FDA Botanical Product Regulation, Quality, and Safety

Medicinal Herbs: drugs or dietary supplements? What are the legal consequences in terms of quality, safety and efficacy of each option?

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Regulation of Botanical Products in U.S.

- Foods, Flavours, Spices, Colors.
- Dietary Supplements
- Drugs
  - *–Non-Prescription*
  - *–Prescription*

Botanical Drug Product Definition

- A drug is an article intended to diagnose, cure, mitigate, treat, or prevent a disease.

- A botanical drug contains as ingredients vegetable materials, which may include plant materials, algae, macroscopic fungi, or combinations thereof. It may be available as (but not limited to) a solution (tea, e.g.), powder, tablet, capsule, elixir, topical or injectable.

- Excluded: fermentation products, highly purified [or chemically modified] botanical substances, genetically modified plants, allergenic extracts and vaccines which contain botanical ingredients

Botanical Drugs: Regulatory Objectives

- Not to create an additional category different from dietary supplements and non-botanical drugs
- Assure the same degree of confidence in quality and clinical usefulness of botanical drugs as non-botanical drugs
- To bring botanical drugs into the mainstream medical use in the U.S.

Basic Principles in the Botanical Final Guidance: June 6, 2004

- Further purification not required
- Identification of active constituents not essential
- Chemistry/Manufacturing controls will be extended to raw materials
- Non-clinical evaluations may be reduced or delayed
- Same level of clinical efficacy/safety requirements as non-botanical drugs

Botanical Applications in FDA (as of December 31, 2007)

- Total of 352 Applications
- 282 INDs (2/3 active); 70 pre-INDs
- 50 in ’90-’98, 302 in ’99-’07
- 3~4 new subm/month in recent yrs
- 40% commercial, 60% research
- 2/3 single herb, 1/3 multiple herbs

Laws Regulating Dietary Supplements

- Dietary Supplement Health and Education Act of 1994 (DSHEA) amended the Federal Food, Drug, and Cosmetic Act (FFDCA)
  - Defined the term dietary supplement
  - Included dietary supplements under the FFDCA adulteration provisions
  - Established requirements for new dietary ingredients

What is a Dietary Supplement?

- Vitamin, mineral, amino acid
- Herb or other botanical
- 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

Other Requirements for Dietary Supplements

- Intended for ingestion
- Pill, capsule, liquid, powder, “other”
- Cannot be represented as a:
  - Conventional food
  - Sole item of a meal
  - Total diet
- Must be labeled as a dietary supplement

Excluded As Dietary Supplements (DSs)

- Articles approved, or authorized for investigation, as a new drug, antibiotic, or biologic that were not first marketed as a dietary supplement or as a food

New Dietary Ingredients (NDIs)

- Those that were not marketed in the U.S. prior to October 15, 1994
- No authoritative list of dietary ingredients that were marketed before October 15, 1994
- The manufacturer of a dietary supplement is responsible for ensuring that it is safe before it is marketed in the U.S. FDA is responsible for taking action against any unsafe dietary supplements after they are marketed in the U.S.
- Manufacturers or distributors must submit a notification to FDA 75 days before a new dietary ingredient is marketed or introduced for marketing in the U.S.

NDI Premarket Notifications

- Amount of the NDI in the dietary supplement(s)
- Conditions of use recommended or suggested in the labeling of the dietary supplement(s)
- History of use or other evidence of safety establishing that the NDI, when used under the conditions recommended or suggested in the labeling, is reasonably expected to be safe.
- Reviewed in 75 days with NDI notification being placed on public display, at FDA's Documents Management Branch in Docket number 95-S-0316, 90 days after the "filing" date

Structure Function Claim Notification

- Mandatory notification of the FDA within 30 days of marketing (21 CFR 101.93)
- 30 day notification contains:
  - Name of the DS including the brand name
  - Name of the company marketing the product and a signature of the submitter
  - Text of the structure function claim (does not need to have the support for the statement included)
  - Name of the dietary ingredient/s in the DS that is subject of the claim
- November 4, 2004: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the FFDCA

Major Safety Concern: Contaminants

Heavy metals

- Environmental origin (i.e., lead) or Accumulated (i.e., arsenic)

– Non-metal environmental contaminants.

- Aflatoxins, Dioxins, Hydrocarbons, from drying with engine exhaust, etc.

– Intentional contaminants

- Steroids, Melamine, Drugs (Viagra)

– From contaminating plants

- Microcystin in blue-green algae
- Substitutions (Aristolochia)
- Other plants inadvertently collected
- Soil, insects, decomposition products, etc.
- Microbial

Current Dietary Supplement Good Manufacturing Practices (CGMP)

- June 25, 2007 - FDA published the DS CGMP rule.
- Require proper controls are in place so dietary supplements are processed in a consistent manner and produce a high quality product that is not adulterated with contaminants or impurities, and are accurately labeled.
- The DS CGMPs should help prevent inclusion of the wrong ingredients, too much or too little of a dietary ingredient, contamination (e.g. natural toxins, bacteria, pesticides, glass, and heavy metals such as lead), and improper packaging and labeling.

Enforcement Discretion

- The requirements of this final rule will not apply to certain health care practitioners based on enforcement discretion (acupuncturists, naturopaths, herbalist, etc.)
- Two potential safeguards : (1) adequate training in the professional practice and (2) an individual client and practitioner relationship.
- Enforcement discretion will not apply to practitioners who prepare batches of herbs and sell them to individual consumers without determining whether the dietary supplement is appropriate for each consumer's needs in a one-on-one personal consultation i.e. provide them for mass sale through the internet or retail outlets.

Major Requirements

- Effective August 27, 2007 the final rule codifies (CFR 21 part 111) the specific current good manufacturing practices (CGMPs) that must be used to manufacture dietary supplements.
- Final DS CGMP rule does not apply to raw ingredient manufacturers, although they will continue to need to meet the food CGMP regulations.
- The CGMPs apply to all domestic and foreign companies that manufacture, package, label or hold dietary supplements, including those involved with the activities of testing, quality control, packaging and labeling, and distributing them in the U.S.

Major Requirements

- Staggered three-year compliance inspection phase-in for small businesses. FDA inspections begin in June 2008 for large companies, June 2009 for companies with 20- 500 employees, and June 2010 for companies with fewer than 20 employees.
- The final rule is organized into 16 subparts that focus on specific aspects of the manufacturing process or addressing specific issues.

Major Requirements

The requirements include provisions related to:

- the design and construction of physical plants that facilitate maintenance,
- cleaning,
- proper manufacturing operations,
- quality control procedures,
- testing final product or incoming and in process materials,
- 100% testing for identity of incoming dietary ingredients
- handling consumer complaints, and
- maintaining records.

Dietary Supplement and Nonprescription Drug Consumer Protection Act

- Starting December 22, 2007 any serious adverse events reported to a manufacture must be reported to FDA through MedWatch 15 business days after the report is received
- Any new medical information must be reported to FDA within 1 year of the initial report and firms are required to maintain records of AERs for six years.
- Serious AERs are defined as death, a life threatening experience, in patient hospitalization, persistent or significant disability or incapacity, congenital abnormality or birth defect, or requires, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described under one of the above examples

What Guidance Does FDA Provide?

- Questions and Answers Regarding Adverse Event Reporting and Recordkeeping for Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act
  http://www.cfsan.fda.gov/~dms/dsaergui.html

- Questions and Answers Regarding the Labeling of Dietary Supplements as Required by the Dietary Supplement and Nonprescription Drug Consumer Protection Act
  - http://www.cfsan.fda.gov/~dms/dsaergu2.html