



Botanical Dietary Supplements: Helpful Hints for Pharmacists & Technicians

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September 21, 2013

ICHP COI Statement

- “Dr. Chapman has no actual or potential conflict of interest in relation to this presentation.”

Goals for the Day

Technicians	Pharmacists
Recognize the most common drug-herb interactions and contraindications for patients who seek botanical dietary supplements.	Identify patients who seek botanical dietary supplements that may be at risk for drug-herb interactions or in whom the use of botanical dietary supplements may be contraindicated.
Describe the requirements of cGMP's in the manufacture, handling and storage of dietary supplement products.	Discuss claims about dietary supplement usage with the patient in the appropriate context.
Select reference materials on botanical dietary supplements of appropriate reliability and validity.	Select reliable and valid information about botanical dietary supplements at an appropriate level of understanding.

Goals for the Day

Technicians	Pharmacists
Locate identifying marks on botanical dietary supplements products related to the assurance of product quality.	Recognize the most commonly adulterated types of botanical dietary supplements and the actions may be taken against their marketing.
Recognize the difference between homeopathic remedies & botanical dietary supplements.	Explain the meaning of homeopathic dosage notation.

In the Context of CAM

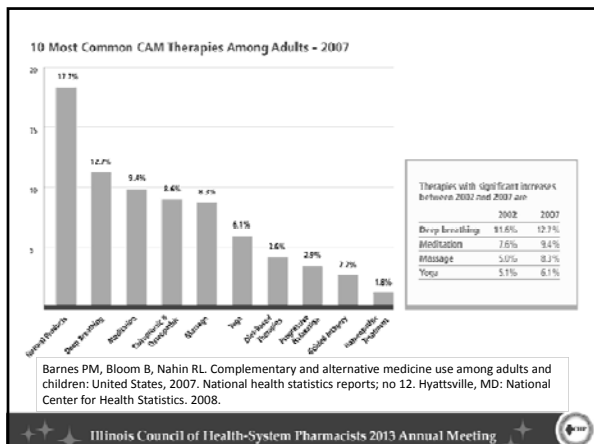
Complementary Alternative Medicine

- Complementary or Integrative Medicine
 - Non-conventional practices with conventional medicine
- Alternative Medicine
 - Non-conventional practices instead of conventional medicine

Examples of CAM

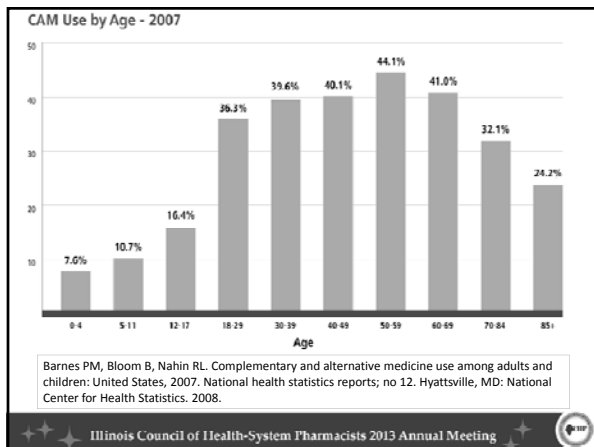
Top 10 Complementary	Approaches in Adults
Chiropractic	Massage
Deep breathing	Meditation
Diet-based therapy	Natural products
Guided imagery	Relaxation
Homeopathy	Yoga

Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. National health statistics reports; no 12. Hyattsville, MD: National Center for Health Statistics. 2008.



CAM Use On Average

- Women > men
- Higher levels of education
- Frequent medical visits recently
- Participate in leisure time physical activity
- Often for pain & other symptom relief
- Hopes to decrease risk of poor health later




“Can I Take This Supplement?”

- Common drug-herb interactions
 - Anticoagulant therapy
 - Cardiovascular agents
 - Psychiatric agents
 - Diabetes & blood glucose control
 - Laxatives
 - Antiviral therapy (HIV/AIDS)


“Can I Take This Supplement?”

- Allergy & hypersensitivity
 - The “daisy family” (*Asteraceae / Compositae*)
 - ❖ Ragweed allergy

Drug Herb Interactions

<ul style="list-style-type: none"> • Anticoagulants <ul style="list-style-type: none"> ➢ Pharmacodynamics <ul style="list-style-type: none"> ❖ Antiplatelet activity ❖ ↓ Platelet aggregation ➢ Pharmacokinetics <ul style="list-style-type: none"> ❖ Metabolic induction ❖ Metabolic inhibition ❖ Drug transport 	<ul style="list-style-type: none"> • Cardiovascular agents <ul style="list-style-type: none"> ➢ Pharmacodynamics <ul style="list-style-type: none"> ❖ Stimulants ➢ Pharmacokinetics <ul style="list-style-type: none"> ❖ Metabolic induction ❖ Metabolic inhibition ❖ Drug transport
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Drug Herb Interactions

- Psychiatric agents
 - Pharmacodynamics
 - ❖ Stimulants
 - ❖ Reuptake inhibition
 - Pharmacokinetics
 - ❖ Metabolic induction
 - ❖ Metabolic inhibition
 - ❖ Drug transport
- Diabetes & blood glucose control
 - Pharmacodynamics
 - ❖ ↑ Hypoglycemic effects



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Drug Herb Interactions

- Laxatives
 - Pharmacokinetics
 - ❖ Delayed absorption
 - ❖ ↓ Half-life
- Antivirals (HIV/AIDS)
 - Pharmacokinetics
 - ❖ Metabolic induction



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“The FDA Doesn’t Regulate Dietary Supplements, Do They?”

The FDA does regulate dietary supplements, but not as “drugs.”

- Dietary Supplement Health & Education Act of 1994 (DSHEA)
 - Amendments to the FDC Act

<http://www.fda.gov/Food/DietarySupplements/default.htm>

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Dietary Supplement

- A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following:
 - Vitamin
 - Mineral
 - Herb or other botanical
 - Amino acid

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Dietary Supplement

- A dietary substance for use by man intended to supplement the diet by increasing the total dietary intake, including a:
 - Concentrate
 - Metabolite
 - Constituent
 - Extract
 - Combination of any of the above ingredients

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Definitions

- A dietary supplement must take these forms:
 - Tablet
 - Capsule, softgel, gelcap
 - Powder
 - Liquid droplet
 - Some other form *not* represented as a food

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Disclaimers Must Appear On the Label

“The statements presented on this package have not been evaluated by the Food and Drug Administration.”

AND

“This product is not intended to diagnose, treat, cure or prevent disease.”

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Claims Allowed In Labeling (Structure/Function Claims)

- Any statements of nutritional support must be truthful and substantiated:
 - A statement that claims a benefit related to a classical nutrient deficiency disease, AND discloses the prevalence of such disease in the United States.
 - A statement that describes the role of a nutrient or dietary ingredient intended to affect structure or function in humans.

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Claims Allowed In Labeling (Structure/Function Claims)

- A statement that characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function.
- A statement that describes general well-being from consumption of a nutrient or dietary ingredient.
- ★ No statements or claims pertaining to disease are allowed, verbal or in print.

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Disease, Or Not Disease?

- Disease
 - Uncommon or serious conditions that may cause significant or permanent harm
- Not disease
 - Common conditions associated with natural states or processes that do not cause significant or permanent harm

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Examples



Allowed

- Supports and maintains prostate health
- Maintains healthy urinary tract function
- Promotes healthy serum lipid profile
- Helps maintain mental alertness & memory
- Helps maintain uterine tone and strength



Not allowed

- Useful for benign prostatic hyperplasia
- Prevents recurrent urinary tract infections
- Lowers high cholesterol
- Prevents Alzheimer's Disease
- Relieves symptoms of PMS

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“Is This a Good Quality Supplement?”

- Good manufacturing practices (cGMP's)
 - Defined by FDA in the Final ruling of June 2007
- Other compendial standards
 - US & worldwide
 - ❖ USP, ESCOP, British, Chinese or Indian Pharmacopeias, German Commission E
 - Misbranding: Represents meeting compendial standards, but fails to do so
- Exclusions
 - Homeopathic remedies

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Good Manufacturing Practices

- Consistency in processing
- Standards for product quality
 - Consistency of identity, purity, strength & composition
 - Operations design, construction, upkeep & maintenance
 - QA of source materials through to final product
- Mechanism for consumer complaints
- Recordkeeping
- Storage and distribution

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Common Failures with Compliance (How Manufacturers May Fail an FDA Inspection)

- Not performing required identity testing on incoming dietary ingredients.
- Not setting appropriate specifications for components and dietary supplements.
- Failure to adopt written procedures, as required in the rule (Lack of documentation).

Baginsky C, May 2011. Recent GMP audits of supplement makers reveal common compliance problems. <http://newhope360.com/regulation-and-legislation/recent-gmp-audits-supplement-makers-reveal-common-compliance-problems>, accessed 8-6-13.

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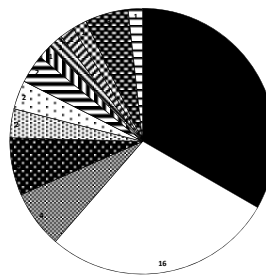
Common Failures with Compliance (How Manufacturers May Fail an FDA Inspection)

- Inadequate preparation and/or failure to follow Master Manufacturing Records and/or Batch Production Records for the manufacture of dietary supplements.
- Personnel charged with conducting required material reviews and making disposition decisions are not qualified to do so.

Baginsky C, May 2011. Recent GMP audits of supplement makers reveal common compliance problems. <http://newhope360.com/regulation-and-legislation/recent-gmp-audits-supplement-makers-reveal-common-compliance-problems>, accessed 8-6-13.

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Dietary Supplement Recalls Sept. 2012 – Aug. 2013



- Male enhancement supplement Undeclared PDE-5 inhibitors
- Weight loss supplement Sibutramine with/without phenolphthalein
- ▨ Weight loss supplement DMAA
- Protein supplement Undeclared soy / milk / shellfish / coconut
- ▨ Natural antioxidant (pomegranate seeds)
- ▨ Hepatitis A contamination
- ▨ Joint health supplement Undeclared soy & milk allergens
- Anti-aging supplement cont. turmeric Metal fragments
- Sleep aid supplement Doxepin
- ▨ Vitamin / multivitamin Anabolic steroid
- ▨ Vitamin / multivitamin Undeclared milk protein & lactose
- ▨ Probiotic supplement Undeclared soy
- Prebiotic supplement Salmonella contamination
- ▨ FeSO4 325 mg tablets substituted with medicine HCl 25 mg tabs

US FDA, Archive for Recalls, Market Withdrawals & Safety Alerts <http://www.fda.gov/Safety/Recalls/ArchiveRecalls/default.htm>, accessed August 9, 2013.

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Marks That Identify a Good Quality Dietary Supplement

- USP <http://www.usp.org/usp-verification-services>
 - USP Verified Dietary Supplements Program
 - ❖ Voluntary to manufacturers
 - ❖ Contains the ingredients listed on the label
 - » Declared potency & amounts
 - ❖ Breaks down & release into the body
 - » Specified amount of time
 - ❖ Prepared according to FDA cGMP's
 - ❖ Less than harmful levels of contamination

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Marks That Identify a Good Quality Dietary Supplement

- USP <http://www.usp.org/usp-verification-services>
 - USP Verified Dietary Ingredients Program
 - ❖ Voluntary to manufacturers
 - ❖ Consistent in quality, batch to batch
 - ❖ Meets label or certificate of analysis claims
 - » Identity, strength, purity, and quality
 - ❖ Prepared according to accepted manufacturing practices
 - ❖ Meets acceptable limits of contamination

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Marks That Identify a Good Quality Dietary Supplement

- ConsumerLab.com, LLC <http://www.consumerlab.com>
 - Independent testing lab & contract analytical labs
 - ❖ Dietary supplements & generic drugs
 - » Identity & ingredient quality
 - » Purity, Strength & Disintegration
 - Manufacturer pays for testing
 - ❖ Tested products obtained from the market
 - Published reviews online
 - ❖ Unlimited access with membership

Marks That Identify a Good Quality Dietary Supplement

- NSF International Mark <http://www.nsf.org>
(National Sanitation Foundation International)
 - Independent testing lab, voluntary certification
 - ❖ Verification of the labeled contents
 - ❖ Assurance that all ingredients present are disclosed on the label
 - ❖ Assurance of no unacceptable levels of contaminants



Marks That Identify a Good Quality Dietary Supplement

- Others
 - Natural Products Association (NPA)
 - ❖ GMP Certification Program – Quality of process
 - ❖ TrueLabel Program – Ingredient identity
 - Manufacturer symbols
 - ❖ Reliability??

“Where Can I Find Valid, Reliable Information For Myself & My Patients?”

- Online and/or print
 - Government sites
 - Databases for professionals & patients
 - Private testing labs
 - Manufacturer web sites
 - ❖ Often subject to commercial bias
 - Professional Associations

“Where Can I Find Valid, Reliable Information For Myself & My Patients?”

- Mobile Apps
 - Lexicomp®
 - My DS
 - Natural Medicines Comprehensive Database

Government Sponsored Sites

FDA Center for Food Safety & Applied Nutrition (FDA CFSAN)
<http://www.fda.gov/Food/DietarySupplements/default.htm>

NIH National Center for Complementary & Alternative Medicine (NCCAM)
<http://nccam.nih.gov/>

NIH Office of Dietary Supplements (NIH ODS)
<http://ods.od.nih.gov/>

NIH ODS Link to PubMed Dietary Supplements Subset
http://ods.od.nih.gov/Research/PubMed_Dietary_Supplement_Subset.aspx

Databases

The Natural Standard
<http://www.naturalstandard.com/>
 Natural Medicines Comprehensive Database (Professionals)
<http://naturaldatabase.therapeuticresearch.com>
 Natural Medicines Comprehensive Database (Consumers)
<http://naturaldatabaseconsumer.therapeuticresearch.com>
 Cochrane Reviews
<http://www.cochrane.org/>

Private Testing Labs

United States Pharmacopeia (USP)
<http://www.usp.org/dietary-supplements/overview>
 ConsumerLab.com, LLC
<http://www.consumerlab.com/>
 National Sanitation Foundation International (NSF)
http://www.nsf.org/consumer/dietary_supplements/index.asp?program=DietarySup

Other

World Health Organization (WHO)
<http://www.who.int/medicines/areas/traditional/en/index.html>
 American Botanical Council
<http://abc.herbalgram.org/site/PageServer>
 Natural Products Association
<http://www.npainfo.org/>
 Herbal Research Foundation
<http://www.herbs.org/herbnews/>
 American Society of Pharmacognosy
<http://www.pharmacognosy.us/>

“What is Homeopathy?”

- Discredited in the Flexner Report of 1910
 - Pseudoscience; unscientific basis; unethical
- Resurgence in 1938
 - Homeopathic Pharmacopeia of the US (HPUS)
 - Elixir sulfanilamide accident
- Assertion of Davenas & Benveniste in *Nature*, 1988
 - “Memory of water” as mechanism of activity in dilutions
 - ❖ Discredited as flawed & biased
- Dilute remedies considered very safe
 - Belladonna in teething remedies (FDA Oct. 23, 2010)
 - Homeopathic HCG (FDA & FTC Nov. 28, 2011)

“What is Homeopathy?”

- ‘Alternative’ medical modality advanced in the late 18th Century
 - “Law of similars” - Let like cure like
 - ❖ That which causes a symptom in a normal, healthy person cures a person ailing of such symptom
 - “Law of infinitesimals”
 - ❖ Serial dilution & succussion of remedies
 - Succussion – vigorous shaking with impact on an elastic surface
 - “Law of proving”
 - ❖ Finding out what substances cause symptoms in people when given in non-dilute doses

Homeopathic Products & Labeling

- Recognized & regulated as drugs (HPUS)
- Requirements in 21 CFR 206, 211 & 503
 - Required to be identified as ‘homeopathic’ 21 CFR 206.10(a)
 - Exempt from expiration dating 21 CFR 211.137(e)
 - Must be stable in original container & not degraded within expected time of use 21 CFR 211.166(e)
 - OTC sales limited to remedies for self-limiting conditions 21 CFR 503(b)

Homeopathic Products & Nomenclature

Latin Terminology


- “crudum” = crude
- “radix” = root
- “flos” = flowering parts
- “herba” = leaves

Mother Tincture

- Original extract or preparation

Common dosage forms

- Multiple units per dose taken at frequent intervals
 - Tablet triturates
 - ❖ Lactose
 - Pellets
 - ❖ Sucrose



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Homeopathic Products & Nomenclature

Dosage Notation

- **Decimal Dilution “X”** Numbers in front of the Roman numeral indicates the number of dilutions.
 - 10-fold serial dilution of the Mother Tincture
- **Centesimal Dilution “C”**
 - 100-fold serial dilution of the Mother Tincture
- **Millesimal Dilution “M”**
 - 1000-fold serial dilution of the Mother Tincture

- 6X is diluted 1:10 parts, 6 times (1:10^{1X6})
- 3C is diluted 1:100 parts, 3 times (1:10^{2X3})

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Final Thoughts on Homeopathy

- World-wide popularity
- Does it work?
 - Effectiveness in self-limiting conditions may involve more than the remedy itself
 - ❖ Rest, fluid intake, avoidance of salt, caffeine, etc.
 - Evidence basis
 - ❖ Cochrane Database publishes reviews of homeopathy as a treatment modality in variety of disorders

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✓ Recognize the most common drug-herb interactions and contraindications for patients who seek botanical dietary supplements.	Identify patients who seek botanical dietary supplements that may be at risk for drug-herb interactions or in whom the use of botanical dietary supplements may be contraindicated.
✓ Describe the requirements of cGMP’s in the manufacture, handling and storage of dietary supplement products.	Discuss claims about dietary supplement usage with the patient in the appropriate context.
✓ Select reference materials on botanical dietary supplements of appropriate reliability and validity.	Select reliable and valid information about botanical dietary supplements at an appropriate level of understanding.

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✓ Recognize the difference between homeopathic remedies & botanical dietary supplements.	Explain the meaning of homeopathic dosage notation.

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References

1. Barnes PM, Bloom B, Nahin RL. *Complementary and alternative medicine use among adults and children: United States, 2007*. National health statistics reports; no 12. Hyattsville, MD: National Center for Health Statistics; 2008.
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3. US Food and Drug Administration, Dietary Supplements. Available at: <http://www.fda.gov/Food/DietarySupplements/default.htm>. Updated May 21, 2013, Accessed August 6, 2013.
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Botanical Dietary Supplements: Helpful Hints for Pharmacists and Technicians
0121-0000-13-059-L01-P
0121-0000-13-059-L01-T
Robert Chapman, PhD

Post Test Questions – Pharmacists:

1. Patients taking ____ may be at risk for interactions with several botanical dietary supplements.
 - A. Clarithromycin
 - B. Prednisone
 - C. Ranitidine
 - D. Warfarin
2. Which of the following claims is appropriate in the context of discussing dietary supplements?
 - A. Useful for benign prostatic hyperplasia
 - B. Lowers high cholesterol concentrations
 - C. Prevents recurrent urinary tract infections
 - D. Helps maintain mental alertness & memory
3. Which site is **LEAST** likely to offer valid, reliable information about dietary supplements to both professionals and consumers?
 - A. Manufacturer's web site
 - B. Independent testing lab
 - C. Comprehensive database
 - D. Government sponsored site
4. During 2012-2013, the most commonly adulterated dietary supplements withdrawn from the market were promoted for:
 - A. Cardiovascular and joint health
 - B. Male enhancement and weight loss
 - C. GI health and sleep aids
 - D. Nutrition and anti-aging
5. Which of the following is **TRUE** for a homeopathic formulation of *Arnica montana* tablets, 30X?

The mother tincture is serially diluted:

- A. 1:10 parts, 30 times
- B. 1:30 parts, 10 times
- C. 1:100 parts, 3 times
- D. 1:300 parts, 10 times

Post Test Questions – Technicians:

1. The most common drug-herb interactions occur in patients taking:
 - A. Antibiotics
 - B. Anticoagulants
 - C. OTC antihistamines
 - D. Anti-inflammatories

2. Which of the following is NOT required of dietary supplement manufacturers under the rules for cGMP's?
 - A. A mark indicating product testing by an independent lab
 - B. Consistency in all phases of the manufacturing process
 - C. Recordkeeping in all phases of the manufacturing process
 - D. Standards for product identity, purity, strength & composition

3. Which government sponsored Internet site, is likely to offer valid, reliable information about dietary supplements to both professionals and consumers?
 - A. ConsumerLab.com
 - B. NIH Office of Dietary Supplements
 - C. The Natural Standard Database
 - D. American Botanical Council

4. A gold circle with a green border superimposed by a black oval with a gold border describes the mark of the:
 - A. ConsumerLab.com, LLC Independent Testing Labs
 - B. National Sanitation Foundation International
 - C. Natural Products Association TrueLabel Program
 - D. USP Verified Dietary Supplements Program

5. Which of the following is **TRUE** about the labels of homeopathic products?
The label must show:
 - A. The word, "homeopathic"
 - B. The expiration date of the product
 - C. The amount of the active ingredients in mg
 - D. The statement, "This product is not intended to cure disease"