FDA’s Dietary Supplement Programs: an Update

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Agenda

• The Bottom Line
• Headlines/Regulatory Cases/Enforcement Tools
• The Law/Definition of Dietary Supplement
• Reviewing a DS Label/Claims Made for DS Products
• New Dietary Ingredient Notification (NDIN) Status
• Good Manufacturing Practices (GMPs)
• Adverse Event Reports (AERs)
• Guidance
• The Take Home
The Bottom Line

- $32.5 Billion USD – Industry (NBJ 2012) +
- Industries within Industry +
- 140 spiked products (2012-2013) +
- 150 Million Americans taking Dietary Supplements +
- 31% Official Action Indicated from cGMPs (2013) +
- only 40-50 NDINs annually + 845 NDINs total since DSHEA +
- IOM estimated in 2004--1,000 new DS introduced each year. Only 4,000 products at the time of DSHEA passage. DSLD—35,450 +
- Per the Dietary Supplement GMPs (21 CFR Part 111) approx. 1,440 firms (including manufacturers, packagers, labelers, holders, distributors, and warehousers) are out there +
- Regulation accomplished by 20+ FTEs within DDSP = Low Risk? +
DMAA in Dietary Supplements

July 16, 2013

DMAA, also known as 1,3-dimethylamylamine, methylhexanamine or geranium extract, is an ingredient found illegally in some dietary supplements and often touted as a "natural" stimulant. DMAA, especially in combination with other ingredients such as caffeine, can be a health risk to consumers. Ingestion of DMAA can elevate blood pressure and lead to cardiovascular problems ranging from shortness of breath and tightening in the chest to heart attack. Dietary supplements containing DMAA are illegal and FDA is doing everything within its authority to remove these products from the market. In 2012, FDA issued warning letters to companies notifying them products with DMAA need to be taken off the market or reformulated to remove this substance. Most companies warned are no longer distributing products with DMAA. While FDA is working to get these products off the market, consumers should not buy or use any dietary supplement product containing DMAA.

On July 2, 2013, as a result of follow-up legal action by FDA, the dietary supplement firm USPlabs voluntarily destroyed its DMAA-containing products located at its facility in Dallas, Texas. The products - USPlab's OxyElite
Reumofan Plus/Reumofan Plus Premium/WOW

* Claims to treat arthritis, bone cancer, osteoporosis and more
* Dozens of serious injuries reported to FDA
* Contains at least 3 hidden Rx drugs: dexamethasone, diclofenac, methocarbamol
Fraudulent Claims

Can a Dietary Supplement Treat a Concussion? No

- Get Consumer Updates by E-mail
- Consumer Updates RSS Feed
- Print & Share (PDF 864 k)

En Español

On this page:
- The Claims

Exploiting the public's rising concern about concussions, some companies are offering untested, unproven and possibly dangerous products that claim to prevent, treat or cure concussions and other traumatic brain injuries (TBIs).

The Food and Drug Administration (FDA) is monitoring the marketplace and taking enforcement actions where necessary.
Beware of Illegally Sold Diabetes Treatments

Search the Consumer Updates Section

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Watch YouTube video "Don't Fall For False Promises"
Get Flickr photos of illegally sold diabetes treatments
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Articulo en español

On this page:
- Warning Letters issued
- A Far Reaching Problem

As the number of people diagnosed with diabetes continues to grow, illegally sold products promising to prevent, treat, and even cure diabetes are flooding the marketplace.

The Food and Drug Administration (FDA) is advising consumers not to use such products. They may contain harmful ingredients or may be otherwise unsafe, or may improperly be marketed as over-the-counter (OTC) products when they should be marketed as prescription products. They carry an additional risk if they cause consumers to delay or discontinue effective treatments for diabetes. Without proper disease management, people with diabetes are...

Sound Too Good To Be True?

Then it's probably a scam. Watch out for these and similar red flags:

- "Lowers your blood sugar naturally!"
- "Inexpensive therapy to fight and eliminate type II diabetes!"

![Image of diabetes natural miracle products]
Research


• -- Known biogenic amines— phenethylamine (PEA), N-methyl phenethyl- amine, tyramine, N-methyltryptamine, tryptamine and N-methyltryptamine

• ---Relative amounts of amines differ significantly in dietary supplements

• -- Twenty of 21 products contained large amounts of PEA

• -- β-methylphenethylamine found in 9 of 21 products – included in the group S6 – stimulants list and is prohibited in sports competition
Polling Question 1

True or False?

New Dietary Ingredients Notifications are the only premarket preventive control with respect to the regulation of dietary supplements.
What Can FDA Use?

- cGMPs
- Serious Adverse Event Reports (SAERS)
- Labeling, Facility Registration, etc.
- New Dietary Ingredient Notifications (NDINs)

* NDINs are the only premarket preventive control with respect to the regulation of dietary supplements
Polling Question 2

True or False

The Council for Responsible Nutrition and the Natural Products Association, two dietary supplement industry trade groups, provided to FDA two authoritative lists of dietary ingredients that were marketed prior to October 15, 1994.
Reviewing a “dietary supplement” entry

– Is it a dietary supplement?
– Does it contain dietary ingredients? (there is no authoritative list) (Herbs of Commerce, one of the industry trade grandfathered lists [NNFA, CRN], or other electronic database)
– Are there any “new dietary ingredients” for which notice is required?
– Does it have acceptable identity and “supplement facts” labeling?
– Are there disease or structure/function claims in labeling?


What is a dietary supplement?

- Defined in section 201(ff) of the FFD&C Act (21 U.S.C. § 321(ff)(1))

- “…a product (other than tobacco) intended to supplement the diet that bears or contains one or more...” dietary ingredients
What are dietary ingredients?

- Vitamin, mineral, amino acid
  - Not limited to “nutritionally essential”
- Herb or other botanical
  - The whole or any physical part of a plant
- Dietary substance for use by man to supplement the diet by increasing the total dietary intake
- Extract, constituent, combination, concentrate, metabolite of any of above
“Dietary substance for use by man”

– Of or pertaining to the usual food or drink of man
  – Does not mean “any” substance
  – Not limited to US diet
  – Limited to human use
– does not include human tissue, pathogenic bacteria
Polling Question 3

Which of the following could be a dietary supplement?

a) A probiotic containing suppository
b) A zinc containing lozenge.
c) A vitamin mineral containing transdermal patch.
d) A human placenta containing product.
“Intended for Ingestion”

– Ordinary and plain meaning of “ingestion”
– Take into stomach and gastrointestinal tract enterally
– Not include:
  – External/topical products, patches
  – Mouthwashes, rinses
  – Nasal/inhaled products
  – Sub-linguals
  – Injection, suppository

21 U.S.C. § 321 (ff)(2)
Types of Dietary Supplement Claims

- Prohibited Disease Claims
- Permissible Health Claims
- Nutrient Content Claims
- Permissible Structure/Function Claims/Disclaimer
  + Affect the normal structure/function of the body
  + Well-being
  + Nutrient deficiency disease claims
“Structure-Function” Claims

• May not claim to diagnose, treat, cure, or prevent any disease

• Disease defined in 21 CFR 101.93(g)(1)

  “[D]amage to an organ, part, structure, or system of the body such that it does not function properly...or a state of health leading to such dysfunctioning...”

• See January 6, 2000 Federal Register (65 FR 1000)
Category of Dietary Ingredient by 201(ff)(1) Type (total unique notifications = 587)

- 201(ff)(1)(A) Vitamin
- 201(ff)(1)(B) Mineral
- 201(ff)(1)(C) Herb or other botanical
- 201(ff)(1)(D) Amino Acid
- 201(ff)(1)(E) A dietary substance for use by man to supplement the diet
- Not a dietary ingredient
- Not provided
FDA Response Letters (RLs): Unique notifications 1995 to August 6, 2014 (total notifications: 587)

- 234, 40%: AKL Acknowledge with no objections
- 190, 32%: IAL Inadequate chemistry or safety data
- 85, 15%: ICL Incomplete Notification
- 78, 13%: NDL Not a dietary ingredient
cGMPs - 21 CFR Part 111

- Authorized FDA to create and promulgate under DSHEA
- Final Rule published in 2007
- 3 year phase-in based on business size
- 1st Warning Letter issued in 3/2010
Current Good Manufacturing Practice (CGMP)s

• Identity, purity, quality issues
  – Identification
  – Contaminants (chemical, filth, pesticides, microorganisms, drugs)
  – Economic adulteration
• Apply to all domestic/foreign firms
• Do not apply to raw material manufacturers

Dietary Supplement Inspections

![Bar Chart]

- Inspections Completed: 308
- No Action Indicated: 76
- Voluntary Action Indicated: 68
- Official Action Indicated: 37
- % Official Action Indicated: 20
- Total: 579

**FY 2013 Domestic**
2013 Dietary Supplement Inspection Outcomes
Hidden Ingredients

- Prescription drug ingredients, including controlled substances
- Analogues of prescription drug ingredients
- Unapproved scheduled controlled substances
- Ingredients with an IND and under clinical investigation
- Novel ingredients that have never been studied in humans
- Ingredients approved as drugs in other countries
- Ingredients that have been removed from the US market for safety reasons
Sexual Enhancement Products (2012-2013)

--90 recalled products
--1 consumer warning (counterfeit ExtenZe)

Hidden Ingredients:

- **sildenafil** – erectile dysfunction drug (Viagra)
- **sulfoaildenafil** — analogue of sildenafil
- **dimethylsildenafil** – analogue of sildenafil
- **dimethylacetildenafil** – analogue of sildenafil
- **desmethylcarbodenafil** – analogue of sildenafil
- **noracetildenafil** – analogue of sildenafil
- **tadalafil** – erectile dysfunction drug (Cialis)
- **aminotadalfil** – analogue of sildenafil
- **thioaidenafil** – analogue of sildenafil
- **vardenafil** – erectile dysfunction drug (Levitra)
- **dapoxetine** – not approved in U.S. (studied as antidepressant and approved in some countries for premature ejaculation)

**Examples:**

- STUD Capsules
- Extenze Tablets
- X-Rock
- Firminte
- Libigrow
- Casanoa
- Night Bullet
- AFFIRM XL
- Super Cheetah
Weight Loss Products (2012-2013)

- 53 recalled products
- 39 Public Notifications

Hidden Ingredients:

**sibutramine** – controlled substance and obesity drug (withdrawn due to safety concerns)

**n-desmethylsibutramine** – analogue of sibutramine

**n-di-desmethylsibutramine** – analogue of sibutramine

**phenolphthalein** – cancer-causing risk

**ephrine alkaloids** – cardiovascular stimulant

**fluoxetine** – antidepressant

**triamterene** – diuretic

Examples:

Ultimate Formula Bee Pollen
Fat Zero
Bethel 30
Beautiful Slim Body
Super Slim
1 Day Diet
Slim Max
Be Inspired
Notable Recent Actions

2014 Recalls and Alerts

- **Mezo** – weight loss – benyzlsibutramine
- **Full Throttle On Demand** – sexual enhancement – propoxyphenyl sildenafil
- **24 Ince** – weight loss – sibutramine
- **3 Hard Knights** – sexual enhancement – Viagra
- **Toxin Discharged Tea** – weight loss – fluoxetine
- **Weekend Warrior** – sexual enhancement -- thiosildenafil
- **SexRx** – sexual enhancement – Viagra and Cialis
- **LX1** – weight loss – DMAA
- **Pro ArthMax** – joint muscle/arthritic pain – diclofenac, ibuprofen, naproxen, indomethacin (previous 4, non-steroidal anti-inflammatory drugs), nefopam (non-narcotic pain relieving drug), chlorzoxazone (muscle relaxant)
- **Arth-Q** – joint muscle/arthritic pain – ibuprofen
- **Japan Hokkaido Slimming Weight Loss** – weight loss – sibutramine, benzocaine (local anesthetic), phenolphtalein and diclofenac
Recalls, Market Withdrawals, and Safety Alerts
http://www.fda.gov/safety/recalls/default.htm

Tainted Sexual Enhancement Products
http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/medicationhealthfraud/ucm234539.htm

Tainted Weight Loss Products
http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/medicationhealthfraud/ucm234592.htm

Tainted Body Building Products
http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/medicationhealthfraud/ucm234523.htm
Import Alerts

- Import Alert #54-14, 4/1/14—Detention without Physical Examination (DWPE) of Dietary Supplement Products from Firms which have not met Dietary Supplement GMPs

- #54-15, 6/16/14—DWPE of Dietary Supplements and Bulk Dietary Ingredients that are or contain *Mitragyna Speciosa* or Kratom – toxicity of multiple organ systems
Guidance for Industry: Distinguishing Liquid Dietary Supplements from Beverages

- Beverages—conventional foods that may NOT be marketed as dietary supplements
- Factors that Distinguish Beverages from Liquid Dietary Supplements—labeling/advertising; product name; product packaging; serving size/recommended daily intake; marketing practices; composition; representations about a product
- Powdered premix products and liquid concentrates may be dietary supplements—when labeled as dietary supplements, provided they are not represented for beverage use or as alternatives to beverages.
- Regulatory requirements for ingredients of beverages and liquid dietary supplements
- Dietary supplement must comply with applicable labeling requirements
The Take Home

• Consumers should have access to dietary supplements that meet quality standards, that are free from contamination and are accurately labeled.
Thanks

- ONLDS: Cara Welch, Fred Hines
- OC: Mallory Kelly, “Matt” Albright, Laurie Bates
- ORA: Gary Coody, Jason Humbert
Questions about:

Structure/Function Claims vs Disease Claims
Report fraudulent products
DS label/labeling questions
DS regulations

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