



*APPROACHES TO REGULATING DIETARY  
SUPPLEMENTS AND THEIR CLAIMS*

*Kenneth M.P. Taylor, Ph.D.*

*Center for Food Safety and Applied Nutrition  
College Park, MD*



# *Dietary Supplement Health and Education Act of 1994*

---

- ◆ *Public Law 103-417*
- ◆ *Signed into law October 25, 1994*
- ◆ *Congressional Record at 108 Stat. 4325*

# *Interpreting DSHEA*

---

- ◆ *DSHEA is a dynamic law subject to interpretation*
- ◆ *FDA's implementation intended to balance Congress' intent and consumer protection*
- ◆ *No legislative history*
  - ◆ *Plain language of the statute*
  - ◆ *Statement of Agreement*
  - ◆ *Congressional Findings*
  - ◆ *Interpretation of Court Decisions and relevant case law*

# *Dietary Supplements Defined*

---

*...a product (other than tobacco) intended to supplement the diet that bears or contains one or more” designated ingredients...*

- ✦ Vitamin, Mineral, Amino acid
  - ✦ Not limited to “nutritionally recognized”**
- ✦ Herb or other botanical
  - ✦ Any part of a plant**
- ✦ Dietary substance for use by man to supplement the diet by increasing the total dietary intake*
- ✦ Concentrate, metabolite, constituent, extract, or combination of any ingredient above*

# *Dietary Supplement Defined*

---

- ◆ *A product that is intended for ingestion*
- ◆ *Pill, capsule, liquid, powder, “other”*
- ◆ *Not represented for use as conventional food*
  - ◆ *Delivery system may resemble conventional food forms*
- ◆ *Not a sole item of a meal or diet*
- ◆ *Labeled a “dietary supplement”*

# *Dietary Supplements Defined*

---

◆ *21 U.S.C. 321(ff)(3)*

◆ *Excludes articles that have been:*

◆ *approved new drug, antibiotic, or biologic*

◆ *authorized investigational new drug, antibiotic, or biologic for which such investigations have been made public...*

*UNLESS “Marketed as a dietary supplement or as a food before such approval or authorization”*

◆ *Relevant to OTCs with an approved NDA or IND under 21 U.S.C 351*



# *Regulatory Considerations for Dietary Supplements*

---

- ✦ *Relevant article of a Dietary Ingredient  
or a Drug*
- ✦ *Nature of the Product*
  - ✦ *Combination Products*
  - ✦ *Ingredient Amount Limitations*
- ✦ *Claims and Substantiation*

# *Relevant Article in Dietary Ingredients*

---

- ◆ *Pharmanex, Inc. v. Shalala, No. 2:97CV262K, 2001 WL 741419 (D. Utah, Mar. 30, 2001)*
  - ◆ *Red yeast rice and lovastatin*
- ◆ *Biostratum, Inc. Citizen Petition – July 29, 2005 (FDA Response ltr January 12, 2009)*
  - ◆ *Pyridorin (pyridoxamine dihydrochloride)*

# *Relevant Article in Dietary Ingredients*

---

## *Active Ingredient*

- “any component intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals”*
- 21 CFR § 210.3 (b)(7)*

## *Active Moiety*

- “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance”*
- 21 CFR § 314.108(a) & 21 CFR § 312.23(a)(7)(i)*

# *Relevant Article in Dietary Ingredients*

---

## *LOVASTATIN*

*Active ingredient in drug Mevacor*

*Active ingredient in supplement Cholestin*

*Marketed in supplement Cholestin*

*Active Ingredient same as Active Moiety*

## *PYRIDOXAMINE DIHYDROCHLORIDE*

*Active ingredient in drug Pyridorin*

*Pyridoxamine is the Active Moiety*

*Pyridoxamine studied for  
pharmacological relevance*

*Active Ingredient & Active Moiety Differ*

# *Relevant Article in Dietary Ingredients*

---

## ◆ *Active Moiety*

- ◆ *Orphan Drug Exclusivity [21 U.S.C. 360aa–360dd]*

- ◆ *Pediatric Marketing Exclusivity [21 U.S.C. 355a]*

- ◆ *Hatch–Waxman Marketing Exclusivity for New Drugs [21 U.S.C. 355j]*

## ◆ *No evidence of prior marketing as a dietary supplement or food before IND*

## ◆ *Conjunctive Elements of Dietary Supplement Definition*

- ◆ *Must satisfy all criteria of the definition*

## ◆ *CONCLUSION: Products containing pyridoxamine are not dietary supplements and may not be marketed as such*

# *Product Regulatory Concerns*

---

## ◆ *Combination Products*

◆ *Bayer HealthCare (FDA warning ltr – October 2008)*

◆ *Bayer Heart Advantage*

◆ *Bayer Women's Low Dose Aspirin + Calcium*

## ◆ *Supplement "Drinks"*

◆ *Redux Beverages, LLC (FDA ltr – July 2008)*

◆ *Cocaine Energy Drink*

## ◆ *Establishing Limits of Ingredients in Supplements*

◆ *Potassium & Iron*

# *Dietary Supplement Claims*

---

## ◆ *Health Claims*

- ◆ *Significant Scientific Agreement*
- ◆ *Qualified Health Claims*

## ◆ *Structure Function Claims*

- ◆ *Section 403(r)(6)*

# *Disease*

---

◆ *Drug: article intended to treat, cure, prevent, mitigate or diagnose a disease*

◆ *Disease or Health-Related Condition*

*“Damage to an organ, part, structure, or system of the body such that it does not function properly (e.g. Coronary heart disease, or a state of health leading to such dysfunctioning (e.g. hypertension) ”*

*(21 CFR 101.14(a)(5)) / 21 CFR 101.93(g)(1)*

# *“Dietary Supplement Claims”*

---

## ◆ *DSHEA (1994)*

- ◆ *Classical nutrient deficiency disease*
- ◆ *Effect on Structure or function of the body*
- ◆ *Mechanism of effect on structure/function*
- ◆ *General well-being*

*[21 U.S.C. 343 (r)(6)]*

# ***STRUCTURE/FUNCTION REGULATION***

---

- ◆ *January 6, 2000 Federal Register (65 FR 1000) [21 CFR §101.93]*
- ◆ *Not limited to serious diseases*
- ◆ *Act doesn't distinguish minor vs. serious conditions*
  - ◆ *Congress was silent on this matter*
- ◆ *Act requires to have substantiation that a claim is truthful and not misleading*

# ***STRUCTURE/FUNCTION REGULATION***

---

- ◆ *December 2008 – Guidance for Substantiation Made Dietary Supplement Claims made under 403(r)(6)*
  - ◆ *Amount, type, and quality of evidence*
  - ◆ *Describes the Agency's current thinking*
  - ◆ *Based upon case law regarding substantiation, Federal Trade Commissions experience and policy, and recommendations from the Commission on Dietary Supplement Labels*

# *What is the substantiation standard?*

---

## ◆ *“Competent and reliable scientific evidence”*

*“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”*

## ◆ *No pre-established formula on how many or what type of studies are needed*

## *What is the substantiation standard?*

---

- ◆ *How many or what type of studies are needed?*
  - ◆ *Will consider what the accepted norms are in the relevant research fields*
  - ◆ *Will consult experts in relevant disciplines*
  - ◆ *May accord deference to a standard developed by a government agency or other authoritative body*

## *Areas Considered For Substantiation Standard*

---

- ◆ *Meaning of the claim being made*
- ◆ *Relationship of the evidence to the claim*
- ◆ *Quality of the evidence*
- ◆ *Totality of the evidence*

## *Identifying the meaning of the claim*

---

- ◆ *Identify each expressed and implied claim*
- ◆ *If more than one reasonable interpretation, must substantiate each one*
- ◆ *Focus on not only individual statements, but expected effect or benefit being promoted when all statements are considered together*
- ◆ *Must substantiate the overall “message” contained when the claims are considered together*

# *Relationship of the evidence to the claim*

---

- ◆ *Similarities in formulation, serving size, route of administration, length/frequency of exposure*
- ◆ *Conditions of use similar to labeled conditions of use*
- ◆ *Presence of other substances that might affect actions?*
- ◆ *End-points appropriate to claimed effect*
- ◆ *Extent, nature, permanence of effect*
- ◆ *Level of scientific certainty*

# *The Quality of The Evidence*

---

- ◆ *Scientific quality of studies*
- ◆ *Type of evidence sufficient for experts in the area*
- ◆ *Clinical human studies*
- ◆ *Animal/in-vitro data supportive only*
- ◆ *Study design and conduct*
- ◆ *Data collection*
- ◆ *Statistical analysis*
- ◆ *Outcome measures*

# *Evidence that May Substantiate a Claim*

---

## ◆ *Primarily Human Studies*

### ◆ *Intervention*

◆ *Evaluate a product's direct effect*

◆ *Controlled exposure to treatment*

### ◆ *Observational*

◆ *Non-controlled exposure*

# *Background Information to Support A Claim*

---

◆ *Alone may not be adequate to support a claim*

◆ *Animal Studies*

◆ *In vitro Studies*

◆ *Testimonials or anecdotal evidence*

◆ *Meta Analysis*

◆ *Review articles*

◆ *Product Monographs*

# *Factors Affecting Study Quality*

---

## ◆ *Bias*

- ◆ *Demographics, number of subjects*

## ◆ *Cofounders*

- ◆ *Variability of dosage*

## ◆ *Quality Assessment Criteria*

- ◆ *Population assessments*

## ◆ *Assessment Intervention or Exposure Outcomes*

- ◆ *Appropriately measured dosing*

## ◆ *Peer Review*

- ◆ *Publication*

# ***Totality of Evidence***

---

- ◆ *All available evidence for quantity and quality*
- ◆ *Relevance of exposure*
- ◆ *Consistency and replication of findings*
- ◆ *All relevant research (favorable and unfavorable)*
- ◆ *Explanations for conflicts or inconsistency of the data*
- ◆ *No general rule for number or types of studies*
  - ◆ *Replication enhances that evidence is adequate*

# *SUMMARY*

---

- ◆ *DSHEA remains a dynamic law subject to interpretation*
- ◆ *FDA's implementation intended to balance Congress' intent and consumer protection*
- ◆ *Regulatory policy presents multiple issues for the agency to address*
  - ◆ *Determining if a product's relevant article (active moiety) is a dietary ingredient*
  - ◆ *Evaluating products' representation and dosage*
  - ◆ *Evaluating that permissible claims meet substantiation standards*

## *Additional References*

---

◆ *Defining disease claims:*

*<http://www.cfsan.fda.gov/~lrd/fr000106.html>*

◆ *Substantiation guidance – supplements*

*<http://www.cfsan.fda.gov/~dms/dsclmgu2.html>*

◆ *Defining health claims <http://www.cfsan.fda.gov/~dms/lab-hlth.html>*

◆ *Substantiation guidance – health claims*

*<http://www.cfsan.fda.gov/~dms/hclmgui6.html>*



***Kenneth M.P. Taylor, Ph.D.***

***Office of Nutrition, Labeling, and Dietary Supplements***

***Center for Food Safety and Applied Nutrition***

***5100 Paint Branch Parkway***

***College Park, MD 20740-3835***

***(301)436-2375***

***(301)436-2639 (fax)***

***[kenneth.taylor@fda.hhs.gov](mailto:kenneth.taylor@fda.hhs.gov)***