USP Open Forum | January 27 & 28, 2021

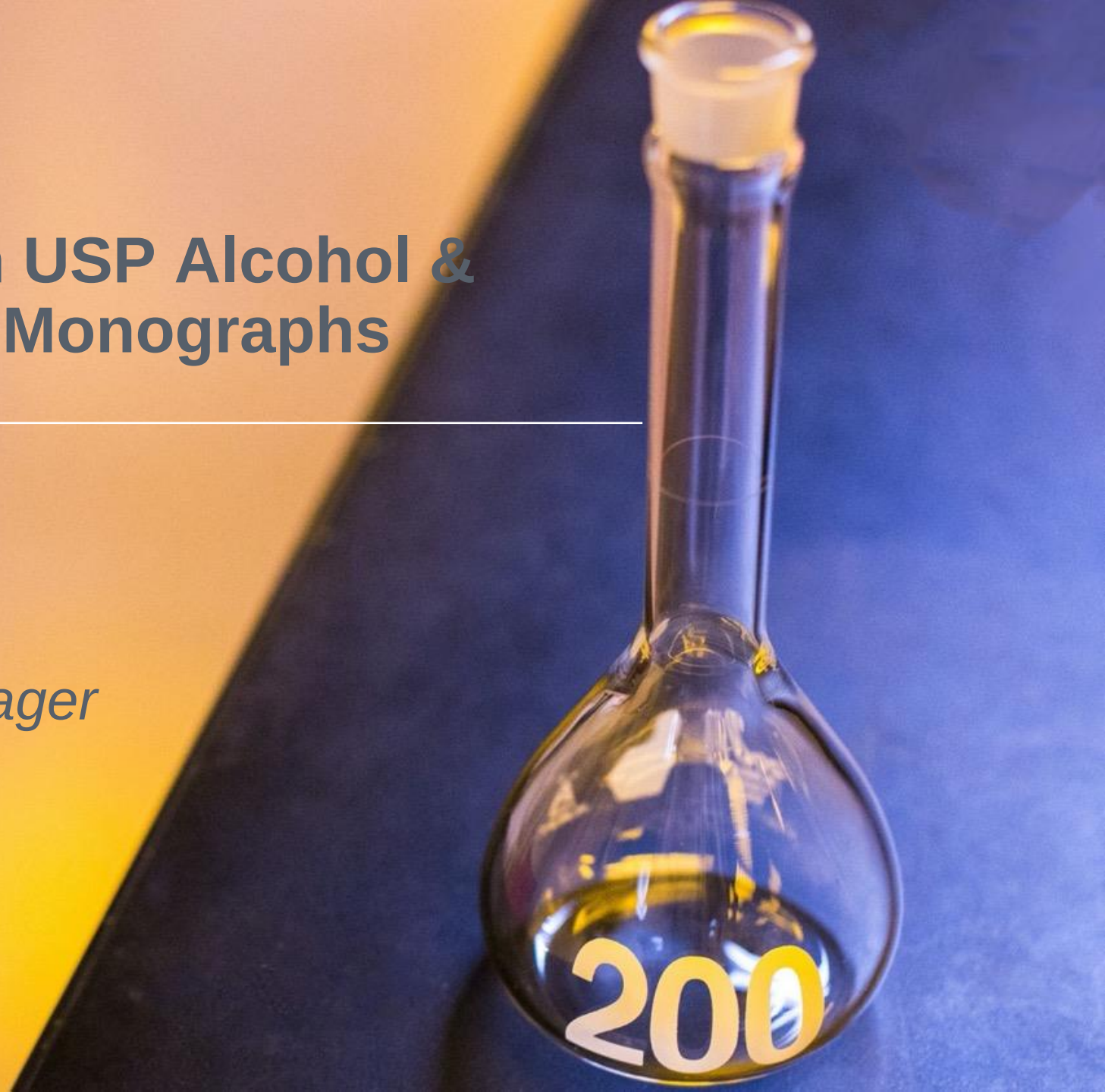
# Manufacturing Alcohol to Combat a Public Health Emergency:

## Insights on Regulatory and Quality Requirements

# Methanol Specification in USP Alcohol & USP Dehydrated Alcohol Monographs

*Robert Lafaver*

*SCD - Technical Service Manager*




200 usp
The standard of trust

# July 30: Letter from the U.S. Food and Drug Administration (FDA)

- FDA reports increasing number of hand sanitizer products contaminated with Methanol.
- FDA requests including a Limit Test for Methanol in the "Identification" section of the Alcohol and Isopropyl alcohol monographs and any related *USP-NF* monographs to help prevent **methanol** contamination.
- The Methanol limit had already been required in the **Organic Impurities** test of the **USP Alcohol** and **USP Dehydrated Alcohol** monographs (200 µL/L).
- If Methanol detection and quantification is part of the "Identification" section
  - CGMP regulations at 21 CFR 211.84(d)(1) would require manufacturers of drug products to detect and quantify any Methanol present for each lot of Alcohol or Dehydrated Alcohol received.
- If Methanol detection and quantification is only part of an "Impurity" test
  - Manufacturer need not include, as part of its identity testing, the detection and quantification of Methanol in the Alcohol or Dehydrated Alcohol. In addition, a manufacturer could deviate from the impurity requirements established in the monograph by labeling the product to indicate that it deviates from the USP test requirements.

# July 31: USP posted *Notice of Intent to Revise*

- USP identified 6 related monographs in the *USP–NF* and *FCC*
  - –*USP* Alcohol
  - –*USP* Dehydrated Alcohol
  - –*USP* Isopropyl Alcohol and *USP* Azeotropic Isopropyl Alcohol monographs
  - –*FCC* Ethyl Alcohol and *FCC* Isopropyl Alcohol monographs
- USP posted a *Notice of Intent to Revise* (NITR) on July 31, 2020 to notify the stakeholders of the upcoming proposed revision of two monographs, ***USP* Alcohol and *USP* Dehydrated Alcohol.**

# USP Proposal: Alcohol and USP Dehydrated Alcohol

- NITR proposes to begin the revision process by first including the *Limit of Methanol* test in the ID section of the *USP* Alcohol and *USP* Dehydrated Alcohol monographs.
- The added *Limit of Methanol* test in the ID section will refer to the currently official *Organic Impurities* test in the *USP* Alcohol and *USP* Dehydrated Alcohol monographs. Methanol Acceptance criteria: 200 µL/L.
- All three Identification tests in the Alcohol monographs are required to be in compliance with USP.

# Stakeholder engagement and assessment of impact

- USP and FDA held joint stakeholder calls with manufacturers, compounding pharmacies and similar facilities on Aug. 10, 2020.
- Similar approach to the 2009 diethylene glycol (DEG) contamination of glycerin products
- Nearly 4000 drug products contain alcohol or dehydrated alcohol as ingredients.
- Manufacturers should evaluate impact on their supply chain and work with FDA to prevent shortages.

# Revision Bulletin: *USP* Alcohol Monographs (1)

**Posted on Aug. 17, 2020; Official from Sept. 1, 2020**

The *Limit of Methanol* testing procedure and acceptance criteria (200 µL/L) is included as Identification C which is the same as that of *Organic Impurities* test in the USP Alcohol and Dehydrated Alcohol monographs.

**IDENTIFICATION**

- **A.** It meets the requirements of the test for *Specific Gravity* ⟨841⟩.
- **B. SPECTROSCOPIC IDENTIFICATION TESTS** ⟨197⟩, *Infrared Spectroscopy*:

***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)

# Revision Bulletin: *USP* Alcohol Monographs (2)

https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/alcohol-rb-notice-20200817.pdf

**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.

***Change to read:***

- **Organic Impurities**

  **Sample solution A:** Alcohol (substance under test)

  **Sample solution B:** 300 µL/L of 4-methylpentan-2-ol in *Sample solution A*

  **Standard solution A:** 200 µL/L of methanol in *Sample solution A*

  ▲◆[ Note— To be prepared for use in *Identification C*]◆▲ (RB 1-Sep-2020)

  **Standard solution B:** 10 µL/L of methanol and 10 µL/L of acetaldehyde in *Sample solution A*

  **Standard solution C:** 30 µL/L of acetal in *Sample solution A*

  **Standard solution D:** 2 µL/L of benzene in *Sample solution A*

  **Chromatographic system**

  (See *Chromatography ⟨621⟩, System Suitability*.)

  **Mode:** GC

  **Detector:** Flame ionization

  **Column:** 0.32-mm × 30-m fused-silica capillary; bonded with a 1.8-µm layer of phase G43

  **Split ratio:** 20:1

  **Temperatures**

  **Injection port:** 200°

  **Detector:** 280°

  **Column:** See *Table 1*.

**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*

**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*).

# *USP* Alcohol and *USP* Dehydrated Alcohol

## Part of the Pharmacopeial Discussion Group (PDG) Excipient Workplan

- Both monographs are harmonized and have been official for many years *including* the Organic Impurities test.
- The current revision will be proposed as a U.S. local requirement indicated by the diamond symbols (♦,♦).
- USP has informed PDG of this revision with detailed explanations through correspondence.
- European Pharmacopeia (EP) and Japanese Pharmacopeia (JP) will be assessing the issue of methanol contamination on their markets.

# Revision Bulletins and FAQs

- Links to the Revision Bulletins:
  - Alcohol:
    https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/alcohol-rb-notice-20200817.pdf
  - Dehydrated Alcohol:
    https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/dehydrated-alcohol-rb-notice-20200817.pdf

- Links to the Frequently Asked Questions :
  - https://www.uspnf.com/notices/alcohols-faq.

# Important Links to Hand Sanitizers

- Link to USP Hand Sanitizer Toolkit:
  - https://www.usp.org/covid-19/hand-sanitizer-information
- Link to FDA Guidance for Hand Sanitizers:
  - https://www.fda.gov/media/136289/download
- Link to WHO practical guide:
  - https://www.who.int/gpsc/5may/Guide_to_Local_Production.pdf
- Link to Alcohol and Tobacco, Tax, and Trade Bureau (TTB) guidance:
  - https://www.ttb.gov/public-guidance/ttb-pg-2020-1a
- Link to European Commission Guidance
  - https://ec.europa.eu/growth/sectors/cosmetics/products/borderline-products_en

# Contact Information for FDA and USP

## FDA

- Contact CDER Drug Shortage Staff at drugshortages@fda.hhs.gov if any access or potential drug shortage issues arise.
- Consumers, manufacturers or distributors who have questions for the FDA regarding hand sanitizers should email: COVID-19-Hand-Sanitizers@fda.hhs.gov

## USP

- Contact USP if you have questions about the USP Alcohol monographs:
  - nfmonographs@usp.org
- Contact USP if you have questions about the FCC Ethyl Alcohol monographs:
  - fcc@usp.org

# Thank You