USP Verification Programs
“truly a unique 3rd party certification program”

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**USP**: a private, not-for-profit, nongovernmental organization, independent from industry, with offices in Europe, India, China, and Brazil.

**Mission**: To improve the health of people around the world through public standards and related programs that help ensure the quality, safety, and beneficial use of medicines and foods.

**Resources**: Offices and laboratory facilities located in the US, India, China and Brazil with local staff for testing and auditing support.
USP Verification Services

USP Dietary Supplement Verification
Launched 2002
Dietary Supplements

USP Dietary Ingredient Verification
Launched 2004
Dietary Ingredients (Vitamins, Minerals, Amino Acids, Botanicals, Non-botanicals)

USP Pharmaceutical Ingredient Verification
Launched 2006
Drug Substances and Excipients
USP Verification Programs

- **Voluntary Program**
  - Market Driven
    - Supplier advertising advantage - product differentiation
    - Purchaser demand

- **Truly a 3rd Party Certification Program**
  - Complies with USP Public Health Mission:
    - Verifies that products are of the right quality
  - Not-for-Profit
    - Supplier pays some costs
    - USP subsidizes program
  - ISO Accreditations
    - USP laboratories accredited to ISO 17025:2005
    - USP Verification Program working towards ISO 65 accreditation

- **Benefit for User of Product**
  - Reduce inspection costs (Supplier Qualification)
  - Gain assurance that comes from USP
    - a trusted, independent, science-based, standards setting body
Key Elements of the Verification Programs

1. Product appropriate for inclusion in program
2. Audit of manufacturing sites for GMP compliance
3. Review of chemistry, manufacturing and controls product documentation
4. Laboratory testing of product samples
5. Review of conformance with mark usage guidelines

Phase I

Phase II

Mark Approval
Performing just an on-site audit does not sufficiently ensure product quality.

PHASE I: Unique Program with Complimentary Process

GMP Quality Systems
On-Site Facility Audit

Indivisible Process

Unique in that it is modeled on the “ANDA” Review and Preapproval Inspection Process
GMP Audit Criteria

Audit for compliance with:

21 CFR Part 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements and
USP General Chapter <2750>
Manufacturing Practices for Dietary Supplements

ICH Q7 Good Manufacturing Practice Guide
for Active Pharmaceutical Ingredients (and Dietary Ingredients)

USP General Chapter <1078>
Good Manufacturing Practices for Bulk Pharmaceutical Excipients
GMP Audit Criteria

GMP Audit focuses on and covers 6 systems:

Quality Management
- Organization & Personnel
- Training Program
- Documentation & Records Management
- Internal Quality Audit Program
- Corrective Action Preventative Action Program
- Discrepancy & Failure Investigations
- Deviation Program
- Complaint Reviews
- Returns & Recalls
- Change Control Program
- Quality Unit Approval Oversight

Facilities and Equipment
- Facilities & Grounds Maintenance
- Pest Control
- Sanitation & Waste Disposal
- Purified Water & HVAC System
- Equipment Qualification (DQ/IQ/OQ/PQ)
- Equipment Maintenance, Calibration & Cleaning
- Computerized Systems & Electronic Records (Part 11)
GMP Audit focuses on and covers 6 systems:

Materials
• Receipt, Storage & Distribution Controls
• Component, Packaging & Labeling Specifications
• System for Testing & Release
• Supplier Qualification Program
• Rejected & Returned Product Management

Production
• Master/Executed Production & Control Records
• In-process Sampling & Testing
• Manufacturing Process Performance Evaluation
• Reprocessing and/or Reworking

Packaging & Labeling
• Label Control & Revision Process
• Master/Executed Packaging & Labeling Records

Laboratory Control
• Appropriate Laboratory Controls
• Laboratory Test Procedures
• Out of Specification (OOS) Investigations
• Analytical Methods Validation
• Stability Evaluation Program
CMC Product Documentation Review Criteria

Review documentation format follows:
ICH M4Q Common Technical Document (CTD) – Quality

ICH and USP guidances referenced include:
ICH Q1, USP <1150> – Stability
ICH Q2(R1), USP <1225> and <1226> - Analytical Validation
ICH Q3, USP <1086> - Impurities
ICH Q6, USP <1080> - Specifications

Product document review uncovers quality issues not discovered during GMP facility audits
CMC Product Documentation Review Criteria

1. General Information
   - Nomenclature, Structure (ingredient) or Formulation (product), General properties

2. Manufacture
   - Manufacturer(s), Description of manufacturing process and process controls; Control of materials; Control of critical steps and intermediates; Process Validation and/or evaluation; Manufacturing process development
   - Executed batch records for lots selected for testing

3. Characterization
   - Elucidation of structure (ingredients); Impurities (ingredients); Contaminants

4. Control of Ingredient(s) and Finished Product
   - Specifications; Analytical procedures; Validation of analytical procedures; Batch analysis

5. Reference Standards or Materials
6. Container Closure System and Labeling
7. Stability
8. Facilities and Equipment
9. Adventitious Agents and Safety Evaluation (ingredients)
Testing for Conformance to Specifications

- Testing in accordance with standards in the current edition of the USP-NF and/or other compendia, when applicable (dependent on manufacturer).

- Testing for conformity with manufacturer’s specifications, where USP–NF or other compendial standards are not available, with supportive analytical validation
  - Procedures will be evaluated for ability to control the quality of the ingredient/product being tested.

- Testing of 3 lots of ingredient/product (sampled during on-site audit)
  - Identification
  - Assay – strength / quantitative label claim
  - Impurities – varies with multiple synthetic approaches for ingredients
  - Contaminants – not to exceed acceptable levels
    - heavy metals, residual solvents, pesticides, PCBs, Dioxins, Furans
  - Performance characteristics
    - Dissolution / disintegration (products), pH, particle size (ingredients)
  - Others as applicable
    - e.g., polymorphism (ingredients), friability (products)
USP Verified Mark for Dietary Supplements

For products meeting the dietary supplement verification program requirements the manufacturer will receive a **notification letter** indicating the verification of each dietary supplement, per manufacturing site.

Manufacturers must submit for USP’s approval, all artwork for labels and promotional materials carrying the mark.

USP will review Mark use for:
- Appropriate proportions and look
- Descriptive statements appearing with Mark
- Clarity and good taste
- Proper representation of verification

USP tagline: USP has tested and verified ingredients, potency, and manufacturing process. USP sets official standards for dietary supplements. See [www.uspverified.org](http://www.uspverified.org)

Manufacturers and their verified dietary supplements are posted on [www.usp.org/USPVerified/](http://www.usp.org/USPVerified/)
Look for the USP-Verified Mark on Your Dietary Supplements

Your assurance

• What’s on the label is in the bottle.

• The supplement does not contain unacceptable levels of contaminants.

• The supplement will break down properly to allow ingredients to be available for absorption by the body.

• The supplement has been made under safe, sanitary, well-controlled manufacturing processes.
For ingredients meeting the USP dietary ingredient, drug substance, or excipient verification program requirements, the manufacturer

- Will receive a **notification letter** indicating the verification of each ingredient, per manufacturing site

- May show customers a USP Verified **Certificate** of Standards Compliance

- May display the USP Dietary Ingredient or Pharmaceutical Ingredient Verified **Mark** on the ingredient’s bulk label and Certificate of Analysis

Manufacturers and their verified ingredients are posted on [www.usp.org/USPVerified/](http://www.usp.org/USPVerified/)
PHASE II: Continuous Surveillance Monitoring

Annual surveillance audit
• currently for dietary supplement product manufacturers only

Annual internal audit report
• used to monitor state of operations within the participant’s site(s) in between audits conducted by USP
  • USP audits performed every 3 years for ingredient manufacturers
  • More frequent audits on a for-cause-basis, or in response to major change

Annual product report (APR)
• Lot history
• List of any deviations
• List of customer complaints
• Key feature of program: USP notification of changes (major, moderate or minor)
  • Type of follow-up action will depend on the nature of the change (e.g., audit, documentation review, testing)

Product testing for conformance to specifications
• $\sqrt{N} + 1$ per dietary supplement product category
• Minimum of 1 lot of each ingredient (typically 3 lots)
Truly a unique 3rd party program that you can trust

USP is a private, not-for-profit, non-governmental organization
  • independent from industry

USP driven by public health mission, not by financial incentives
  • USP verifies that products are of the right quality
  • USP charges below actual costs and subsidizes program

 Manufacturers have to earn the right to use the USP Verified Mark
  • Mark cannot be bought
  • USP has the liberty to not grant certification
  • USP will not jeopardize its reputation in the healthcare industry
  • It might take a company more than a year to achieve verification
Benefits of USP Dietary Supplement Verification

Rebuilds consumer **trust and confidence**

- Authoritative third-party verification restores consumer confidence in dietary supplement products

Brings **clarity** to a confusing market

- USP verification mark helps patients make informed decisions about their dietary supplement products

Improves **quality** of dietary supplements

- USP works with dietary supplement manufacturers to improve their quality systems to ensure consistency in the quality of dietary supplement products
Benefits of USP Ingredient Verification

Benefits for **users** of dietary ingredients and excipients:
- Not just a US program; also can be used worldwide
- Reduce auditing costs
- Gain assurance that comes from USP
  - a trusted, independent, science-based, standards setting body
- Reduces the risk of inconsistent and substandard quality ingredients
- Continuous surveillance monitoring

Benefits for **suppliers**:
- Demonstrate to users the quality of the product, using USP name and reputation for high quality, differentiating it from other products and questionable producers
- Obtain a rigorous and thorough scientific review and evaluation of the firm’s quality system and manufacturing operations for continual improvement

Benefits for **regulatory authorities**:
- Promote the public health by improving quality at participating companies
- Augment the resources of regulatory authorities (risk assessment input)
- Reduce the regulatory burden by creating a common review and audit function in participating countries
Items on the USP website:

- Participants manual
- Process flow chart
- List of participants
- List of manufacturing sites
- List of verified products
Pharmaceutical Ingredient Verification Participants
(with products approved or in-process)

- **Doctor Reddy’s Laboratories** (India):
  - Ramipril, Clopidogrel Bisulfate (Form I), Finasteride (Form III), Olanzapine (Form I), Naproxen, Naproxen Sodium, and Nizatidine

- **Arch Pharmalabs** (India):
  - Clopidogrel Bisulfate (Form I), Lamivudine, Zidovudine, and Stavudine

- **Malladi Drugs** (India):
  - Psuedoephedrine Hydrochloride, Phenylephrine Bitartrate, and Phenylephrine Hydrochloride

- **Jubilant Life Sciences Limited** (India):
  - Losartan Potassium, Olanzapine

- **Ulkar Kimya** (Turkey):
  - Omeprazole, Lansoprazole, Pantoprazole, Etodolac, Meloxicam, Irbesartan, Aripiprazole, Olmesartan

- **International Specialty Products (ISP)** (USA):
  - Povidone – Iodine, Povidone, Crospovidone, and Copovidone

- **Evoniks - Rexim S.A.S. Degussa Group** (France):
  - L-Methionine

- **BASF – The Chemical Company** (Germany):
  - Povidone – Iodine, Povidone, Crospovidone, and Copovidone

- **Deepak Fertilizers and Petrochemicals, Corp.** (India):
  - Isopropyl alcohol

- **Brahmar Cellulose Products Private Limited** (India):
  - Microcrystalline Cellulose
Dietary Ingredient Verification Participants
(with products approved or in-process)

- **Ocean Nutrition (Canada)**
  - Natural Fish Oils, Fish Oil Concentrates, Fish Oil Ethyl Esters
- **Inter Farma, S.A. (Argentina)**
  - Chondroitin Sulfate Sodium
- **Arjuna Natural Extracts, Ltd. (India)**
  - Standardized extract of Tumeric (Bio-Curcumin®)
- **Bioriginal (Canada)**
  - Borage Oil
- **Ganzhou Julong (China)**
  - Rebaudioside A, Stevia Glycosides
- **OmniActive Technology Limited (India)**
  - Free Lutein Concentrate, Lutein Ester Concentrate, Zeaxanthin Concentrate
- **PuraPharm International (H.K.), Ltd. (Hong Kong)**
  - ONCO-Z Coriolus Versicolor Extract
- **Xiamen Kingdomway Group Company (China)**
  - Coenzyme Q10
- **Yantai Dongcheng Biochemical Co., Ltd. (China)**
  - Glucosamine HCl, Chondroitin Sulfate Sodium
Dietary Ingredient Verification Participants
(with products approved or in-process)

- Hetian Dichen Pharmaceutical & Bio-technology Co. Ltd. (China)
  - Cistanche Tubulosa extract, Grape seed extract
- Huaian MDC Chemistry Co. Ltd. (China)
  - Chondroitin Sulfate Sodium
- Kaiyuan Hengtai Fine Chemicals Factory (China)
  - L-Carnitine L-Tartrate, L-Carnitine
- Shenzhou Biology & Technology Co. Ltd. (China)
  - Coenzyme Q10
- Tangshan Sanxin Biochemical Products Co. Ltd. (China)
  - Chondroitin Sulfate Sodium
- Zhejiang Medicine Co., Ltd.; Xinchang Pharmaceutical Factory (China)
  - Beta-carotene, Vitamin E, Coenzyme Q10, Biotin
- Zhucheng Haotian Pharm. Co., Ltd.
  - Rebaudioside A
- Parry Nutraceuticals (India)
  - Organic Spirulina
- Sigma-Tau Health Science, Inc. (US)
  - Glycine Propionyl L-Carnitine Hydrochloride, Acetyl L-Carnitine Arginate Dihydrochloride
Brands Carrying the USP Verified Mark:

- Berkley & Jensen
- Safeway
- Kirkland Signature
- Nature Made
- TruNature
- Schiff Nutrition International

Dietary Supplement Verification Participants

Manufacturers:

- Pharmavite, LLC (participant for 10 years)
- Banner Pharmacaps, Inc.
- IVC Nutrition Corporation
- International Vitamin Corporation
- Natural Factors Nutritional Products
- NBTY, Inc.
- Northwest Natural Products
- Perrigo Company of South Carolina
- Robinson Pharma, Inc.
- Schiff Nutrition
- Uni-caps, LLC

Participant’s Advertising of USP’s Mark

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- USP®
- Kirkland
- Nature Made
- Tri-Max

Clinical studies show Vitamin E helps to strengthen the body’s immune and brain functions, as well as protect the eye, skin, and brain from harmful substances. In addition, it supports the heart, helps to maintain normal blood lipids, and aids in the synthesis of certain structural proteins such as collagen. Vitamin E is a powerful antioxidant that protects the body’s natural substances from the harmful effects of free radicals, which can damage the heart, skin, and brain. It helps to maintain the structural integrity of the body’s cells, tissues, and organs.

Vitamin E is produced in the body, but food sources can also provide it. Good sources of vitamin E include grains, seeds, nuts, and vegetables. It is also available in the form of supplements. Take 1000 mg of vitamin E per day as a supplement, which is safe for adults. For children, take 500 mg of vitamin E per day as a supplement, which is safe for children.

VITAMIN E STUDY

Vitamin E contributes to a healthy heart.

Nature Made® was the first brand of vitamins to receive the United States Pharmacopeia (USP) seal of approval by adhering to strict standards on purity and potency. A non-profit organization, USP has set standards for pharmaceutical medicine for over 100 years. Your body can take full advantage of the nutrients in Nature Made® supplements.

Thank you for purchasing Nature Made products. We hope you enjoy your 5% coupon! Remember to keep buying our points. Each coupon you earn after this one will be worth $7/!

Nature Made® offers a wide range of high-quality products that contain the most beneficial ingredients to enhance the well-being of you and your family. Nature Made uses the best-known brands and the United States Pharmacopeia (USP) certification for its products. A USP mark seals that the product is manufactured to a high, professional standard that is consistent with the same standards that are used in the production of products. It is also consistent with a high level of excellence in the industry. USA: USP has been setting official public standards for dietary supplements, prescription drugs, and over-the-counter medicines since 1820.


For more information, visit www.naturemade.com.
The USP Verified Mark

Makes It Easy for Consumers at NaturalMedicines.com & MedicalGuide.org
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Thank You
Questions