U.S. PHARMACOPEIA
The Standard of Quality℠

INDIA-LAC INTERNATIONAL PHARMA MEET
JUNE 2007, HYDERABAD

Setting Standards for Dietary Supplements & enabling standards compliance

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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 – A BRIEF OVERVIEW

USP Mission

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
- Convention meets every five years in Washington, D.C. (2005)
- 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

USP – International Presence

Towards carrying forward its Mission of Public Health USP is reaching out Globally;

- European Office started in 2005 at Basel, Switzerland
- USP-India Estabished & 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**

DIETARY SUPPLEMENTS – DEFINITION, LEGALITY & REGULATION

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

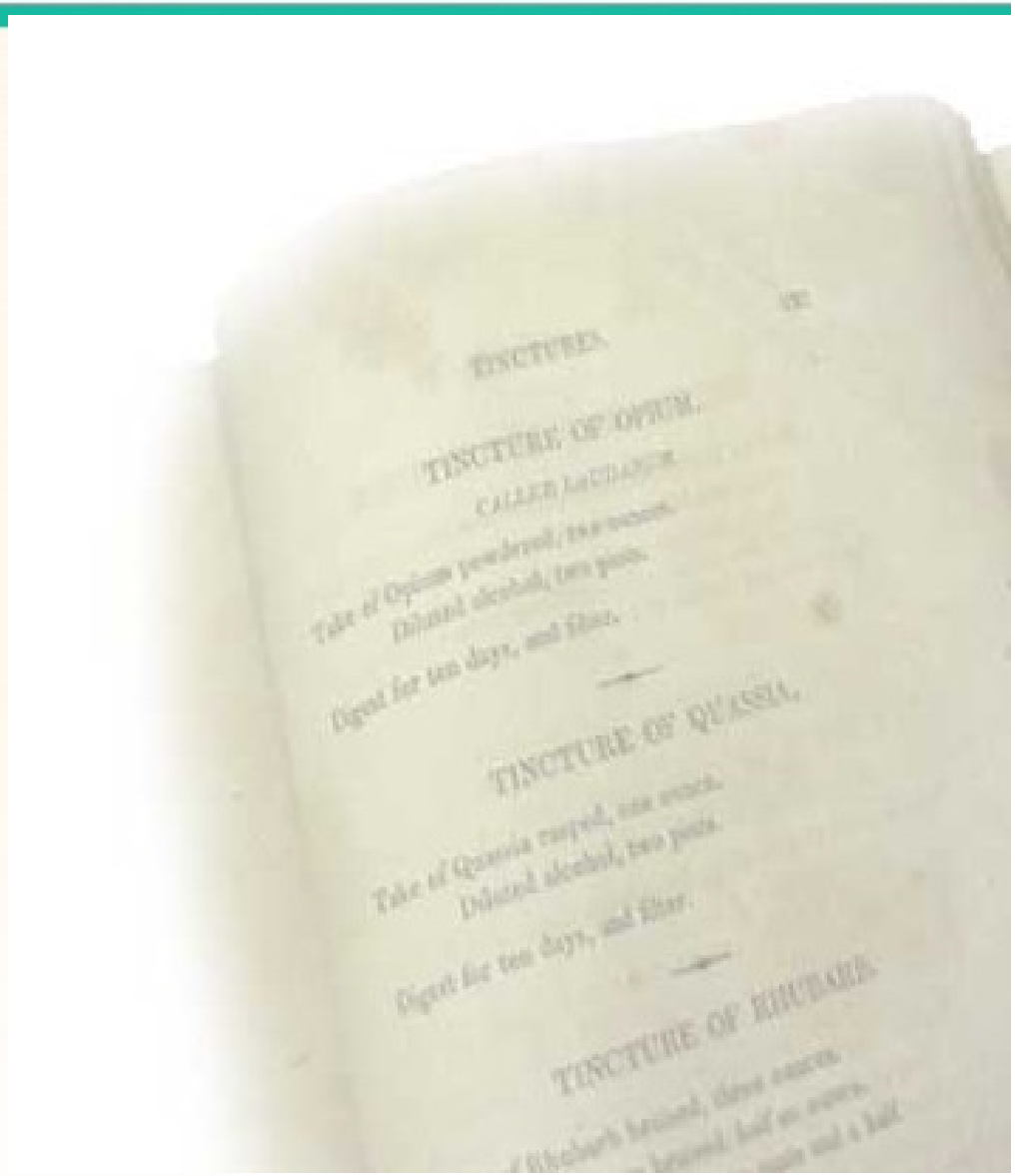
- **Dietary Supplement Health & Education Act (DSHEA)**
  Section 403(s)(2)(D) of the FD&C Act
  A dietary supplement represented as conforming to *USP–NF* specifications shall be deemed misbranded if it fails to do so.

Conformance is optional, but enforceable by FDA

USP DIETARY SUPPLEMENT STANDARDS

USP & 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

1942

USP monographs for single ingredient vitamins and minerals

1990

USP adopted a resolution to expand monograph development for vitamins and minerals

1820-1940

USP developed over 600 botanical monographs

Timeline of USP on Dietary Supplements Publication

1995

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

2003

***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.**

2008

USP Dietary Supplement Monographs

Test \ DS Type	Vitamin	Minerals	Non Botanicals	Botanicals
Identity	IR, HPLC RT, UV, Chemical	Chemical	IR, HPLC RT, UV, Chemical	Microscopy, TLC, HPLC, GC
Purity	Chromatographic purity, Limit Tests, Microbial, Heavy Metals	Chemical Limit tests, Limit of foreign metals by AA, ICP	Chrom. purity, Limit Tests, Microbial, Heavy Metals, PCBs-Dioxins	Toxins, Aflatoxins, Heavy Metals, Pesticides, Foreign Matter, Residue On Ignition, Microbial, Negative Markers
Quality	Packaging, Labeling, Uniformity. Dissolution, Disintegration	Packaging, Labeling, Uniformity, Dissolution, Disintegration	Packaging, Labeling, Uniformity, Dissolution, Disintegration	Packaging, Labeling, Extractable Matter, Uniformity, Dissolution, Disintegration
Content	Spectroscopy, HPLC, Microbial	AA, ICP, Titration	Spectroscopy, HPLC, Titration	HPLC, GC

USP – STRENGTHENING BOTANICAL STANDARDS

USP - Strengthening Botanical Standards

Top selling Botanicals (Journal of American Botanical Council, 2004)

- 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

USP - Strengthening Botanical Standards

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,

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

6. 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

USP - Strengthening Botanical Standards

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.

USP - Strengthening Botanical Standards

Collaboration with the Indian Stakeholders

- MOU with Indian Pharmacopoeia Commission
- MOU with PHARMEXCIL
- R&D alliances with Industry & Institutions

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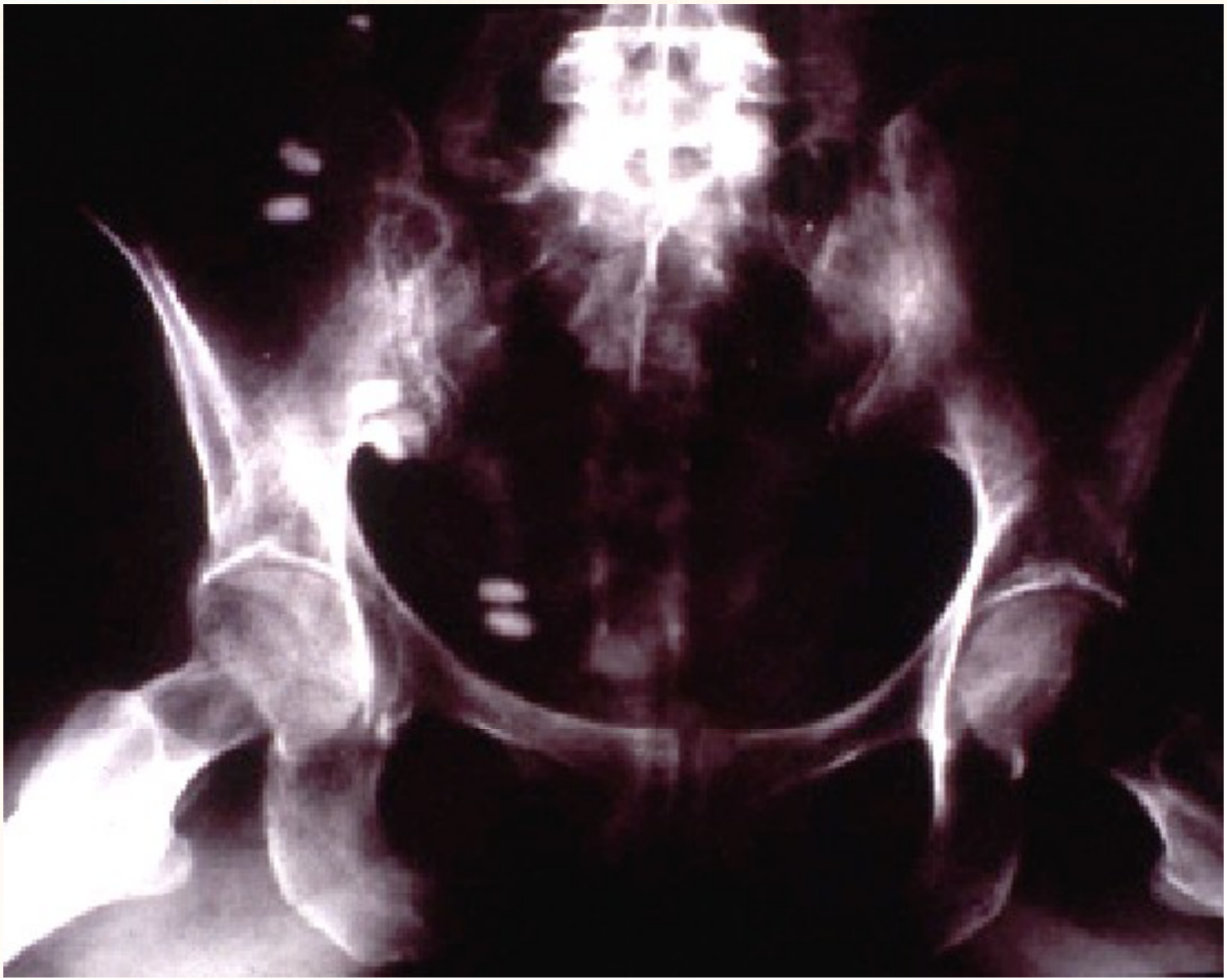
DIETARY SUPPLEMENTS – THE NEED FOR USP VERIFICATION

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

All Supplements Are Not Created Equal !

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

USP Ingredient Verification Programs

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

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USP's Verification Products

For Dietary Supplement Finished Products

For Dietary Supplement Ingredients

For Pharmaceutical Ingredients, including Drug Substances and Excipients

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USP Verified Dietary Supplements

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

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USP Dietary Supplement Ingredient Verification

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

USP Dietary Supplement Ingredient Verified Mark

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

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USP Pharmaceutical Ingredient Verification

Ingredients covered by this program

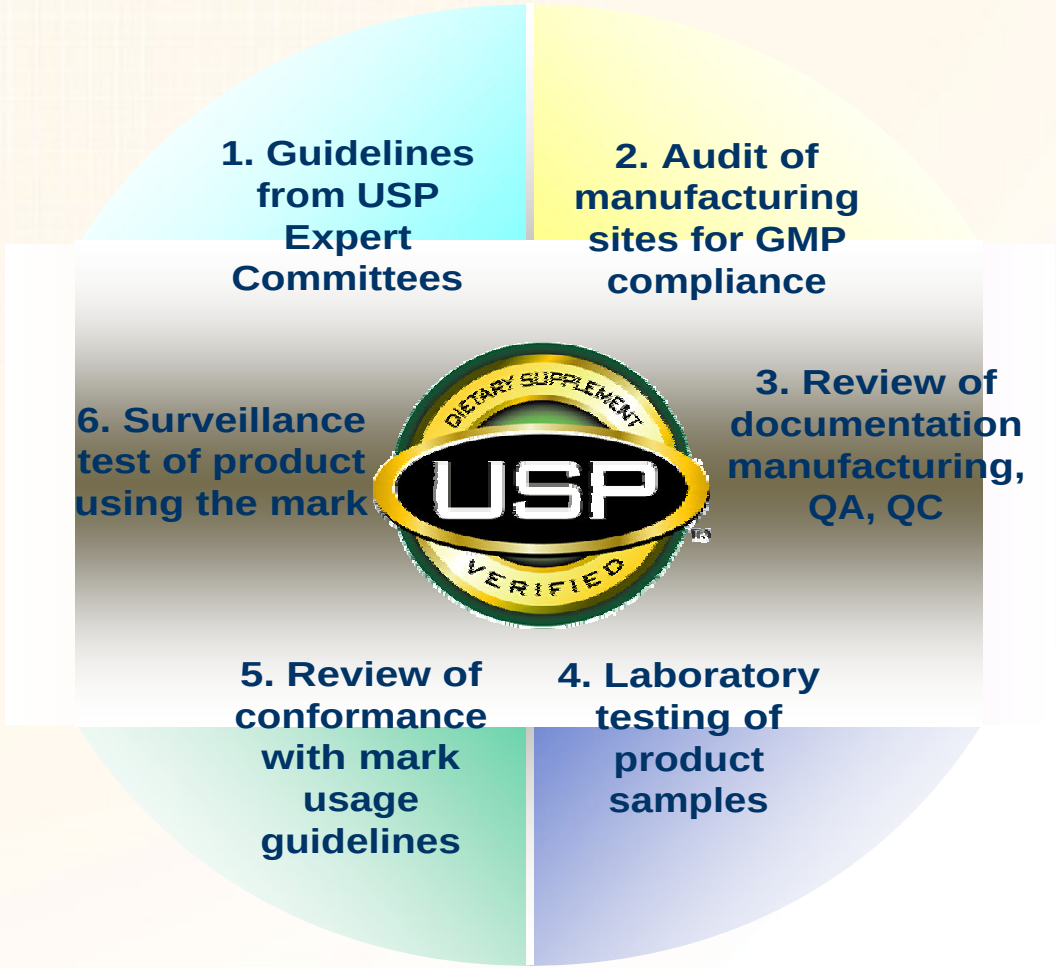
- Drug substances used in the manufacture of pharmaceutical products
- Excipients

USP Pharmaceutical Ingredient Verified Mark

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



The Verification Benefit

Succesful 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 <u>Regulatory authorities</u>**
  - 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

USP India – Contact Information

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Thank You