Ensuring Quality Hand Sanitizer Production During COVID-19 Seminar

USP Ingredient Verification Program (IVP)

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Quality alcohol used for drug products matters

Case in point: Hand sanitizer shortages & surges

Ingredient Quality Issues

Between June 2020 - January 23, 2021, the FDA placed

220 **hand sanitizer products on a Do Not Use List**

Public health impact

During May and June 2020,

15 **people in Arizona and New Mexico were hospitalized**

after ingesting hand sanitizer containing methanol.

3 **of those were left with visual impairments**

4 **of those died as a result**

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use

FDA encourages USP to update monographs

- *The following is part of the 2010-10-12 Letter from FDA to USP:*

We believe that USP's current monograph modernization program is a good start toward achieving our objective. However, it is important that the initiative be completed with urgency and that USP's efforts focus on drug products and ingredients that have the most potential for problems. In addition to the currently identified "top 200 small molecules monographs and 96 excipient monographs," we encourage USP to update all monographs that include non-specific assay or identification tests, and to re-evaluate antiquated methodologies in general. FDA strongly believes that monographs utilizing outdated analytical procedures are vulnerable to economically motivated adulteration (EMA), and current advancements in science and technology can help to fill the void. We are similarly concerned about outdated OTC monographs, and will be sending you our expert input on OTC monographs that need to be revised.

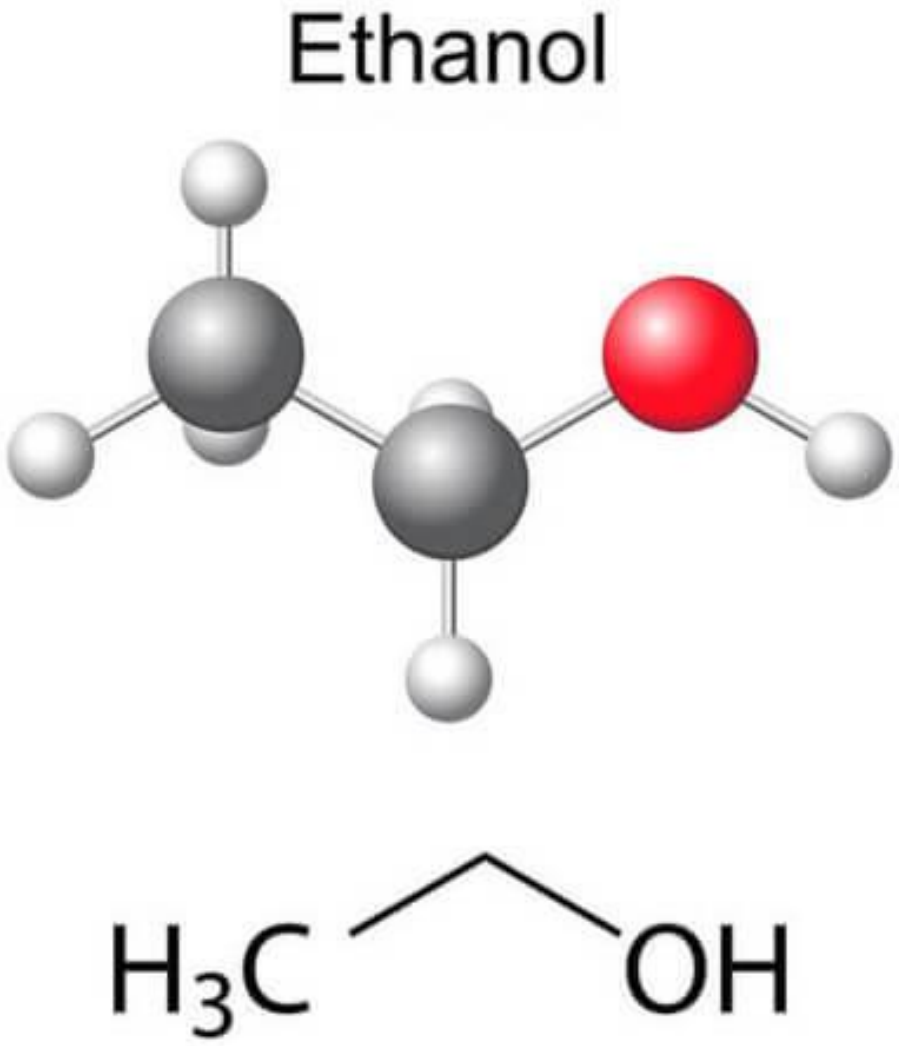
FDA has established a new task group in CDER to focus on the USP monograph modernization initiative. This group is responsible for developing a strategy to identify priority products for monograph modernization to provide requested FDA assistance to USP in your modernization efforts.

USP/FDA correspondence is available here:
https://www.usp.org/get-involved/partner/monograph-modernization-history

FDA Temporary Policy for Manufacture of Alcohol for Incorporation into Alcohol-Based Hand Sanitizer Products

- Issued March 2020; Updated August 2020
- Alcohol derived from synthetic processes may be considered for use in hand sanitizer only if it meets *USP or FCC**
- Alcohol produced in facilities normally producing fuel or technical grade alcohol may be considered for use in hand sanitizer provided the following circumstances are present…*
  - …(ii) the alcohol meets *USP* or *FCC* grade requirements…
  - …(iii) the alcohol has been screened for any other potentially harmful impurities not specified in the *USP* or *FCC* requirements but potentially present based on the specific manufacturing environment.

* Circumstances that FDA will look for when considering its exercise of enforcement discretion https://www.fda.gov/media/136390/download



USP Alcohol/Ethanol Monograph

Alcohol

Portions of this monograph that are national *USP* text, and are not part of the harmonized text, are marked with symbols (•◆) to specify this fact.

C_2H_6O 46.07
Ethanol;
Ethyl alcohol [64-17-5].

DEFINITION

•Alcohol contains NLT 92.3% and NMT 93.8%, by weight, corresponding to NLT 94.9% and NMT 96.0%, by volume, at 15.56°, of C_2H_5OH.◆

IDENTIFICATION

- **A.** It meets the requirements of the test for *Specific Gravity* ⟨841⟩.
- **B. Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: 197F or 197S. Neat.

Add the following:

▲• **•C. Limit of Methanol**

[Note—This test must be performed to be in compliance with USP, in addition to *Identification A* and *B* above.]

Sample solution A, Standard solution A, Standard solution B, Chromatographic system, and **System suitability:** Proceed as directed in *Organic Impurities*.

Analysis: Proceed as directed in the *Organic Impurities* test, *Methanol calculation*.

Acceptance criteria: Meets the requirements in *Table 2* for methanol.◆▲ (RB 1-Sep-2020)

IMPURITIES

- **Limit of Nonvolatile Residue**

Sample: 100 mL of Alcohol

Analysis: Evaporate the *Sample* in a tared dish on a water bath, and dry at 100°–105° for 1 h.

Acceptance criteria: The weight of the residue is NMT 2.5 mg.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	0	40	12
40	10	240	10

Linear velocity: 35 cm/s
Carrier gas: Helium
Injection volume: 1.0 µL

System suitability

Sample: *Standard solution B*

Suitability requirements

Resolution: NLT 1.5 between the first major peak (acetaldehyde) and the second major peak (methanol)

Analysis

Samples: *Sample solution A, Sample solution B, Standard solution A, Standard solution B, Standard solution C,* and *Standard solution D*

Methanol calculation

▲• [Note—To be performed as a part of *Identification C*.] ◆▲ (RB 1-Sep-2020)

$$\text{Result} = (r_U/r_S)$$

r_U = peak area of methanol from *Sample solution A*
r_S = peak area of methanol from *Standard solution A*

Acetaldehyde calculation (sum of acetaldehyde and acetal)

$$\text{Result} = \{[A_E/(A_T - A_E)] \times C_A\} + \{[D_E/(D_T - D_E)] \times C_D \times (M_{r1}/M_{r2})\}$$

A_E = peak area of acetaldehyde from *Sample solution A*
A_T = peak area of acetaldehyde from *Standard solution B*
C_A = concentration of acetaldehyde in *Standard solution B* (µL/L)
D_E = peak area of acetal from *Sample solution A*
D_T = peak area of acetal from *Standard solution C*
C_D = concentration of acetal in *Standard solution C* (µL/L)

Acceptance criteria: See *Table 2*.

Table 2

Name	Acceptance Criteria
Methanol	NMT 0.5, corresponding to 200 µL/L
Acetaldehyde and acetal	NMT 10 µL/L, expressed as acetaldehyde
Benzene	NMT 2 µL/L
Sum of all other impurities[a]	NMT 300 µL/L

[a] Disregard any peaks of less than 9 µL/L (0.03 times the area of the peak corresponding to 4-methylpentan-2-ol in the chromatogram obtained with *Sample solution B*).

SPECIFIC TESTS

- **•Specific Gravity** ⟨841⟩: 0.812–0.816 at 15.56°, indicating 92.3%–93.8%, by weight, or 94.9%–96.0%, by volume, of C_2H_5OH.◆
- **Ultraviolet Absorption**

Analytical wavelength: 235–340 nm
Cell: 5 cm
Reference: Water
Acceptance criteria
Absorbance: NMT 0.40 at 240 nm; NMT 0.30 between 250 nm and 260 nm; NMT 0.10 between 270 nm and 340 nm
Curve: The spectrum shows a steadily descending curve with no observable peaks or shoulders.

- **•Clarity of Solution**

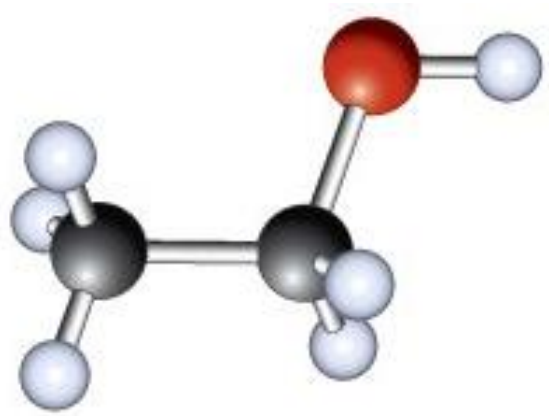
[Note—The *Sample solution* is to be compared to *Standard suspension A* and to water in diffused daylight 5 min after preparation of *Standard suspension A*.]

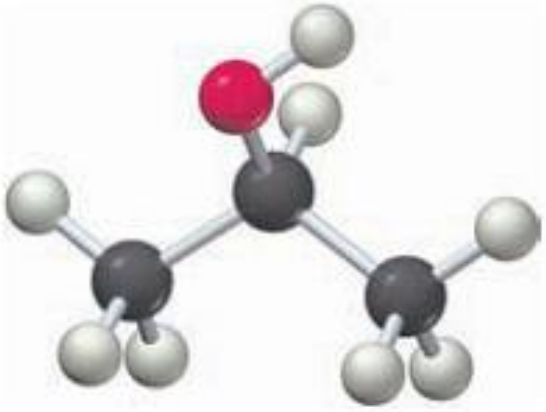
Hydrazine solution: 10 mg/mL of hydrazine sulfate in water. Allow to stand for 4–6 h.
Methenamine solution: Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.
Primary opalescent suspension: Transfer 25.0 mL of *Hydrazine solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 h. This suspension is stable for 2 months, provided it is

FDA Policy for Testing of Alcohol and Isopropyl Alcohol for Methanol

Issued in January 2021

- Expands applicability to pharmaceutical alcohol used as an API or inactive ingredient in any drug
- Methanol contamination is not only in the US.
- The USP Alcohol Monograph methanol test can also be used to test for methanol in IPA.
  - FDA considers the 200 ppm methanol limit for ethanol to be suitable for IPA, and may consider any IPA results greater than 200 ppm methanol to be adulterated under section 501 of the FD&C Act
- Repackers and distributors of pharmaceutical alcohol should perform testing



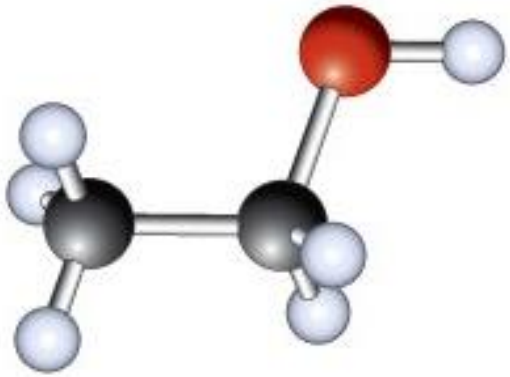


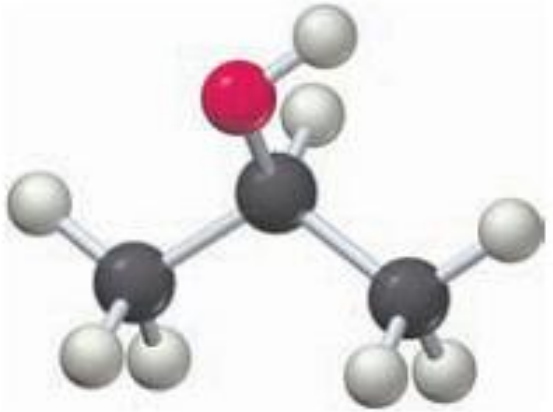
https://www.fda.gov/media/145262/download

FDA Policy for Testing of Alcohol and Isopropyl Alcohol for Methanol

Many Hand Sanitizer Manufacturers…

- Neither complied with cGMP nor manufactured their products consistent with FDA's temporary policy
- Failed to adequately perform identity testing on each lot, and did not properly evaluate identity testing data
- Relied on the COA or a test result sheet provided by the ethanol supplier, without adequately validating the supplier's COA
  - Many instances ethanol was substituted with methanol or contaminated with methanol
- Could not identify the true source of the alcohol





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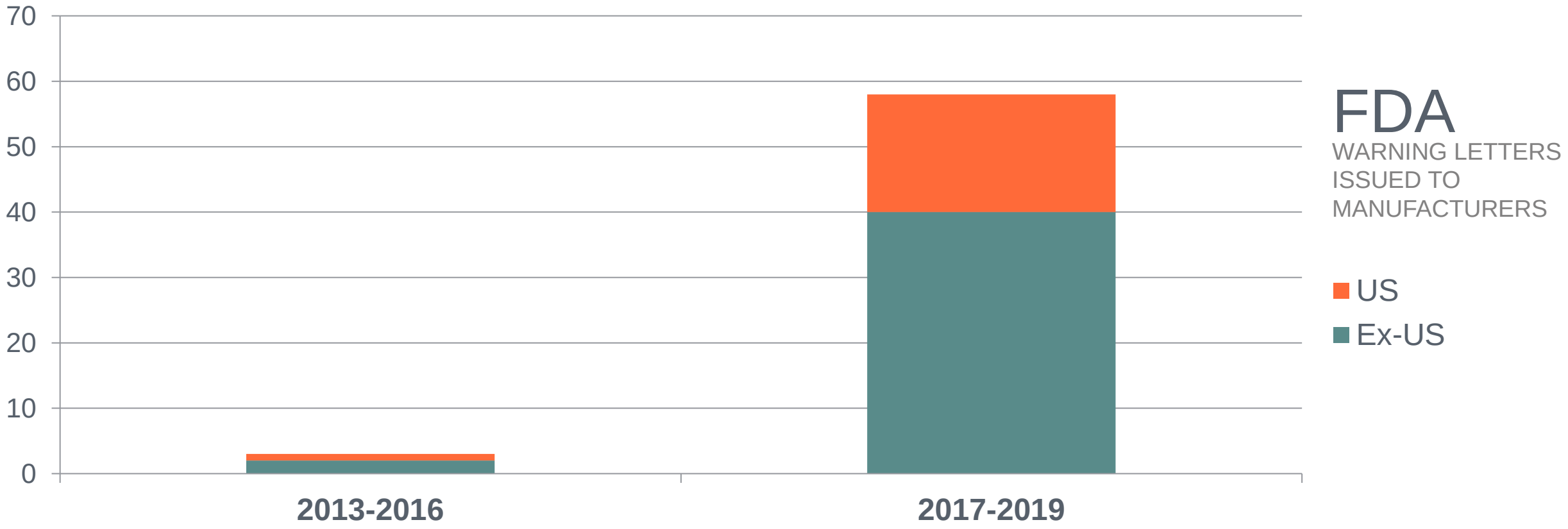
US Law: 21 CFR 211.84(d)(1) & (2)

Samples shall be examined and tested as follows:

1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

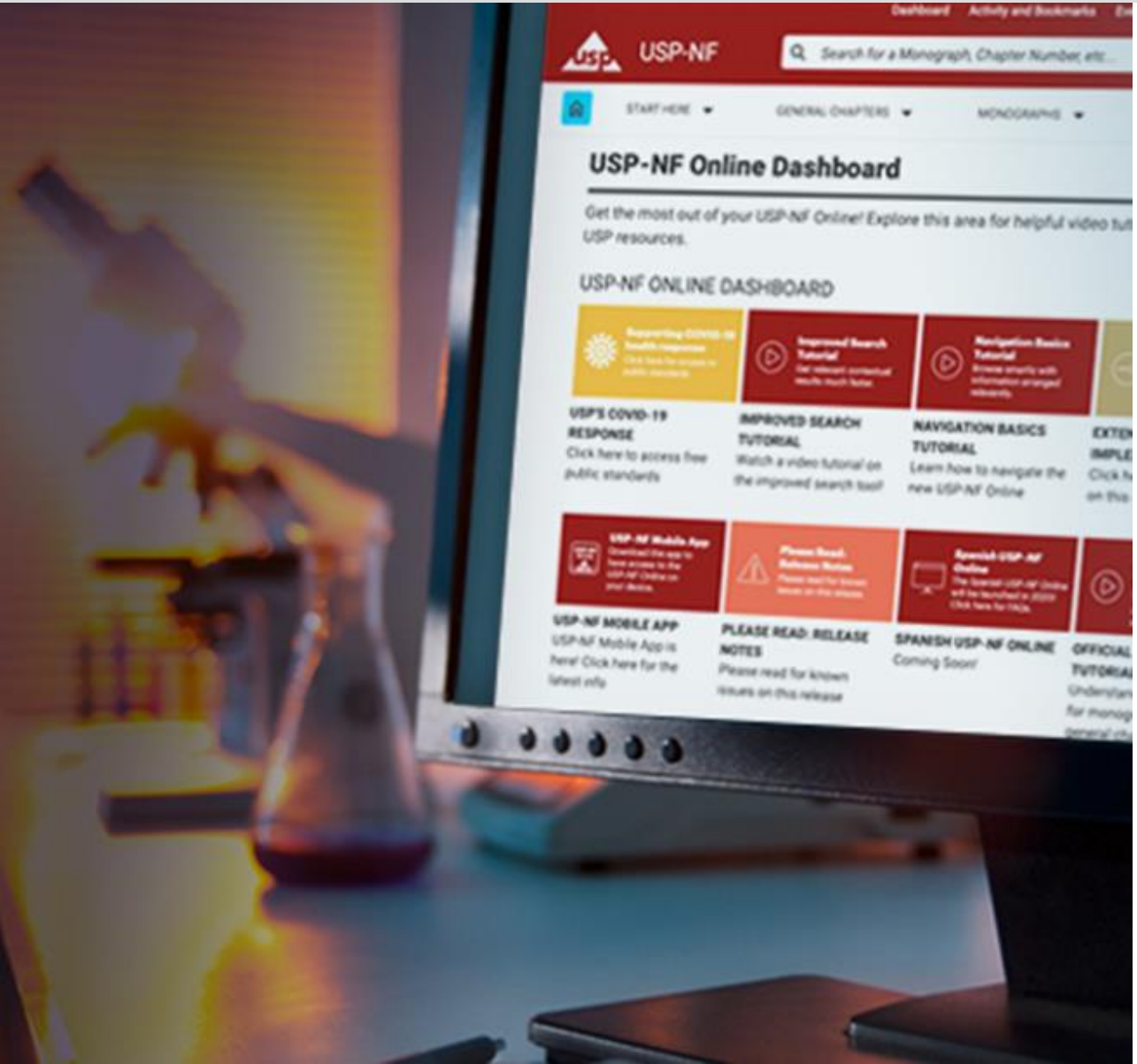
2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

FDA warning letters citing excipient testing issues



Sharp increase in warning letters citing **lack of excipient ID testing** of every incoming lot and/or **inappropriate reliance on supplier COA** for attribute testing

Ingredient manufacturers are not alone



USP has services and programs to help!

- USP Ingredient Verification Program
- USP Educational Courses
- Documentary Standards (monographs & general chapters)
- Reference standards
- Stakeholder Engagement Events – *Let your voice be heard!*

Supplier qualification

What it does & does not do

- Paper audit
  - Confirms they have a Quality Management System (QMS)
    - …But not how well it is implemented
    - …Also, is information trustworthy?
- On-site audit
  - Shows implementation of QMS
  - Quality of facility, general maintenance & procedures
    - …But it is only a periodic snapshot in time.

USP Verification helps reduce risks

Why USP Verification?

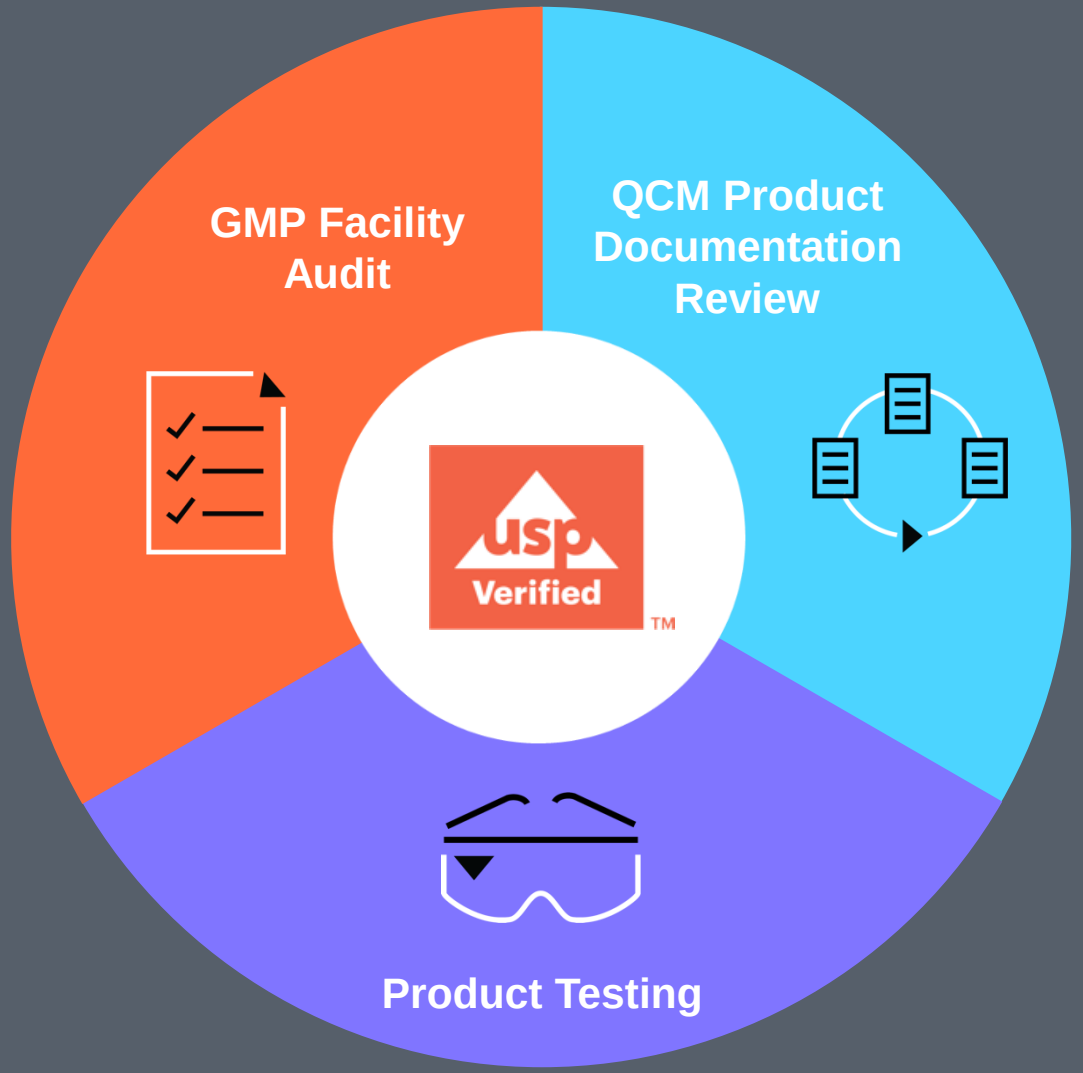
Demonstrate compliance with applicable Good Manufacturing Practice (GMP) requirements

Verify conformance to appropriate specifications for identity, potency, purity, and quality

Meet acceptable limits for impurities and contaminants

Ensure ingredient consistency from batch to batch

USP's Ingredient Verification Program services



Annual Continuous Surveillance

Good Manufacturing Practices Facility Audit

The facility audit ensures manufacturing sites comply with GMPs based on regulatory and industry best practice:

1. **Quality Management System**
2. **Facilities and Equipment System**
3. **Material System**
4. **Production System**
5. **Packaging and Labeling System**
6. **Laboratory Control System**

- ***ICH Q7*** *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* ***APIs***
- **USP General Chapter ⟨1078⟩** *Good Manufacturing Practices for Bulk Pharmaceutical* ***Excipients***
- **ANSI 363** *Good Manufacturing Practices (GMP) for Pharmaceutical* ***Excipients***

Good Manufacturing Practices Facility Audit (cont.)

Auditor qualifications & training:

1 **Program Certification**
- ✓ ISO 17020

2 **Qualifications**
- ✓ ASQ CQA certification
- ✓ Relevant industry experience
- ✓ Relevant audit experience
- ✓ Thorough understanding with the specific regulations or guidelines

3 **Training Provided**
- ✓ USP specific training
- ✓ USP program training

Quality Control and Manufacturing Process Evaluation

Documentation review uncovers quality issues not discovered during GMP facility audits

During the Quality Control and Manufacturing (QCM) Process Evaluation, USP reviews:

- General information
- Manufacture
- Control of raw materials and finished product
- Reference standards or materials
- Container closure system and labeling
- Stability ICH Q1, USP <1150>

Product Testing

The USP Ingredient Verification Program tests ingredients for four key quality attributes:

- **Identity**
- **Purity**
- **Assay**
- **Specific test for Quality**

Becoming USP Verified

Through the USP Verification multi-step process, we are here to help your company assure proper quality controls every step of the way.

Key: USP | Company | Both

Good Manufacturing Practice (GMP) Facility Audit

Conduct Audit and Issue Report → Respond to Audit Observations → Assess and Address Audit Observations → Everything Addressed and Reviewed?

Quality Control & Manufacturing (QCM) Process Evaluation

Provide QCM Documentation → Evaluate Documentation and Issue Report → Respond to Evaluation Observations → Assess and Address Evaluation Observations → Everything Addressed and Reviewed?

Product Testing

Provide Product Samples, Analytical Methods, and Supporting Information → Assess Methods, Perform Testing, and Issue Report

→ usp Verified™

Once program requirements are met:

- Notification letter
- USP Verified Certificate of Standards Compliance
- USP Verified Mark on bulk label and Certificate of Analysis
- USP Verified Mark on marketing

usp Verified™ Active Pharmaceutical Ingredient

usp Verified™ Excipient

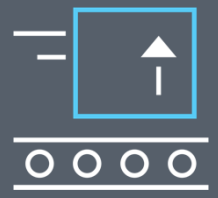
Benefits for ingredient manufacturers

The USP Ingredient Verification program:

- Offers continuous surveillance monitoring
- Demonstrates quality of ingredients to your customers
- Helps differentiate ingredients from others in the market
- Strengthens confidence that GMP and product quality standards have been met for continual improvement
- Potentially reduces number and costs of customer GMP audits
- Reduces the risk of inconsistent and substandard quality ingredients

- Is not just a US program; also can be used worldwide to verify compliance with…
  - Attributes listed in USP as well as any other pharmacopoeia claimed by participant
  - ANSI 363-2016 Good Manufacturing Practices (GMP) for Pharmaceutical Excipients
  - USP <1078>Good Manufacturing Practices for Bulk Pharmaceutical Excipients
- Gives customers assurance that comes from USP, a trusted, independent, science-based, standards setting body
- Makes the quality of your ingredients visible

Benefits for finished product manufacturers



The USP Ingredient Verification program:

- Mitigates risks to your supply chain
- Offers continuous surveillance monitoring
- Gives drug companies across the world assurance in not only attributes listed in USP as well as any other pharmacopoeia claimed by the participant
- Helps to qualify suppliers
- Provides strong assurance to drug manufacturers of the quality of their supplier base
- Potentially reduces inspection costs
- Builds confidence in ingredient quality
- Reduces risk of inconsistent, substandard quality ingredients
- Reduces risk for drug companies who pull from COA/perform reduced testing

Learn more about USP Verification

www.usp.org/IVP

- List of manufacturing sites
- List of verified products
- Manual for participants
- Verification summary poster
- Education courses

In the news:

Pharmaceutical Technology

[COVID-19's Impact: Help Ensure Quality and Manage Risk]

Tablets & Capsules

[COVID-19's Impact on FDA Inspections and Manufacturer Risk]

Industry today

[Hand Sanitizer & COVID-19: A Public Health Crisis]

You have the power to impact global health

- USP programs and services help ingredient and product manufacturers!
- Participate in the USP Ingredient Verification program to demonstrate the quality of your ingredients!
- For additional information, contact Danita Broyles
  - Danita.Broyles@usp.org
  - 301-412-7412
  - https://www.usp.org/verification-services/ingredient-verification-program

Thank You

Empowering a healthy tomorrow