Third Party Verification of Excipients

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protects public health by establishing public standards and programs to ensure the quality, safety and benefit of medicines and foods.
USP Verification Programs

USP Dietary Supplement Verification
Launched 2002

USP Dietary Ingredient Verification
Launched 2004
Dietary Ingredients
Traditional Chinese Medicine Ingredients
Ayurvedic Medicine Ingredients

USP Pharmaceutical Ingredient Verification
Launched 2006

USP Excipient Verification
Launched 2006
Key Elements of the Excipient 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
6. Continuous surveillance: Triennial GMP audit, Internal audit reports, Annual product reviews, Product testing
1. Excipient Eligible for Inclusion

- Participants provide list of excipients for submission

- Factors to consider:
  - Regulatory and/or patent status
  - Compendial presence and/or scientific feasibility
  - Safety concerns

- USP Staff, in consultation with USP’s Expert Committee, review products and ingredients to confirm that they are appropriate for inclusion in the program
Performing just an on-site audit does not sufficiently ensure product quality.

Unique in that it is modeled after the FDA “ANDA” review and pre-inspection approval process.
2. Audit Criteria

Audit for compliance with:

USP General Chapter <1078>
*Good Manufacturing Practices for Bulk Pharmaceutical Excipients*

Good Manufacturing Practice (GMP) Audit focuses on and covers 6 systems:

1. Quality Management
2. Facilities and Equipment
3. Materials
4. Production
5. Packaging and Labeling
6. Laboratory Controls
3. Product Documentation Review Criteria

Chemistry, Manufacturing and Controls (CMC) format:
ICH M4Q Common Technical Document (CTD) – Quality

ICH and USP guidance referenced includes:
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 CMC documentation review uncovers quality issues not discovered during GMP site audits
3. Product Documentation Review Criteria

1. General Information
   • Nomenclature, structure, and general properties

2. Manufacture
   • Description of manufacturing process and process controls
   • Control of materials
   • Control of critical steps and intermediates
   • Process validation
   • Manufacturing process development

3. Characterization
   • Elucidation of structure
   • Impurities

4. Control of Ingredient
   • Specifications
   • Analytical procedures and validation
   • Batch analysis

5. Reference Standards or Materials

6. Container Closure System and Labeling

7. Stability
4. Product Testing

• Testing in accordance with USP-NF and/or other compendia (dependent on manufacturer)

• Testing for conformity with manufacturer’s specifications, when compendial standards do not exist
  • Test procedures require validation and must control excipient quality

• Test 3 lots for conformance to specifications:
  - Identification
  - Assay / potency
  - Contaminants
  - Performance
5. Label Review

- Manufacturers receive **notification letter** indicating verification of each excipient per manufacturing site
- USP reviews all uses of the USP Verified Mark for proper representation of the Mark
For ingredients meeting program requirements, manufacturers

- may show customers a USP Verified Certificate of Standards Compliance
- may display the **USP Verified Mark** on the ingredient’s bulk label, Certificate of Analysis, and the company website

Manufacturers and their verified ingredients are posted on **www.usp.org/USPVerified/**
6. PHASE II: Continuous Surveillance Monitoring

**USP surveillance audit**
- Performed triennially for excipients
- More frequent audits on a for-cause-basis, or in response to major change

**Annual internal audit report**
- used to monitor state of operations at excipient manufacturer’s site in between audits conducted by USP

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

**Product testing for conformance to specifications**
- Full specification testing on 1 or more lots (typically 3 lots)
USP Supplier Qualification Program (SQP)
Key Elements of Excipient Supplier Qualification Program

1. Product appropriate for inclusion in program
2. Audit of manufacturing sites for GMP compliance
3. Review of chemistry, manufacturing and controls documentation
4. Laboratory testing of product samples *
5. Review of conformance with mark-usage guidelines
6. Continuous surveillance: Triennial GMP audit, Internal audit reports, Annual product reviews, Product testing

Phase I

Phase II

Supplier Qualification Report & Letter

* optional
Characteristics of USP Verification Programs

Truly a unique 3rd party program that you can trust

- USP is private, not-for-profit, and independent from industry
- USP is driven by its public health mission, not by financial incentives
- Manufacturer has to earn the use of the Mark and Certificate
  - The Mark and Certificate cannot be bought
  - USP has the freedom to not grant verification approval
  - USP will not jeopardize its reputation in the public health industry
- A company may require more than a year to achieve verification, but USP will continue to work with the company to help them pass
Benefits of USP Excipient Verification

Benefits for users of excipients:

• Not just a US program; also can be used worldwide
• Reduce inspection 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 of USP Excipient Verification

Benefits for *suppliers* of ingredients:

- Demonstrate to users the quality of their excipient, using USP’s 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 of USP Excipient Verification

Benefits for regulatory authorities:

• Promote the public health
• Augment the resources of regulatory authorities
• Reduce the regulatory burden by creating a common review and audit function in participating countries
Items on the USP website:

• Manual for Participants
• List of manufacturing sites
• List of verified products
Thank You
Questions