Agenda

- USP – A BRIEF OVERVIEW
- DIETARY SUPPLEMENTS – DEFINITION, LEGALITY & REGULATION
- USP DIETARY SUPPLEMENT STANDARDS
- USP – STRENGTHENING BOTANICAL STANDARDS
- DIETARY SUPPLEMENTS – THE NEED FOR USP VERIFICATION
USP promotes the public health by establishing and disseminating officially recognized standards of quality and authoritative information for the use of medicines and other health care technologies by health professionals, patients, and consumers.
What is USP

- Established in 1820 by Lyman Spaulding
- Mission is to protect public health by establishing public standards
- Independent; not for profit science based Standard setting organization
- Unique volunteer based organization
- Headquartered in Rockville, MD
What USP does

Through a unique & open Public process USP;

- Establishes Public Standards for drug substances, drug products, excipients & Dietary supplements
- Establishes General test Methods, definitions & Information
- Supplies Reference Standards to enable analytical tests for Standards compliance
Towards carrying forward its Mission of Public Health USP is reaching out Globally;

- European Office started in 2005 at Basel, Switzerland
- **USP-India Established & Started operations in 2006**
- **USP-China Established & Start operations in 2007**
- **USP-Brazil Site approved by Board of Trustees & is slated to start operations 2008**
Objectives of USP International Operations

- Work closely with the Regional Industry & with Regulators & other stakeholders
- Involve the Regional Pharmaceutical Industry in the Standard Setting Process
- Offer USP Verification Services to the Industry & other Stakeholders
- Increase awareness of & availability of USP’s Pharmacopeial products and services like Reference Standards & Pharmacopeial Education Courses etc.
- Establish collaborative testing Lab for Reference Standard candidate material
- Enlist regional pharmaceutical scientists in Council of Experts
- Facilitate structured information exchange through Scientific Meetings – **USP 7th ASM – India will be held in February 2008 at Hyderabad**
The Legality

- Dietary Supplements Health and Education Act (DSHEA) was Enacted by the U.S. Congress in October 1994.

- DSHEA Recognizes the USP Standards for Dietary Supplements.
What is a Dietary Supplement?

Dietary Supplement as per DSHEA...

“is a product that is intended to supplement the diet and contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.”
USP Standards — Official Recognition

- **Federal Food, Drug, and Cosmetic Act**
  Sections 201 (g) and (j), 501(b), 502(g)
  USP and NF standards FDA enforceable for all drugs.
  Conformance is generally not optional and is enforced by FDA

- **Dietary Supplement Health & Education Act (DSHEA)**
  Section 403(s)(2)(D) of the FD&C Act
  A dietary supplement represented as conforming to USP-NF specifications shall be deemed misbranded if it fails to do so.

  **Conformance is optional, but enforceable by FDA**
USP DIETARY SUPPLEMENT STANDARDS
USP’s tryst with Dietary Supplements’ started way back in 1820 when it published standards for natural medicines in the first *Pharmacopoeia*. 
Historical Perspective

1820-1900
USP’s standards compendium included only natural medicines. e.g. Chamomile, Valerian, and Ginger

1820-1940
USP developed over 600 botanical monographs

1942
USP monographs for single ingredient vitamins and minerals

1990
USP adopted a resolution to expand monograph development for vitamins and minerals
In response to DSHEA, USP explored the feasibility of establishing standards and information for botanical and non-botanical Dietary Supplements with a GMP General Chapter.

USP 27–NF 22 includes a separate dietary supplements section with more than 200 monographs for botanicals, nonbotanicals, and vitamin-mineral combination products used in nearly 900 dietary supplement products.
## USP Dietary Supplement Monographs

<table>
<thead>
<tr>
<th>DS Type Test</th>
<th>Vitamin</th>
<th>Minerals</th>
<th>Non Botanicals</th>
<th>Botanicals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identity</strong></td>
<td>IR, HPLC RT, UV, Chemical</td>
<td>Chemical</td>
<td>IR, HPLC RT, UV, Chemical</td>
<td>Microscopy, TLC, HPLC, GC</td>
</tr>
<tr>
<td><strong>Purity</strong></td>
<td>Chromatographic purity, Limit Tests, Microbial, Heavy Metals</td>
<td>Chemical Limit tests, Limit of foreign metals by AA, ICP</td>
<td>Chrom. purity, Limit Tests, Microbial, Heavy Metals, PCBs-Dioxins</td>
<td>Toxins, Aflatoxins, Heavy Metals, Pesticides, Foreign Matter, Residue On Ignition, Microbial, Negative Markers</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Packaging, Labeling, Uniformity, Dissolution, Disintegration</td>
<td>Packaging, Labeling, Uniformity, Dissolution, Disintegration</td>
<td>Packaging, Labeling, Uniformity, Dissolution, Disintegration</td>
<td>Packaging, Labeling, Extractable Matter, Uniformity, Dissolution, Disintegration</td>
</tr>
<tr>
<td><strong>Content</strong></td>
<td>Spectroscopy, HPLC, Microbial</td>
<td>AA, ICP, Titration</td>
<td>Spectroscopy, HPLC, Titration</td>
<td>HPLC, GC</td>
</tr>
</tbody>
</table>
USP – STRENGTHENING BOTANICAL STANDARDS

- Garlic
- Echinacea
- Saw Palmetto
- Ginkgo
- Soy
- Cranberry
- Ginseng
- Black Cohosh
- St. John’s wort
- Milk thistle

- Evening primrose
- Valerian
- Green tea
- Bilberry
- Grape seed
- Horny goat weed
- Yohimbe
- Horse Chestnut
- Eleuthero
- Ginger
Recently Established USP Standards

- Black Cohosh
- Soy Isoflavones
- Turmeric
- Green Tea Extract
- Bilberry Extract
- Senna pods

USP Standards at different stages of development

- Grape seeds extract
- Boswellia oleo-gum resin
- Fenugreek seeds
- Spirulina blue green algae
- Guggul oleo-gum resin
- Ashwaganda roots

Articles for which USP seeks to Establish Standards on Priority

- Aloe vera gel
- Cinnamon bark
- Passionflower flowering and fruiting tops
- Elderberry flowers and berries
- Mangosteen fruits
- Reishi mushrooms
- Noni fruits
- Black currant oil
- Stevia leaves
- Cranberry fruit extract
- Linseed oil
- Olive leaves
- Borage oil
- Artichoke leaves and flower heads
- Pau d’arco bark
- Shiitake mushrooms
USP - Strengthening Botanical Standards

Criteria for Consideration of Articles Proposed for Placement in the USP-NF

1. **Human data**: safety studies, clinical studies, post-marketing surveillance, adverse events, interactions, publicly available data

2. **Pharmacological data**: including reproductive toxicity, experimental animal studies, pharmacokinetics, therapeutic index, presence of toxic constituents

3. Contemporaneous extent of use globally and in the U.S.; including misuse and abuse and taking into account fluctuations of use; historical use,

4. **Regulatory status** in the U.S. and other countries: regulatory actions, OTC status, GRAS status, etc.

5. **Existence of Official Pharmacopeial Monographs**
USP - Strengthening Botanical Standards

USP Dietary Supplement General Chapters relevant to Botanicals;

- <563> IDENTIFICATION OF ARTICLES OF BOTANICAL ORIGIN
- <565> BOTANICAL EXTRACTS
- <2021> MICROBIAL ENUMERATION TESTS-NUTRITIONAL AND DIETARY SUPPLEMENTS
- <2022> MICROBIOLOGICAL PROCEDURES FOR ABSENCE OF SPECIFIED MICROORGANISMS-NUTRITIONAL AND DIETARY SUPPLEMENTS
- <2023> MICROBIOLOGICAL ATTRIBUTES OF NONSTERILE NUTRITIONAL AND DIETARY SUPPLEMENTS
- <2030> SUPPLEMENTAL INFORMATION FOR ARTICLES OF BOTANICAL ORIGIN
- <2040> DISINTEGRATION AND DISSOLUTION OF DIETARY SUPPLEMENTS
- <2091> WEIGHT VARIATION OF DIETARY SUPPLEMENTS
- <2750> MANUFACTURING PRACTICES FOR DIETARY SUPPLEMENTS
Revisions to General Chapters & New General Chapters under consideration;

- The use of polymerase chain reactions (PCR) in botanical identification.
- The use of electron microscopy in botanical identification.
- Bioassay of the antioxidant activity of dietary supplements including botanicals.
- Revision to the pesticides testing in the USP General Chapter <561>, *Articles of Botanical Origin*.
- Heavy metals in botanicals – limits and testing procedures for individual heavy metals.
Collaboration with the Indian Stakeholders

- MOU with Indian Pharmacopoeia Commission
- MOU with PHARMEXCIL
- R&D alliances with Industry & Institutions
DIETARY SUPPLEMENTS – THE NEED FOR USP VERIFICATION
All Supplements Are Not Created Equal!
All Supplements Are Not Created Equal!

- 27 multivitamin / multi-mineral products tested – 9 failed
- 1 prenatal vitamin had only 75% and 1 multi had only 50% of its claimed amount of folic acid
- 2 products had less than 40% of their labeled amount of beta-carotene, 1 had excessive amounts
- 1 product failed to disintegrate
- The remaining failures either had excess or were deficient in labeled content
- A study of Coenzyme Q10 showed that consumers could go from 175% to 0% of the labeled amount by simply changing brands
Recent survey of 10 herbs in 20 retail stores showed:

- A total of 880 products
  - 37% were deficient in labeling information
- 92 products for Echinacea (27 brands)
  - Strengths on product labels varied by a factor of five
- 42 products for Goldenseal (15 brands)
  - Strengths on product labels varied by a factor of twenty

J. Garrard et al, Arch Inter Med, 163 p.2290.
All Supplements Are Not Created Equal!

Routine problems associated with Dietary Supplement Ingredients:

- Failure to meet an assay consistently
- Failure to meet a minimum impurity profile consistently
- Failure to meet GMP requirements
- Heavy metals and pesticide contamination
- Microbial contamination
- Adulterated materials
A Public Health opportunity

- Increased Regulatory pressure in most countries for imports & for dosage form manufacturers
- Increasing risk in global supply chain
- Hyper-competitive market drives need to visibly demonstrate quality
- Liability remains high for high-margin markets, driving need for quality assurance can help reduce risk
- Trending towards uniformity in quality standards will allow for independent certification to serve multiple purposes
USP’s Verification Products

For Dietary Supplement Finished Products

For Dietary Supplement Ingredients

For Pharmaceutical Ingredients, including Drug Substances and Excipients
The USP Verified Mark means:

- What’s on the label is in the bottle.
- The supplement does not contain harmful levels of contaminants.
- The supplement will break down properly to allow ingredients to dissolve in your body.
- The supplement has been made under safe, sanitary, manufacturing processes.
Customers use USP to show quality
Ingredients covered by this program

- **Vitamins**
- **Minerals**
- **Amino acids**
- **Powdered botanicals and botanical extracts**
- **Non-botanical dietary supplements covered by DSHEA and legally marketed in the U.S. (e.g. fish oil, chondroitin sulfate sodium, glucosamine, etc.)**
- **Excipients**
The USP Verified Mark means:

- Pre-audit documentation – approved
- On-site GMP audit – approved
- Quality control documentation – approved
- Manufacturing documentation – approved
- Drug substance samples tested – approved
Sigma-tau HealthScience advertisement for the USP Verified Ingredients

And The Seal Of Approval Goes To...

ArginoCarn™
GlycoCarn™

Sigma-tau HealthScience
Ingredients covered by this program

- Drug substances used in the manufacture of pharmaceutical products

- Excipients
The USP Verified Mark means:

✓ Pre-audit documentation – approved

✓ On-site GMP audit – approved

✓ Quality control documentation – approved

✓ Manufacturing documentation – approved

✓ Drug substance samples tested – approved
The Verification Process

1. Guidelines from USP Expert Committees
2. Audit of manufacturing sites for GMP compliance
3. Review of documentation manufacturing, QA, QC
4. Laboratory testing of product samples
5. Review of conformance with mark usage guidelines
6. Surveillance test of product using the mark
Successful conclusion of the Verification process will entitle the Client to:

- Certificate of Standards Compliance valid for 3 years
- Right to use the ‘USP Verified’ mark on the Ingredient/ Product packaging & on the certificate of Analysis
The Value of USP Verification

- **For ingredient producers**
  - Demonstrate the quality of your product
  - Differentiate your product from others
  - Show that you meet world class quality requirements
  - Earn preferred supplier status with brokers, distributors, and manufacturers

- **For distributors, brokers, and finished product manufacturers**
  - Reduce the risk of inconsistent and sub-standard quality from suppliers
  - Reduce the time and effort needed to qualify incoming product
  - Reduce the likelihood that ingredients will be rejected and must be returned
The Value of USP Verification

**Benefits for Regulatory authorities**

- Promote the public health
- Build on Extended regulatory capacities
- Reduce the regulatory burden by creating a common review and audit function in participating countries
- Get the assurance of USP, a name associated with Quality & recognized world-wide and working as an independent, science based organization driven by its mission for ensuring Good Pharmaceutical care for all
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Thank You