The Regulatory Environment, the FDA, Classification of Dietary Supplements and Role of Patents on development of herbal drugs

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New Use Agriculture & Natural Plant Products Program
Department of Plant Biology and Pathology
NJAES and Cook College, Rutgers University
Outline

- Dietary supplements/Functional foods/Phytomedicines, the market status and regulations in the USA
- Major steps for botanical drug development under our US Federal Drug Administration (FDA) with Veregen as a case study
- Phytomedicines in Europe
Nature’s most powerful healing combination is right in your kitchen!

OLIVE OIL & GARLIC CURES:

ARTHRITIS • BLADDER INFECTIONS • CANCER
CANKLES • CHOLESTEROL • Colds • FATIGUE
HEARING LOSS • HEART DISEASE • HIGH BLOOD PRESSURE • IMMUNE SYSTEM IMPOTENCE
INFLUENZA • LONGEVITY • SKIN PROBLEMS • SORE MUSCLES • WEIGHT

ARTHABITIS PAIN! TIRENESS! Colds & Flu!
Say goodbye to hospitals, doctors and high medical bills!

MIRACLE HOME REMEDIES!

You can create miracle cures for dozens of common ailments in your own home, easily and cheaply, says a top medical expert.

The amazing home remedies are rapid and extremely effective, according to Anthony G. Fielding, a leading researcher and author of more than a dozen books. "And no one has to worry about the side effects," he adds. "If symptoms persist, consult your family physician immediately."

Many of these cures are far easier to create than physician-prescribed treatments. In Fielding's words, "You cannot make a cure that is more effective than nature's own."

Here are some tips from Dr. Fielding on how to create these treatments:

- DIARRHEA
- FLU
- HEMORRHOIDS
- OSTEOPOROSIS
- ARTHRITIS
- BACK PAIN
- GENITAL HERPES
- INFERTILITY
- ASTHMA
- COLD
- HEADACHES
- INSOMNIA
- BAD BREATH
- CONSTIPATION
- KIDNEY STONES
- BLADDER INFECTIONS
- CALLUSES
- PMS
- ATHLETE'S LOG
- BODY ODOR
- ECZEMA
- HEARTBURN
- KIDNEY STONES

They're cheap, easy to use — & available in supermarkets everywhere!
BIBLE CURES Revealed!

TOP HERBALISTS and doctors agree: the Bible is more than a historical document and religious relic – the Good Book is also a great guide to a longer, healthier and happier life.

The Bible is chock full of miracle cures that use standard healing herbs to treat a variety of disorders. These herbs are medicines in the truest sense of the word, plants that can help humans.

Herbs... the crux of ancient medicine.

HERBS not only help the body process and absorb nutrients, but also to detoxify and nourish. Herbs are powerful medicines, and are especially effective today as conventional medicine becomes increasingly drugs-based.

Herbal Medicine... back to the future.

Herbs have been shown to help treat a variety of conditions... including colds, heart disease, colds, thyroid disorders, diabetes and more.

Herbs are simple medicines... made from the plants that we eat.

Herbs are safe... when used appropriately.

Herbs can help anyone, at any age.

HERBS have been used for thousands of years. 

Herbs are not synthetic... they are made from pure plant materials.

Herbs... the food of the future.

Herbs are safe when used appropriately.

HERBS are the medicine of today.

Herbs can help everyone, at any age.
How To Burn Off Body Fat Hour by Hour
With 14 Amish Folk Medicine Ingredients

An amazing book called The Wisdom of Amish Folk Medicine reveals 14 Amish folk medicine ingredients that promise fast weight loss. You can start losing weight the very first day. In addition, it also gives you over 700 drug-free home remedies and folk medicine for many everyday health problems.

The Amish philosophy is “What's old is the good.” They claim their folk medicines handed down from generation to generation, still work today for everything from colds to age-pretz: foot fungus.

An encyclopedia of their natural health secrets, called The Wisdom of Amish Folk Medicine, is now available to the general public. It has hundreds of proven home remedies using simple items you have around your home like vinegar, salt, soda, onions—even olive oil. You’ll be amazed at the ordinary spices and herbs the Amish use for their health qualities.

This extraordinary health guide was inspired by a collection of little-known folk medicine gathered by the home remedy editor of a magazine published for the Amish.

Speaking of these health secrets, she says, “A doctor was usually called at a last resort, after everything else failed, and this wasn’t often.”

Step back to simpler times with the Amish natural folk medicine secrets for common health problems like these:

- **Backache**? This home-made liniment has been used for years to relieve aches and pains.
- **Poor memory**? The Amish trust this common seed to sharpen the memory.
- **Can't take aspirin**? Discover the natural ingredients that have pain killing properties.
- **Allergies**? Learn how to use nature’s antihistamine.
- **Arthritis pain**? An all-natural tonic can give hours of relief.
- **Prostate trouble**? A good dose of this ordinary tea is the Amish secret.
- **Want to stop smoking**? Learn age-old ways to kick the habit.
- **Trouble sleeping**? This simple remedy is said to induce a peaceful slumber.
- **Nervous**? Enjoy this little tranquility without drugs.
- **Thinning hair**? Proof of this remedy is seen in Amish people’s luxuriant hair and beards.

The Wisdom of Amish Folk Medicine also reveals natural health tips for: constipation, cold sores, menopausal problems, sinus trouble, hemorrhoids, varicose veins, age spots, flu and more.

These are only a few of the many trusted home remedies in The Wisdom of Amish Folk Medicine. Learn how to make “Go Back” drops, the Amish stomach remedy. Prepare their “Green Mountain Salve” for boils and sores. Mix up some “Good Samaritan Oil” for colds. Discover 6 ways to relieve muscle cramps, how the Amish use red beets to fight infection, which vegetables and fruits can cleanse and heal, and the Amish natural weight loss method that promises good results.

After a tiring day, you might want to try the Amish care for an aches muscle. That’s their need for the aches that come from a long buggie ride, but it works for any kind of muscle fatigue.

Right now, as part of a special introductory offer, you can receive a special press run of The Wisdom of Amish Folk Medicine for only $6.95 plus $1 postage and handling. Your satisfaction is 100% guaranteed. You must be completely satisfied, or simply return it within 90 days for a full refund

**HERE’S HOW TO ORDER:** simply print your name and address and the words “Amish Folk Medicine” on a piece of paper and mail it along with a check or money order for only $6.95 to: THE LEADER CO., INC. Publishing Division, Dept. AM602, P.O. Box 3347, Canton, Ohio 44711. (Make checks payable to The Leader Co., Inc.)

**6 STEPS TO STOP BACK**

**Let the who's talk back. You problem in the following seven steps from a top expert...**

“Even the shrewd child who gives his parents... says Chris Brown.

For you see, New York psychotherapist good news is that have to put our... CAN be cured.

Here are steps to succeed your child to... back:

1. **Start every child with a warm bath into a pattern... young as they... back, so deal... immediately.**

When you look to your firmly repeat...
Congress defined: A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The "dietary ingredients" in these products may include: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. They can also be in other forms, such as a bar, but if they are, information on their label must not represent the product as a conventional food or a sole item of a meal or diet. Whatever their form may be, DSHEA places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labeled a dietary supplement (From FDA website)
A dietary supplement is taken by mouth intended to supplement the diet;

- It contains one or more of the following dietary ingredients:
  - vitamins, minerals, herbs, amino acids, enzymes, organ tissue, metabolites, extracts or concentrates;
- Dietary supplements can be in the form of pills, tablets, capsules, liquids or powders;
- Its label clearly states that it is a dietary supplement.
Sales demonstrated steady growth in multiple market channels

- Herbal dietary supplements are sold in the United States through a variety of market channels, including health and natural food stores; outlets FDM (food, drug, and mass market retailers); warehouse stores; convenience stores; mail order, radio and television direct sales, and Internet sales; companies that sell directly to the consumer (often called network marketing or multi-level marketing [MLM] companies); health professionals in their offices (e.g., acupuncturists, chiropractors, naturopaths, some conventional physicians), and other channels.

- Herb dietary supplements: >$4.8 billions (2007)
Table 1. Total Estimated Herb Sales in All Channels 1994—2007

<table>
<thead>
<tr>
<th>Year</th>
<th>$ Total Sales (millions)</th>
<th>% Increase (-decrease)</th>
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</thead>
<tbody>
<tr>
<td>1994</td>
<td>2,020</td>
<td>N/A</td>
</tr>
<tr>
<td>1995</td>
<td>2,470</td>
<td>22.3</td>
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<tr>
<td>1996</td>
<td>2,990</td>
<td>21.1</td>
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<td>1997</td>
<td>3,557</td>
<td>19.0</td>
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<td>1998</td>
<td>4,002</td>
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<td>1999</td>
<td>4,110</td>
<td>2.7</td>
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<td>2000</td>
<td>4,260</td>
<td>3.6</td>
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<td>2001</td>
<td>4,397</td>
<td>3.2</td>
</tr>
<tr>
<td>2002</td>
<td>4,315</td>
<td>-1.9</td>
</tr>
<tr>
<td>2003</td>
<td>4,210</td>
<td>-2.4</td>
</tr>
<tr>
<td>2004</td>
<td>4,320</td>
<td>2.6</td>
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<tr>
<td>2005</td>
<td>4,410</td>
<td>2.1</td>
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<tr>
<td>2006</td>
<td>4,590</td>
<td>4.1</td>
</tr>
<tr>
<td>2007</td>
<td>4,791</td>
<td>4.4</td>
</tr>
</tbody>
</table>


*Nutrition Business Journal* (NBJ) primary research includes NBJ surveys of supplement manufacturers, distributors, MLM firms, mail order, Internet and raw material and ingredient supply companies, as well as numerous interviews with major retailers (Wal-Mart, Costco, etc.), manufacturers, suppliers and industry experts. Secondary sources include Information Resources Inc., SPINS, ACNielsen, *Natural Foods Merchandiser*, *Whole Foods Magazine*, Insight, The Hartman Group, company data and other published material.
Table 2: 25 Top-Selling Herbal Dietary Supplements in the Food, Drug, and Mass Market Channel in the United States for 2007

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Latin Name</th>
<th>$2007 Sales (USD)</th>
<th>$2006 Sales (USD)</th>
<th>2006 Rank</th>
<th>% Change 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Soy</td>
<td>Glycine max</td>
<td>25,607,360</td>
<td>30,811,880</td>
<td>1</td>
<td>-16.89</td>
</tr>
<tr>
<td>2. Cranberry</td>
<td>Vaccinium macrocarpon</td>
<td>23,776,000</td>
<td>19,240,930</td>
<td>3</td>
<td>23.57</td>
</tr>
<tr>
<td>3. Garlic</td>
<td>Allium sativum</td>
<td>20,504,280</td>
<td>23,483,000</td>
<td>2</td>
<td>-12.68</td>
</tr>
<tr>
<td>4. Ginkgo</td>
<td>Ginkgo biloba</td>
<td>17,796,270</td>
<td>15,929,620</td>
<td>5</td>
<td>11.72</td>
</tr>
<tr>
<td>5. Saw Palmetto</td>
<td>Serenoa repens</td>
<td>16,953,710</td>
<td>18,054,700</td>
<td>4</td>
<td>-6.10</td>
</tr>
<tr>
<td>7. Black cohosh</td>
<td>Actaea racemosa†</td>
<td>8,641,608</td>
<td>8,682,563</td>
<td>8</td>
<td>-0.47</td>
</tr>
<tr>
<td>8. Milk Thistle</td>
<td>Sillybum marianum</td>
<td>8,622,245</td>
<td>8,398,151</td>
<td>10</td>
<td>2.67</td>
</tr>
<tr>
<td>9. Ginseng*</td>
<td>Panax ginseng</td>
<td>8,389,630</td>
<td>8,758,258</td>
<td>7</td>
<td>-4.21</td>
</tr>
<tr>
<td>10. St. John’s wort</td>
<td>Hypericum perforatum</td>
<td>8,132,429</td>
<td>8,615,591</td>
<td>9</td>
<td>-5.61</td>
</tr>
<tr>
<td>11. Green Tea</td>
<td>Camellia sinensis</td>
<td>4,977,682</td>
<td>5,347,117</td>
<td>11</td>
<td>-6.91</td>
</tr>
<tr>
<td>12. Evening Primrose</td>
<td>Oenothera biennis</td>
<td>4,154,262</td>
<td>4,559,142</td>
<td>12</td>
<td>-8.88</td>
</tr>
<tr>
<td>14. Horny goat weed</td>
<td>Epimedium spp.</td>
<td>2,220,767</td>
<td>2,258,881</td>
<td>14</td>
<td>-1.69</td>
</tr>
<tr>
<td>15. Bilberry</td>
<td>Vaccinium myrtillus</td>
<td>1,814,102</td>
<td>2,003,993</td>
<td>15</td>
<td>-9.48</td>
</tr>
<tr>
<td>16. Grape seed</td>
<td>Vitis vinifera</td>
<td>1,713,729</td>
<td>1,883,251</td>
<td>16</td>
<td>-9.00</td>
</tr>
<tr>
<td>17. Yohimbe</td>
<td>Pausinystalia johimbe</td>
<td>1,192,684</td>
<td>1,399,628</td>
<td>17</td>
<td>-14.79</td>
</tr>
<tr>
<td>18. Red clover</td>
<td>Trifolium pratense</td>
<td>1,149,684</td>
<td>1,314,696</td>
<td>18</td>
<td>-12.55</td>
</tr>
<tr>
<td>19. Horse chestnut seed</td>
<td>Aesculus hippocastanum</td>
<td>994,735</td>
<td>1,261,516</td>
<td>19</td>
<td>-21.15</td>
</tr>
<tr>
<td>20. Ginger</td>
<td>Zingiber officinalis</td>
<td>658,572</td>
<td>820,053</td>
<td>20</td>
<td>-19.69</td>
</tr>
<tr>
<td>21. Aloe vera</td>
<td>Aloe vera</td>
<td>655,563</td>
<td>623,291</td>
<td>21</td>
<td>5.18</td>
</tr>
<tr>
<td>22. Elderberry</td>
<td>Sambucus nigra</td>
<td>525,274</td>
<td>542,140</td>
<td>22</td>
<td>-3.11</td>
</tr>
<tr>
<td>23. Olive leaf</td>
<td>Olea europaea</td>
<td>296,372</td>
<td>331,150</td>
<td>24</td>
<td>-10.50</td>
</tr>
<tr>
<td>24. Hawthorn</td>
<td>Crataegus laevigata</td>
<td>234,158</td>
<td>233,165</td>
<td>26</td>
<td>0.43</td>
</tr>
<tr>
<td>25. Kava kava</td>
<td>Piper methysticum</td>
<td>231,912</td>
<td>265,738</td>
<td>25</td>
<td>-12.73</td>
</tr>
</tbody>
</table>

Total All Herb Sales (including herbs not shown) $267,757,500 † $248,874,000 † 7.6

Source: Information Resources Inc. (http://us.informes.com/)

*It is not clear from the IRi data whether this figure also includes the sales of American ginseng root products (made from Panax quinquefolius), the sales of which are not as high as sales from supplements made from Asian ginseng (Panax).
† The commonly used synonym and previously accepted binomial is Cimicifuga racemosa.
‡ The total annual sales of herbal dietary supplements in the FDM channel shown here does not include sales from Wal-Mart and warehouse clubs (e.g., Costco, Sam’s) and constitutes approximately 5.4% of total herb sales in 2006 and 5.6% in 2007.
Consumer Use of Herbal/Dietary Supplements

Weekly Basis:
- 81% adults medicated with Rx or OTC weekly
- 57% used Rx drug weekly, from 1-10
- 40% used vitamin or mineral;
- 14% used herbals and supplements;
- 16% of those w/ Rx also concurrently used herbs/supplements

Slone Survey, Kaufman et al. JAMA 2002
The Regulatory Dilemma

- Ginseng: FDA’s position is that legally ginseng is a dietary supplement with no proven therapeutic values, with none in the purported arena of sexual potency, and not to be sold for medicinal purposes, vs.

- Ginseng: TCM practitioners in the USA would state that ginseng is a medicine with ‘positive action as a nerve and cardiac stimulant, increasing metabolism, retarding impotence, regulating blood pressure and blood sugar’

- Ginseng: From western Europe: It is used as an OTC with beneficial effects said to be primarily adaptogenic in nature. Traditional claims of efficacy are allowed.

*From Robber and Tyler.*
The Regulatory Dilemma - con’t

- Folkloric and historical use;
- Accumulation of anecdotal evidence;
- Vs.
- Standards of randomized, double-blind, placebo, crossover clinical trials to meet drugs claims in the USA.
The Regulatory Dilemma - con’t

- **Food and Drugs Act (1906):** Required only that drugs meet standards of strength and purity.
- **Federal Food, Drug and Cosmetic Act (1938):** Required the manufacturer to prove the safety of a drug before it could be marketed;
- **Durham-Humphrey Amendment (1951):** Defined prescription drugs as those unsafe for self medication and which therefore should be used only under a doctor's supervision.
- **Kefauver-Harris Drug Amendments (1962):** Before marketing a drug, manufacturer must provide proof of the effectiveness and safety for the products intended use.

- *Herbal medicines were grandfathered as drugs, but the FDA put them in regulatory ‘limbo’ to be sold as foods.*
The Regulatory Dilemma - con’t

- **Nutrition Labeling and Education Act (1990):** Required consistent, scientifically based labeling for almost all processed foods. Herbal medicines were left in “limbo”.

- **Dietary Supplement Health and Education Act (1994):** Includes herbal medicines in the definition of a dietary supplement, assures consumers access to all supplements on the market as long as they are not unsafe, and allows for structure and functions claims on the label.

- The DSHEA Act of 1994 actually opened the door to a vast number of new dietary supplements- herbs from China and around the world.
For over 50 years, FDA either ignored or attacked botanical drugs.

Botanicals, once the core of businesses such as Parke Davis, Merck, Upjohn and Lilly.

Between 1900 and 1960, vast majority of botanicals lost their USP status.

Without industrial support and patent protection, research funds disappeared.

Unable to meet the stricter new drug approval requirements, most of the botanicals relegated under OTC drug review system, and only handful of botanicals are still recognized as OTC active ingredients such as capsaicin (Category I), senna, cascara sagrada (Category III) and Slippery elm bark (a crude drug), and fewer are still listed in the US Pharmacopia (Mint, witch hazel, and a few others).
After several unsuccessful attempts, the Utah botanical industry joined and laid out a set of legislative principles.

In 1992, Senator Orrin Hatch introduced the Health Freedom Act modeled after the Utah template.

In 1994, this legislation passed as Dietary Supplement Health and Education Act (DSHEA)
DSHEA Act

- DSHEA defined dietary supplements to include herbs and botanicals and provided a safe haven for herbal medicines.
- DSHEA provides a presumption of safety, since FDA must prove a botanical is unsafe before it can be removed from the market.
- DSHEA allows statements on the label describing the products role in affecting or maintaining structure in humans.
- DSHEA requires labeling to include: “This product has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure or prevent disease”.
DSHEA Act-con’t

- DSHEA also sets standards for the distribution of third-party literature. Must be generic in nature, can be available in connection to the sale of the dietary supplement but not attached to the product, and to provide a balanced view of the scientific literature.

- There is another board- marketing one that evaluates and reviews labels and claims and statements.

- DSHEA pushes the industry to develop GMPs and ensure QC and QA procedures.
DSHEA Act-con’t

- DSHEA called for an Office of Dietary Supplements (ODS) within the National Institute of Health (NIH) with the following mission:

  1. to explore the potential role of dietary supplements in the improvement of health;
  2. to promote the scientific study of supplements for maintaining health and preventing chronic disease;
  3. to compile a database of scientific research related to supplements and
  4. to coordinate NIH funding related to research on dietary supplements.
Examples of a dietary supplement label

**Directions for use:**
Adults take 5mL three times per day. Try mixing the recommended dose in fruit juice or adding it to your food.

Children (over two years) take 2.5mL three times per day with food or as prescribed by your healthcare practitioner.

**Shake well.**

**Naturamedics**

**GOOD HEALTH NATURALLY**

**Olive Leaf Extract**

**EXTRA HIGH STRENGTH**

WITH TRACE MINERALS
Each 5mL (6g) contains approx. 1041.5mg of Olea europaea leaf extract dry equiv. Standardised to contain oleuropein 25mg

**100% Natural**
Suitable for Vegans • Dietary Supplement

**AUST L 124017**

**500mL**

**Indication:**
Olive leaf has been used traditionally as an antioxidant, antibacterial, and as a tonic for good health.
The compound in Olive leaves responsible for the maintenance of a healthy or normal cardiovascular system is oleuropein.
Olive leaves contain components that are potent antioxidants and free radical quenchers.
Olive leaf has traditionally been prescribed in South Africa as a hypotensive.
Olive leaf supports normal healthy blood pressure.
Phenolic compounds present in Olive leaves possess antioxidant properties that may assist with supporting a healthy cardiovascular system.
Scientists discovered a compound in Olive leaf called oleuropein; this compound has antioxidant properties to promote a healthy circulatory and immune system.
Olive leaf was traditionally used to relieve the symptoms of a fever. Traditionally, Olive leaf has been shown to act as an antimicrobial remedy.

**Warnings:**
If symptoms persist consult your healthcare practitioner.
Not to be used in children under two years of age without medical advice.

**Guarantee:**
Our Olive Leaf Extract is made from the finest Leaf. The product contains no additives other than vegetable glycerin to sweeten the flavour of the Oleuropein which is naturally very bitter.

**SUGAR, ALCOHOL & GLUTEN FREE.**
Store below 30°C

**® 13651**
Use by: NOV/09

**info@naturamedics.com**
Examples of a dietary supplement label-con’t

Eyebright (Euphrasia officinalis) is a small annual herb native to Europe. It was traditionally used as a wash or taken internally to support the eyes.

Questions? Call 1-800-9NATURE or visit naturesway.com. Our Eyebright is carefully grown, tested and produced to certified quality standards.

SATISFACTION GUARANTEED. Freshness & safety sealed with printed outer shrink-wrap and printed inner seal. Do not use if either seal is broken or missing. Keep out of reach of children.

** Recommendation: ** Take 2 capsules daily, preferably with food.

** Supplement Facts **

- **Serving Size:** 2 Capsules
- **Servings Per Container:** 50

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Carbohydrate</td>
<td>1g</td>
<td>&lt;1%†</td>
</tr>
<tr>
<td>Eyebright (stem, leaf, flower)</td>
<td>860mg</td>
<td>**</td>
</tr>
</tbody>
</table>

†Percent Daily Values are based on 2,000 calorie diet.
**Daily Value not established.

Other ingredients: Gelatin (capsule)

Did you know? Eyebright flowers have tiny stripes, with the appearance of “bloodshot eyes,” which sparked its use in European folk traditions for eye concerns.
Examples of a dietary supplement label - con’t

**Z-Slim Plus™**

- Increased Energy **
- Rapid Weight Loss **
- Dietary Supplement  90 Capsules

**Suggested Use:** For maximum weight loss, take two capsules with a full glass of water, 15 - 30 minutes before main meals. Remember, the calorie-reducing properties of Z-Slim Plus are activated by food. For a significant energy boost, take 2 capsules anytime as needed.

**DO NOT EXCEED 6 CAPSULES PER DAY**

**NOTE:** Limit the use of caffeine-containing medications, foods or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness and occasionally, rapid heart beat.

**WARNING:** This product is not intended for use by those with a serious medical condition, or pregnant or lactating women. Consult your physician before use. For occasional use only.

- **Proprietary Blend:** 1312 mg
- Yerba Mate (leaf) (powder and extract)
- Caffeine USP
- Guarana (seed) (powder and extract standardized to 22% caffeine)
- **Damiana (leaf) (powder and extract):**
- L-Carnitine L-Tartrate
- Schizonepeta extract (Schizonepeta tenuifolia) (herb)
- Green Tea (leaf)
- Piper Nigrum (fruit)
- Tibetan Ginseng (Rhodiola crenulata) (root)
- Panax Ginseng (root)
- Maca (root) (standardized to 0.6% glucosinolates)
- Cocoa extract (seed)
- Kola Nut (seed) (standardized to 10% caffeine)
- Tea Sinensis Complex (leaf) (camellia sinensis) (standardized to 50% polyphenols)

**Supplement Facts**

<table>
<thead>
<tr>
<th>Serving Size: 2 Capsules</th>
<th>Servings Per Container: 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount per serving</td>
<td>% Daily Value</td>
</tr>
<tr>
<td>Niacin (as niacinamide)</td>
<td>50 mg  250%</td>
</tr>
</tbody>
</table>

*Daily value not established

Other ingredients: Gelatin, magnesium stearate, silicon dioxide.

**Nature’s Solution**

**Ft. Worth, TX 76180**

www.3-weight-loss-pills.com
Other developments affecting the regulatory status of botanicals

- U.S. Pharmacopia: In July 1996, USP held a open conference to discuss approaches for establishment of quality standard and use information for botanicals, and have published some monographs on commonly used botanicals in the US market, e.g. valerian, ginger, garlic and ginkgo.

- FDA: There were signs of activity within FDA to be organizing a botanical review committee within the Center for Drug Evaluation and Research (CDER).
Purpose of USP standards

- To legitimize and distinguish quality botanicals in the mind of public and professionals.
- Open the way for FDA drug review and approval of botanicals as drugs for which USP standards may exist.
- Become an authoritative source of usage information for health care professionals.
- Set a stage for reimbursement or insurance coverage for botanicals.
- Create incentives for compliance with GMP’s in order to meet USP standards.
Federal Trade Commission (FTC)

- Guide to Advertising and Claims for Dietary Supplements

- The following information used in the next series of slides comes from the FTC. For more details, see: www.ftc.gov, or:

Use of DSHEA Disclaimer in Advertising

- Under DSHEA, all statements of nutritional support for dietary supplements must be accompanied by a two-part disclaimer on the product label: *that the statement has not been evaluated by FDA and that the product is not intended to "diagnose, treat, cure or prevent any disease."*

- Although DSHEA does not apply to advertising, there are situations where such a disclosure is desirable in advertising as well as in labeling to prevent consumers from being misled about the nature of the product and the extent to which its efficacy and safety have been reviewed by regulatory authorities.

- At the same time, the inclusion of a DSHEA disclaimer or similar disclosure will not cure an otherwise deceptive ad, particularly where the deception concerns claims about the disease benefits of a product.
Dietary supplement advertisers should be aware that the use of newspaper articles, abstracts of scientific studies, or other "third party literature" to promote a particular brand or product can have an impact on how consumers interpret an advertisement and on what claims the advertiser will be responsible for substantiating. For dietary supplement labeling, Section 5 of DSHEA provides an exemption from labeling requirements for scientific journal articles, books and other publications used in the sale of dietary supplements, provided these materials are reprinted in their entirety, are not false or misleading, do not promote a specific brand or manufacturer, are presented with other materials to create a balanced view of the scientific information, and are physically separate from the supplements being sold.

FTC will generally follow an approach consistent with the labeling approach when evaluating the use of such publications in other contexts, such as advertising. Although the FTC does not regulate the content or accuracy of statements made in independently written and published books, articles, or other non-commercial literature, FTC law does prohibit the deceptive use of such materials in marketing products. As a practical matter, publications and other materials that comply with the elements of the DSHEA provision, particularly with the requirement that such materials be truthful, not misleading and balanced, are also likely to comply with FTC advertising law.
In Sum Guidelines from the DSEA:

- Under DSHEA, supplement marketers are allowed to make two kinds of claims on labeling: 1) *health claims specifically authorized by the FDA*; and 2) *statements of nutritional support*.

- Health claims — representations about the relationship between a nutrient and a disease or health-related condition — are permitted only if they have been authorized by an FDA finding that there is "significant scientific agreement" to support the claim.

- The Food and Drug Administration Modernization Act of 1997 (FDAMA) also now allows health claims that are based on "authoritative statements" from certain federal scientific bodies, such as NIH and the National Academy of Sciences.

- Aside from these authorized claims, supplement marketers are prohibited from making any labeling claim about the diagnosis, mitigation, treatment or cure of a disease.

- In contrast to health claims, "*structure/function* claims", within the broader category of "statements of nutritional support," refer to representations about a dietary supplement’s effect on the structure or function of the body for maintenance of good health and nutrition.
In Sum for FTC Guidelines:

- Marketers of dietary supplements should be familiar with the requirements under both DSHEA and the FTC Act that labeling and advertising claims be truthful, not misleading and substantiated. The FTC approach generally requires that claims be backed by sound, scientific evidence, but also provides flexibility in the precise amount and type of support necessary.

- This flexibility allows advertisers to provide truthful information to consumers about the benefits of supplement products, and at the same time, preserves consumer confidence by curbing unsubstantiated, false, and misleading claims.

- Dietary supplement advertisers should follow two important steps: 1) careful drafting of advertising claims with particular attention to how claims are qualified and what express and implied messages are actually conveyed to consumers; and 2) careful review of the support for a claim to make sure it is scientifically sound, adequate in the context of the surrounding body of evidence, and relevant to the specific product and claim advertised.
Following the DSHEA

On June 22, 2007, the US Food and Drug Administration (FDA) announced publication of its final rules for Good Manufacturing Practices (GMPs) for dietary supplements (DS).

HerbalGram. 2007;75:6
The new GMPs cover rules for handling, processing, labeling, and storing ingredients and DS products, which includes quality control, standardized operating procedures, record-keeping, qualifications for technical personnel, handling customer complaints, etc. FDA also published a proposed interim rule on whether companies should be required to test 100% of all ingredients for identity or whether the frequency of such testing can be reduced, depending on whether certain other requirements are met. Public comment on this proposal was due September 24, 2007.
Manufacturers will have 1-3 years to comply with the GMPs: 1 year for companies over 500 employees, 2 years for companies with less than 500 (the size of most), and 3 years for companies with 20 or less. The GMPs will not apply to licensed practitioners who compound and dispense DS preparations within a clinical practice, nor do they pertain to retail establishments.
KAVA-CONTAINING DIETARY SUPPLEMENTS MAY BE ASSOCIATED WITH SEVERE LIVER INJURY

The Food and Drug Administration (FDA) is advising consumers of the potential risk of severe liver injury associated with the use of kava-containing dietary supplements. Kava (Piper methysticum) is a plant indigenous to the islands in the South Pacific where it is commonly used to prepare a traditional beverage. Supplements containing the herbal ingredient kava are promoted for relaxation (e.g., to relieve stress, anxiety, and tension), sleeplessness, menopausal symptoms and other uses. FDA has not made a determination about the ability of kava dietary supplements to provide such benefits.

http://www.cfsan.fda.gov/~dms/addskava.html
Dietary supplement/Functional food/Phytomedicine the market status and regulations in the USA

Major steps for botanical drug development under FDA (Veregen)

Phytomedicines in Europe
**FDA regulation on botanical drug development in the US**

- **Guidance for Industry:** *Botanical Drug Products*

- **History:** From 2000, FDA established a working group to develop this botanical guidance document to the industry.

- Botanicals and other natural products, under this US regulatory process, can be developed as “New” drugs (IND/NDA pathway).
Guidance for Industry

Botanical Drug Products

Copies of this Guidance are available from:

Division of Drug Information (HFD-240),
Office of Training and Communications,
Center for Drug Evaluation and Research (CDER),
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573

Internet at http://www.fda.gov/cder/guidance/index.htm

Guidance for Industry
Botanical Drug Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance explains when a botanical drug may be marketed under an over-the-counter (OTC) drug monograph and when FDA regulations require approval for marketing of a new drug application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 355(b). In addition, this document provides sponsors with guidance on submitting investigational new drug applications (INDs) for botanical drug products, including those botanical products (or botanicals) currently lawfully marketed as foods (including conventional foods and dietary supplements) in the United States.
The Botanical Review Team under CDER, FDA (Botanical Team)

- The Botanical Team consists of a team leader, projector manager, medical officer(s), and pharmacogonosist(s).

- Review Divisions:
  - Chemistry, Manufacturing, and Control (CMS) information review
  - Clinical pharmacology/biopharmaceutics information review
  - Noclinical pharmacology and toxicology information review
  - Medical/Statistical information review

Historic Milestone - Veregen

- **Veregen**, the first marketing approval of the botanical “new” drug by the FDA in October 2006 is considered the beginning of the long waiting botanical drug entry into the US market.

- **Veregen**, extract of green tea as a prescription drug for the topical (external) treatment of genital warts caused by the human papilloma virus (HPV), was developed by MediGene, a German company, and will be marketed in the United States by Bradley Pharmaceuticals of Fairfield, NJ.
“This is a regulatory breakthrough, said Mark Blumenthal, Founder and Executive Director of the nonprofit American Botanical Council. “It is the first time a complex herbal preparation has come to market as a prescription drug in the U.S. in more than half a century.”

Freddie Ann Hoffman, MD, an expert on this botanical drug process, said, “A new drug industry has just been born -- perhaps ‘reborn’ -- in the United States: the polymolecular botanical drug industry.” Dr. Hoffman is a former FDA official and is founder of HeteroGeneity, LLC, a Washington, D.C.-based consulting firm advising companies seeking to market botanically-based drugs.
The active drug ingredient, Polyphenon® E, represents a proprietary mixture of phytochemicals produced from a partially purified water extract of green tea leaves with high levels of highly antioxidant polyphenolic compounds known as catechins.

Polyphenon® E has been shown to have significant pharmacological activities when tested both internally and externally in animals and humans. For FDA drug approval, the safety and efficacy of Polyphenon® E Ointment were studied in two prospective, randomized, double-blind clinical studies in nearly 400 adults with external genital and anal warts ranging in number from 2 to 30. Test subjects applied the ointment three times daily until complete clearance of all warts. In each of these clinical trials, the median time to clear warts completely was 16 weeks and 10 weeks, respectively. Changes in the skin over the site of use were the most commonly reported side effects and included redness, itching, burning, pain/discomfort, ulceration, swelling, and local hardening of the skin.
The development of Polyphenon E Ointment is an example of increasing global trade and cooperation. In 1997, a patented method of treating external genital warts through the topical application of Polyphenon E green tea extract was licensed by Epitome Pharmaceuticals Ltd., a privately owned Canadian company (Halifax, Nova Scotia) from the food company Mitsui Norin, Ltd. (Tokyo, Japan). Epitome sublicensed the technology to MediGene AG of Martinsried/Munich, Germany, which collaborated in numerous multi-center clinical trials in both Europe and the Americas. Medigene submitted the New Drug Application (NDA) to the FDA Center for Drug Evaluation and Research in September 2005, which was accepted for filing in early December 2005.

MediGene is the first German biotech company to obtain marketing authorization for a drug in the United States. The company predicts peak sales potential for Polyphenon E Ointment of up to $100 million annually. Medigene’s marketing partner, Bradley Pharmaceuticals, Inc. (NYSE: BDY), will commercialize the product in the United States through its subsidiaries, Doak Dermatologics and Kenwood Therapeutics division.
Green tea polyphenols (PACs)

Structures of the Target Compounds:

(+)-Catechin (C_{15}H_{14}O_{6}, MW: 290)

(+)-Epicatechin (C_{15}H_{14}O_{6}, MW: 290)

(-)-Gallocatechin gallate (C_{22}H_{18}O_{11}, MW: 458)

(-)-Epigallocatechin gallate (C_{22}H_{18}O_{11}, MW: 458)

(-)-Epigallocatechin (C_{15}H_{14}O_{7}, MW: 306)

(-) Catechin gallate (C_{22}H_{18}O_{10}, MW: 442)

(-) Epicatechin gallate (C_{22}H_{18}O_{10}, MW: 442)
UV Chromatogram of Green Tea Products
Major steps for botanical drug development (Veregen)

1. Pre-IND meeting with FDA
2. POC study under the FDA supervision
3. Out licensing (price and conditions)
4. Co-development in the US/EU
The Veregen Case

- Safety is still one of the top concern
- Chemistry and bioactivities are well investigated
- Clinical application is well documented and/or recognized
- Patent protection
NIH funds other centers for botanical research under different programs. An example: Center of Excellence for Research on Complementary and Alternative Medicine (CERC) for Alzheimer’s disease With an Emphasis on grape derived polyphenolic compounds

Protective Roles of Grape-Derived Polyphenols in Alzheimer’s disease

- Principal Investigator: Giulio Maria Pasinetti, M.D., Ph.D.
- Institution: Mount Sinai School of Medicine, New York, NY

- Project 1: Cabernet Sauvignon (*Vitis vinifera* L.) and Concord purple grape juice: promotion of non-amyloidogenic α-secretase processing of APP
- Project 2: Resveratrol, role in promoting Aβ clearance by proteolysis.
- Project 3: “Grape seeds proanthocyanidins: Aβ oligomerization and spatial memory impairment in transgenic mouse model of Alzheimer’s disease”

With a group at Purdue, we at the NUANPP at Rutgers, co-lead the botanical and metabolic profiling core in this center
About 1400 herbal drugs are used in EU and among which about 200 are the most used ones.

Sales of herbal remedies: ~$6 billons in 1994 (~$2 billion in the US).

As OTC drugs, phytomedicine consumers can be classified into two categories: either they use phytomedicines as a self-medication or they prefer natural products, considering them as an alternative lifestyle.

The term “herbal remedies” is not automatically linked to the OTC status. In Germany, more rarely in France, a small proportion of prescriptions consists of herbal remedies.
Phytomedicines, simply called herbal remedies, are commonly used and very popular in Germany. The German government saw the need to create a process to affirm their safety and effectiveness.

In 1978 the German government (The Federal Health Office, renamed in 1994 as Federal Institutes for Drugs and Medical Devices) established a committee, called Commission E, comprised of physicians, pharmacologists, toxicologists, representatives of the pharmaceutical industry and lay persons.
The legal status of phytomedicines in Germany-con’t

- The Commission E Reviewed bibliographic information on approximately 300 herbs sold in Germany, including historical and traditional use, chemical studies, pharmacological and toxicological research, clinical studies, epidemiological data and even patient case files. Their evaluations resulted in the establishment of "reasonable certainty" of the safety and effectiveness of the herb reviewed.

- The Commission E has since then published over 400 (including revisions) monographs covering over 300 herbs.

- Of these monographs, about 200 are positive (they approve the use) and about 100 are negative assessments (usually based on either lack of sufficient data and/or significant toxicity concerns).
Developed by a Special Expert of the German Federal institute for Drugs and Medical Devices

Translated into English by American Botanical Council
In 1980, an expert panel was created at the Ministry of Health in Paris. The goals of the group were to:

- 1) avoid anarchy on the market
- 2) define a high level of phytopharmaceutical quality
- 3) respect major criteria: quality, safety, efficacy

In 1990, useful important guidelines and results of selection were completed.
“Notice to applicants for marketing authorization”

- A list of 174 plants was initially established on the basis of all scientific information available in the botanical, chemical, pharmacological, toxicological and clinical fields.

- A additional list of 31 other species known for their laxative effects was also added.
Content of the pharmaceutical dossier

- Botanical identity and origin
- Knowledge of manufacturing process
- Qualitative and quantitative control of starting material, intermediate and final products
- Stability test on the finished product
- Reference monographs (HPLC or GC profiles)
Toxicological documentation

- Total exemption for:
  - Herbal drugs for tea (infusion)
  - Aqueous extracts
  - Hydroalcoholic extracts (< 30 alcohol)
  - Tinctures of traditional use

- Further toxicological information required for:
  - Non traditional tinctures
  - Hydroalcoholic extracts (> 30 alcohol)
  - Non traditional powders of whole plants
**Regulations in other European counties**

- **United Kingdom:** No license required when herbal medicines are used and proscribed by herbal practitioner and if no written recommendation is giving to the consumer. The review process for licensed phytomedicines was completed in 1990 and an information sheet for license holder was published in 1985 by MCA. In 1995 a new guideline “A guide to what is a medicinal product”, and it tries to give examples to clarify the borderline between medicinal products and, for instance, cosmetics or foodsuffs.

- **Italy:** In 1981 a guideline was issued by the Italian Health Authority clarifying herbal products as health food products or as medicines. Plants used for nutritional purposes, sold outside pharmacies, do not need an approval and are not allowed to claim therapeutic effects. Herbal products with therapeutic claims, are considered as medicines and are allowed to be only through pharmacies.
Further actions from European Union

- The European Union recently published draft quality-control guidelines applying to a new European Directive called the Traditional Herbal Medicinal Products Directive (THMPD). This Directive allows the licensing and over-the-counter sale of herbs that have a history of use anywhere in the world for at least 30 years, 15 of which must be in an EU Member State.

- On June 20, 2005, the European Medicines Agency (EMEA) published an updated draft guidance document entitled Guideline on Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products. The deadline for public comment was September 15, 2005. This updated draft guidance aims to make clarifications and corrections to the earlier Note for Guidance on Specifications, which went into effect January 2002. The stated objective of the new guideline is to provide general principles on the setting and justification of uniform specifications for herbal medicines in order to support the process of applying for marketing authorization or registration according to EU Directives 2001/82/EC3 and 2001/83/EC4 respectively.
Regulations Vary by Country

- The market status of herb dietary supplements in the USA and Europe is complex and yet in the USA, with DSHEA of 1994, the door to botanical herbs from around the world including China opened.

- Reviewing the dynamic regulatory environment for botanical derived products of dietary supplements and botanical drugs is critical for your intended use and to provide research that supports new products and market penetration.

- Quality is a key consideration and this will only become of increasing importance overtime particularly when exporting into any of these markets (Authentication, Adulteration, Purity and traceability)