall 2002-2008



## Dietary Supplements: Safety Issues

- Enforcement efforts
  - ◆ 72 weight loss products for undeclared drugs and/or chemicals
  - ◆ Sibutramine (Schedule IV controlled substance)
  - ◆ Also Lasix, Prozac, laxatives



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## FDA Enforcement Actions

- 3,225 dietary supplement detentions at import entry 2002 through March, 2008
  - ◆ Half were due to the potential presence of a poisonous or unsafe substance
- 27 seizures & six injunctions 2002 to July, 2008
  - ◆ 19 seizures and all injunctions regarded products promoted to treat, cure, or prevent diseases
- 19 criminal cases 2002 to July 31, 2008
  - ◆ 14 convictions



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## Adverse Event Reporting

- Dietary Supplement and Nonprescription Drug Consumer Protection Act, Public Law 109-462
- “Serious adverse event”
  - ◆ Death; a life-threatening experience; inpatient hospitalization; a persistent or significant disability or incapacity; or a congenital anomaly or birth defect; or
  - ◆ Requires, based on reasonable medical judgment, a medical or surgical intervention to prevent such an outcome



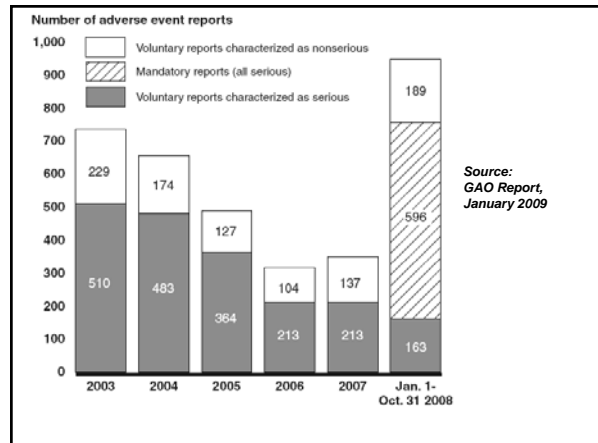
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## Adverse Event Reporting

- Effective December 22, 2007
  - ◆ “Responsible person” (i.e., company named on label) must submit serious AERs (and “new medical information”) to FDA within 15 days of receipt
  - ◆ Maintenance/inspection of all AERs also required/permitted
  - ◆ Requires “domestic address” or “domestic phone number” on labels



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## Good Manufacturing Practices: 21 CFR Part 111

- Final rule published June 25, 2007
  - ◆ Three year phase-in
- Based on both food and drug cGMP
- Requires written procedures and records throughout manufacturing
- Companies must set and meet specifications for identity, purity, strength, and composition



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## Current Good Manufacturing Practices (cGMP's) for Dietary Supplements

- 21 CFR Part 111 → establishes minimum cGMP's to manufacture, pack, label, or hold dietary supplements to ensure the quality of the dietary supplement
  - ◆ Manufacture, package, label or hold a dietary supplement
  - ◆ Package, label or distribute product manufactured by another firm
  - ◆ Sell in bulk to a distributor
  - ◆ Import or offer for import



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## Current Good Manufacturing Practices (cGMP's) for Dietary Supplements

- Applies to domestic firms
- Applies to foreign firms that want to export dietary ingredients or dietary supplements into the US
- Manufacturers must comply with other applicable regulations (Seafood HACCP or Juice HACCP)



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## Current Good Manufacturing Practices (cGMP's) for Dietary Supplements

- Protect consumers from adulterated product
- Protect consumers from products that do not contain what is claimed on the label
- Provide consistent industry-wide requirements
- Ensure quality of product, not efficacy of dietary ingredients



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## Good Manufacturing Practices: 21 CFR Part 111

- Quality defined in §111.3 in 21 CFR  
*"... that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition, and limits on contaminants, and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration..."*



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## Current Good Manufacturing Practices (cGMP's) for Dietary Supplements

- Requirement for 100% identity testing of dietary ingredients (Subpart E § 111.75)
- *"...before using a component you must...conduct at least one appropriate test or examination to verify the identity of any component that is a dietary ingredient."*
- Must include at least one of the following:
  - ◆ Gross organoleptic analysis
  - ◆ Macroscopic analysis
  - ◆ Microscopic analysis
  - ◆ Chemical analysis
  - ◆ Other scientifically valid methods



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## Current Good Manufacturing Practices (cGMP's) for Dietary Supplements

- Sources of Methods
  - ◆ AOAC, USP, other Compendia
  - ◆ Peer reviewed journals
  - ◆ In-House or proprietary methods
  - ◆ Organoleptic
  - ◆ Microscopic



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## 100% Identity Testing

- Industry-wide need for rigorous identification of source material, where the "active principle(s)" may not be known
- Batch-to-batch variation of constituents, and lack of "biomarker" reference compounds for many ingredients
- AOAC is in the process of developing methods for 39 materials, 60+ individual compounds, and 8 classes of compounds
- USP is developing a separate dietary supplement section with 200+ monographs
- Industry proprietary methods



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## Current Good Manufacturing Practices (cGMP's) for Dietary Supplements

- "...dietary supplement manufacturers are best positioned to develop a system to ensure dietary ingredient identity, according to their particular specifications."
- You may rely on a certificate of analysis for specifications (except for the identity of the dietary ingredient) only if you satisfy certain criteria, which include qualifying the supplier of the components
- Firms may NOT rely upon a certificate of analysis provided by suppliers to determine the identity of a dietary ingredient before use



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## cGMP: Master Manufacturing Record

- Prepare and follow a written master manufacturing record for each unique formulation of dietary supplement
- Master record must include
  - ◆ Batch file with label
  - ◆ Batch production record must be established every time you manufacture a batch
  - ◆ Specifications where control is necessary to prevent adulteration
  - ◆ Weight or measure for each component
  - ◆ Instructions for adding, mixing, sampling, testing
  - ◆ Expected yields
  - ◆ Specifications for packaging and label to use
  - ◆ Retention of master manufacturing record



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## cGMP: Product & Contaminant Specifications

- 21 CFR 111.70(b) → "...You must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement."



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## cGMP: Contaminant Specifications

- Not practical or necessary to test for all possible contaminants for every dietary supplement
- Manufacturer has responsibility to determine what types of contamination likely or certain to contaminate a given product and to determine what types of tests to conduct and when to test for such contamination



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## cGMP: Production & Process Specifications

- Production & process control specifications are needed to ensure the identity, purity, strength, and composition established as specified in the master manufacturing record
  - ◆ Determination of process control specifications
  - ◆ Determine whether specifications met
  - ◆ What to do if process control specifications are not met
  - ◆ Material reviews and disposition decisions → in-process adjustments and reprocessing
  - ◆ Retain representative samples & reserve samples
  - ◆ Record Keeping



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## Required Written Procedures

- Personnel → Health & hygiene
- All sanitation procedures, including pest control
- Calibrating instruments and controls and for calibrating, inspecting, and checking equipment
- Maintaining, cleaning, and sanitizing equipment and utensils
- Production & process controls
- Laboratory operations
- Packaging and labeling operations
- Holding and distributing operations
- Returned dietary supplement product
- Product complaints



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## cGMP Definition "Product Complaint"

- "... any communication that contains any allegation, written, electronic, or oral, expressing concern, for any reason, with the quality of a dietary supplement, that could be related to current good manufacturing practice..."
  - ◆ Foul odor
  - ◆ Off taste
  - ◆ Illness or injury
  - ◆ Disintegration time
  - ◆ Color variation
  - ◆ Tablet size or size variation
  - ◆ Underfilled container
  - ◆ Foreign material
  - ◆ Improper packaging
  - ◆ Mislabeling,
  - ◆ Drug or other contaminant (e.g., bacteria, pesticide, mycotoxin, glass, lead)

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## Criteria for Specifications?

	AHPA	NSF	USP
<b>Aerobic Plate Count</b>	10 <sup>7</sup> cfu/g	10 <sup>4</sup> - 10 <sup>7</sup> cfu/g	10 <sup>5</sup> cfu/g
<b>Yeast/mold</b>	10 <sup>5</sup> cfu/g	10 <sup>3</sup> - 10 <sup>5</sup> cfu/g	10 <sup>3</sup> cfu/g
<b>Total Coliform</b>	10 <sup>4</sup> cfu/g	10 <sup>2</sup> - 10 <sup>4</sup> cfu/g	10 <sup>3</sup> cfu/g
<b>Salmonella</b>	absent/10g	absent	absent
<b>E. coli</b>	n.d. /1g	absent 10 <sup>2</sup>	absent/10g
<b>Total aflatoxins</b>	20 ppb	20 ppb	--

Non-liquid supplements

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## U.S. Pharmacopeia (USP-NF)

- **Class A: Admitted into the Compendia**
  - ◆ available evidence does not indicate a serious risk to health or other public health concern.
- **Class B: Not admitted into the Compendia**
  - ◆ available evidence indicates a serious risk to health or other public health concern.

Source: <http://www.usp.org/USPNF/devProcess>

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## Dietary Supplement Inspections

- Prior to first wave of cGMP compliance (2002-08)
  - ◆ FDA conducted 804 inspections
  - ◆ State partners conducted 105 inspections
- 49% of facilities → lack of quality control and/or unsanitary conditions

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## Example FDA cGMP Inspection

- Boca Raton Aug 25 to Sept 5, 2008
  - ◆ 13-page report
  - ◆ labels sampled
  - ◆ department heads interviewed
  - ◆ processes (including training) reviewed
  - ◆ on-site laboratory operations examined
  - ◆ handling of customer complaints reviewed
  - ◆ every aspect of the facility's operations from raw material arrival to finished product release for shipping

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## Good Manufacturing Practices

- FDA plans to add dietary supplement inspections as an option for state contract agreements
  - ◆ increase dietary supplement inspections performed by state officials
- FDA is considering 3<sup>rd</sup> party audits

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January 2009

## DIETARY SUPPLEMENTS

### FDA Should Take Further Actions to Improve Oversight and Consumer Understanding

## GAO Recommendations 2009

- Commissioner of FDA should seek additional authority:
  - ◆ Require dietary supplement facilities to self-identify as part of existing registration requirements
  - ◆ Provide a list of their products and a copy of the labels
  - ◆ Report all adverse events related to dietary supplements
- HHS should issue guidance to clarify when an ingredient is considered a new dietary ingredient

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## GAO Recommendations 2009

- Evidence needed to document the safety of new dietary ingredients
- Appropriate methods for establishing ingredient identity
- HHS should direct the Commissioner of FDA to provide guidance to industry to clarify when products should be marketed as either dietary supplements or conventional foods formulated with added dietary ingredients

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## Thank You

### Acknowledgments:

- *Rena Pierami, Division VP of Auditing and Technical Services*
- *Gustavo Gonzalez, Director of Technical Services*

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