Global Expertise
Trusted Standards
Improved Health

The USP Excipients Stakeholder Forum
Meeting # 2
June 18, 2014

Third Party Verification of Excipients

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jba@usp.org

USP
U.S. Pharmacopeial Convention

Global Expertise
Trusted Standards
Improved Health

U.S. Pharmacopeia

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

USP Verification Programs

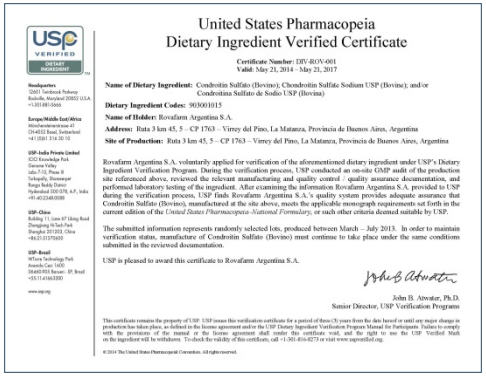
USP Dietary Supplement Verification
Launched 2002

USP Dietary Ingredient Verification
Launched 2004

Dietary Ingredients

Traditional Chinese Medicine Ingredients

Ayurvedic Medicine Ingredients



United States Pharmacopeia
Dietary Ingredient Verified Certificate

Certificate Number: DIV-ROV-001
Valid: May 21, 2014 – May 21, 2017

Name of Dietary Ingredient: Condroitin Sulfato (Bovino); Chondroitin Sulfate Sodium USP (Bovina); and/or Condroitina Sulfato de Sodio USP (Bovina)

Dietary Ingredient Codes: 90300115

Name of Holder: Rovafarm Argentina S.A.

Address: Ruta 3 km 45, 5 – CP 1763 – Virrey del Pino, La Matanza, Provincia de Buenos Aires, Argentina

Site of Production: Ruta 3 km 45, 5 – CP 1763 – Virrey del Pino, La Matanza, Provincia de Buenos Aires, Argentina

Rovafarm Argentina S.A. voluntarily applied for verification of the aforementioned dietary ingredient under USP's Dietary Ingredient Verification Program. During the verification process, USP conducted an on-site GMP audit of the production site referenced above, reviewed the relevant manufacturing and quality control / quality assurance documentation, and performed laboratory testing of the ingredient. After examining the information Rovafarm Argentina S.A. provided to USP during the verification process, USP finds Rovafarm Argentina S.A.'s quality system provides adequate assurance that Condroitin Sulfato (Bovino), manufactured at the site above, meets the applicable monograph requirements set forth in the current edition of the *United States Pharmacopeia–National Formulary*, or such other criteria deemed suitable by USP.

The submitted information represents randomly selected lots, produced between March – July 2013. In order to maintain verification status, manufacture of Condroitin Sulfato (Bovino) must continue to take place under the same conditions submitted in the reviewed documentation.

USP is pleased to award this certificate to Rovafarm Argentina S.A.

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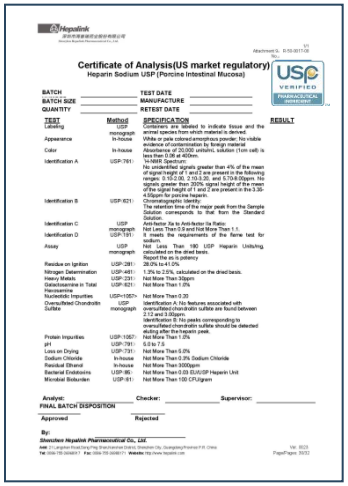
Senior Director, USP Verification Programs

USP Pharmaceutical Ingredient Verification
Launched 2006

Meitek
硫酸软骨素钠
Chondroitin Sulfate Sodium

Packaging Sequence No.:
Storage Condition:store in a dry place and keep sealed.
Gross weight:
Net weight:
FDA 注册号: 11074920328
FDA REG No.: 11074920328
USP证书号: VER-DrMEI-001
USP Certificate No: VER-DrMEI-001



Hospitalink

Certificate of Analysis(US market regulatory)
Heparin Sodium USP (Porcine Intestinal Mucosa)

BATCH
BATCH SIZE
QUANTITY
TEST DATE
MANUFACTURE
RETEST DATE

TEST	Method	SPECIFICATION	RESULT
Labeling	USP monograph	Label shall be labeled to indicate tissue and the animal species from which material is derived.	
Appearance	In-house	White or pale colored amorphous powder; No visible evidence of contamination by foreign material	
Color	In-house	Absorbance of 20,000 units/mL solution (1cm cell) is not more than 0.100 at 420nm.	
Identification A	USP-781i	In NMR Spectrum: No unidentified signals greater than 4% of the mean of signal height of 1 and 2 are present in the following ranges: δ 1.6-2.00, 2.10-3.30, and 5.70-6.05ppm. No unidentified signals greater than 2% of signal height of the mean of the signal height of 1 and 2 are present in the 3.30-4.95ppm for porcine heparin.	
Identification B	USP-621i	Chromatographic Identity: The retention time of the major peak from the Sample Solution corresponds to that from the Standard Solution.	
Identification C	USP monograph	Anti-factor Xa to Anti-factor IIa Ratio: Not Less Than 0.9 and Not More Than 1.1.	
Identification D	USP-191i	It meets the requirements of the flame test for sodium.	
Assay	USP monograph	Not Less Than 180 USP Heparin Unit/mg, calculated on the dried basis. Report the ash is potency	
Residue on Ignition	USP-281i	26.0% to 41.0%	
Nitrogen Determination	USP-461i	1.3% to 2.6%, calculated on the dried basis.	
Heavy Metals	USP-231i	Not More Than 30ppm	
Galactosamine in Total Hexosamine	USP-821i	Not More Than 1.0%	
Nucleotide Impurities	USP<1057>	Not More Than 0.30	
Oversulfated Chondroitin Sulfate	USP monograph	Identification A: No features associated with oversulfated chondroitin sulfate are found between 2.12 and 2.30ppm. Identification B: No peaks corresponding to oversulfated chondroitin sulfate should be detected eluting after the heparin peak.	
Protein Impurities	USP-1057	Not More Than 1.0%	
pH	USP-791i	5.0 to 7.5	
Loss on Drying	USP-731i	Not More Than 6.0%	
Sodium Chloride	In-house	Not More Than 0.3% Sodium Chloride	
Residual Ethanol	In-house	Not More Than 5000ppm	
Bacterial Endotoxins	USP-85i	Not More Than 0.03 EU/USP Heparin Unit	
Microbial Bioburden	USP-61i	Not More Than 100 CFU/gram	

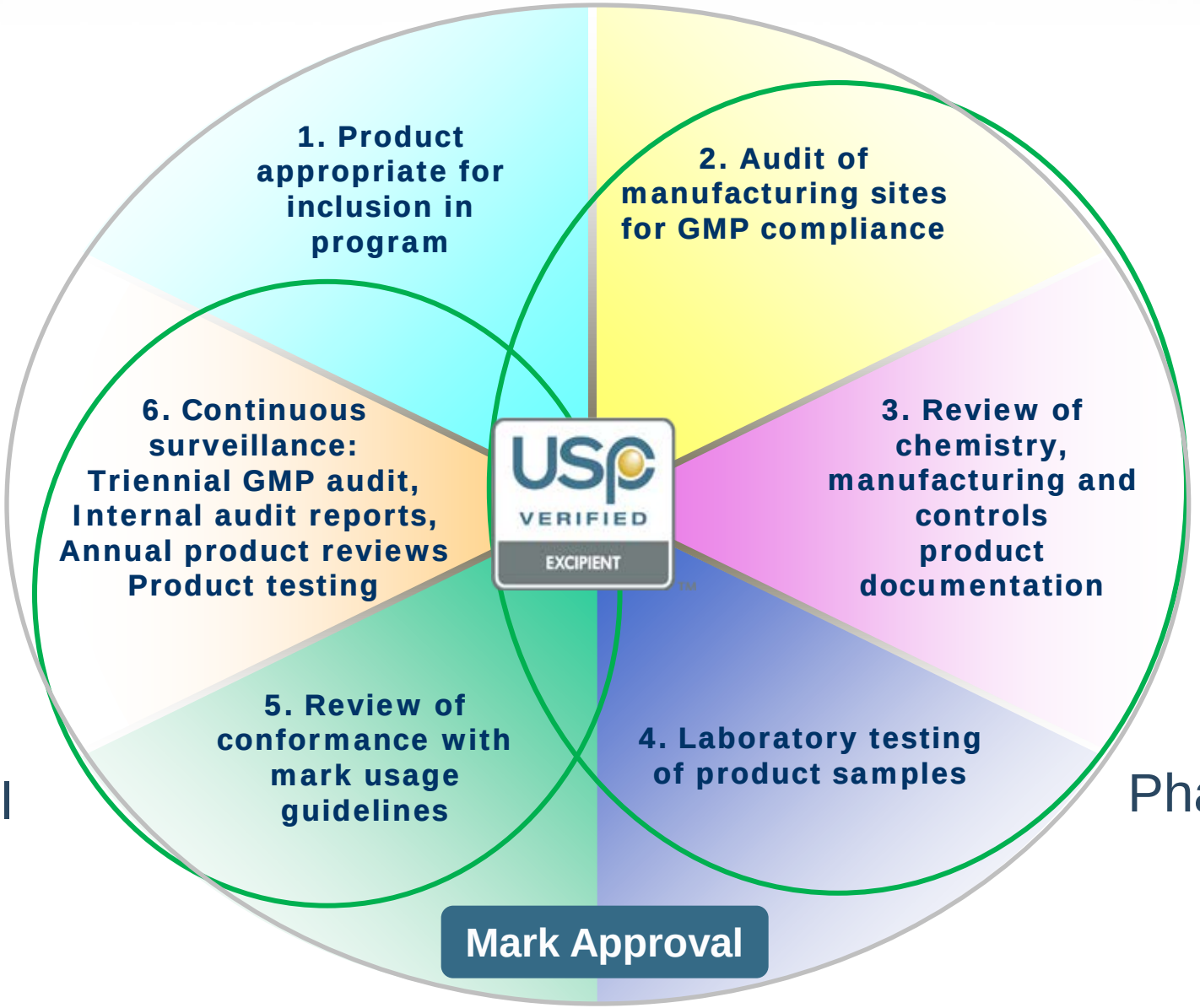
Analyst: Checker: Supervisor:

FINAL BATCH DISPOSITION
Approved Rejected

By:
Shenzhen Hepalink Pharmaceutical Co., Ltd.

USP Excipient Verification
Launched 2006

Key Elements of the Excipient Verification Programs



Phase II

Phase I

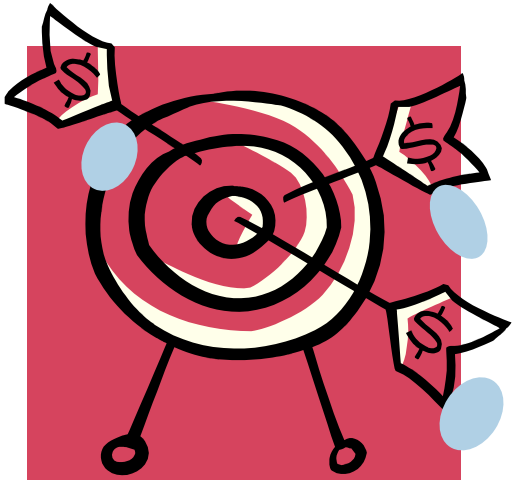
1. Excipient Eligible for Inclusion

- 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

PHASE I: Unique Program with Complimentary Process

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

GMP
Quality Systems
Audit



Product
Documentation
Review

Product
Testing

Indivisible Process

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


Checklist for Manufacturing Documentation
Submitted for Review Under USP DSVP

4. Product Testing

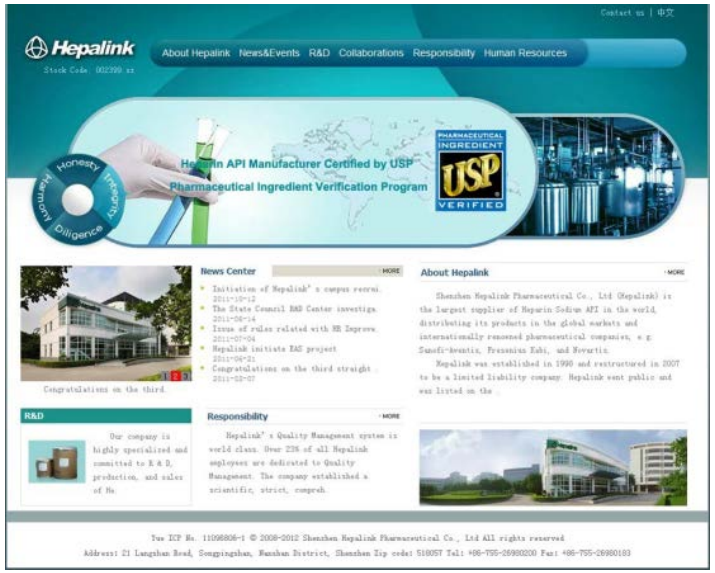
- Testing in accordance with *USP-NF* and/or other compendia (dependent on manufacturer)

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

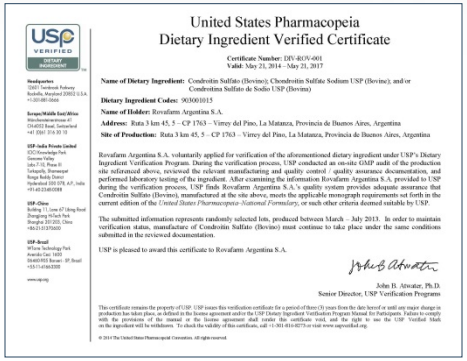
  - Test **3 lots** for conformance to specifications:
    - Identification
    - Assay / potency
    - Contaminants
    - Performance

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



USP Verified Mark and Certificate



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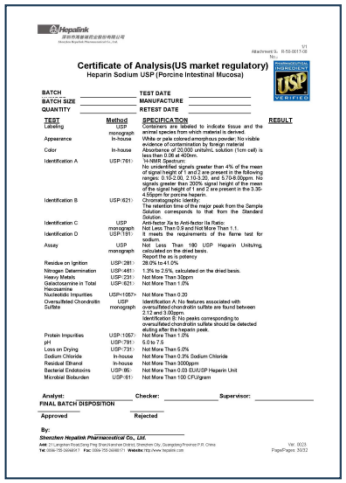
For ingredients meeting program requirements, manufacturers

- 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



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TEST	Method	SPECIFICATION	RESULT
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Appearance	In-house	White to yellowish amorphous powder; No visible evidence of contamination by foreign material	
Color	In-house	Absorbance of 20,000 units/mL solution (1cm cell) is less than 0.06 at 400nm.	
Identification A	USP-781	1H-NMR Spectrum: The signals at chemical shifts greater than 4% of the mean of signal height of 1 and 2 are present in the following ranges: 0.10-2.00, 2.10-3.20, and 5.70-6.00ppm. No signals greater than 200% signal height of the mean of the signal height of 1 and 2 are present in the 3.35-3.70ppm and 4.00-5.50ppm regions.	
Identification B	USP-821	Chromatographic identity: The retention time of the major peak from the Sample Solution corresponds to that from the Standard Solution.	
Identification C	USP monograph	Ratio Factor 3a to Anti-factor Ia Ratio: Not Less Than 0.9 and Not More Than 1.1. It meets the requirements of the flame test for sodium.	
Identification D	USP-191		
Assay	USP monograph	Not Less Than 180 USP Heparin Unit/mg, calculated on the dried basis. Report the as is potency.	
Residue on Ignition	USP-281	28.0% to 41.0%	
Nitrogen Determination	USP-461	1.3% to 2.6%, calculated on the dried basis.	
Heavy Metals	USP-231	Not More Than 30ppm	
Galactosamine in Total Hexosamine	USP-823	Not More Than 1.0%	
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Analyst: Checker: Supervisor:
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Shenzhen Hepalink Pharmaceutical Co., Ltd.

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)

Global Expertise
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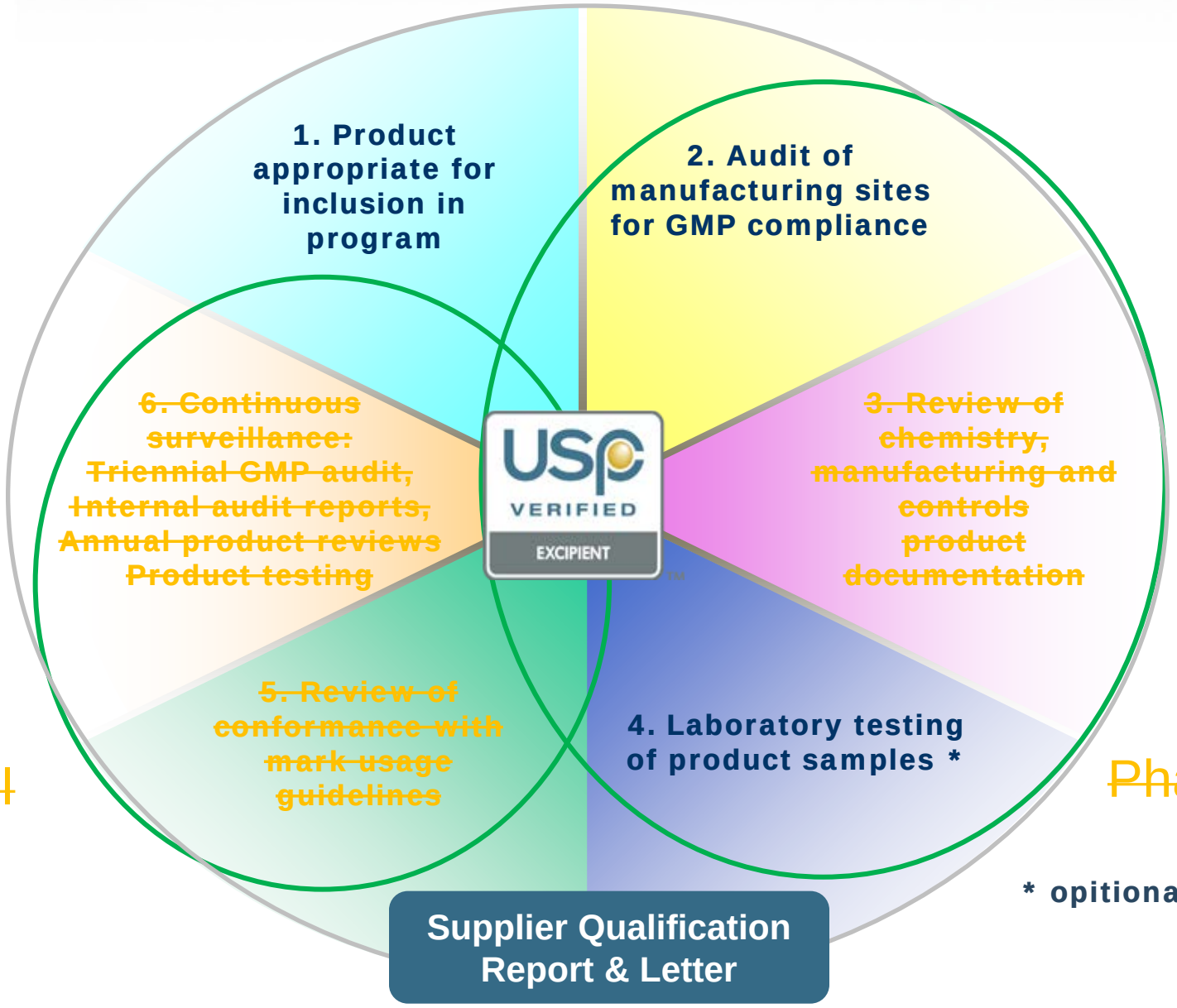
U.S. Pharmacopeial Convention

USP Supplier Qualification Program (SQP)

Key Elements of Excipient Supplier Qualification Program



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 <u>suppliers</u> 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 <u>regulatory authorities</u>:

- 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

www.usp.org/USPVerified/

Items on the USP website:

- Manual for Participants
- List of manufacturing sites
- List of verified products

Thank You

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Questions

U.S. Pharmacopeial Convention

Global Expertise
Trusted Standards
Improved Health