Alcohol

Type of Posting	Revision Bulletin
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Official Date	01–Sep–2020
Expert Committee	Excipient Monographs Expert Committee 2
Reason for Revision	Safety, Urgent

To address the serious hazards associated with the use of methanol-containing alcohol and dehydrated alcohol, the Excipient Monographs Expert Committee 2 has revised the Alcohol Monograph. These revisions are consistent with a request from, and guidance issued by, the U.S. Food and Drug Administration (FDA).

The purpose for these revisions is to strengthen the *Identification* section of the monograph by including the test for *Limit of Methanol* as an additional *Identification C* test. This is intended to address the patient safety issue outlined in the Notice of Intent to Revise (NITR) posted on July 31, 2020 to alert stakeholders to this urgent matter and to announce the intended revisions. Additional information about this topic, including correspondence from the U.S. FDA to USP and responses to Frequently Asked Questions, is available here.

The revisions to the Alcohol monograph include:

- Under *Identification*, a new *Identification C*: *Limit of Methanol* test is added. The test is referring to the methanol relevant sections of the currently official *Organic Impurities* test in the same monograph. The testing procedure and acceptance criterion for methanol remains unchanged. This is a USP local requirement indicated by the diamond symbols (♦). USP has informed the Pharmacopeial Discussion Group (PDG) of this revision.
  A note was also included within *Identification C* to emphasize that compliance of identity is determined by meeting the requirements for all identification tests in the monograph as shown below:
  [Note - This test must be performed to be in compliance with USP, in addition to *Identification A* and *B* above.].
- Under *Organic Impurities*, two *Notes* are added to the *Standard solution A* and to the *Methanol calculation* subsection under *Analysis*, to indicate that the information in these sections is referenced in *Identification C*. These *Notes* are also marked by the diamond symbols (♦).

As a note to stakeholders, USP Methyl Alcohol RS (item number 1424109) was evaluated by USP and found suitable for preparing *Standard solution A* and *B*. Please also note that USP Residual Solvent Class 2 – Methanol RS contains methanol as a solution in DMSO and is not suitable for this test.

The Alcohol Revision Bulletin supersedes the currently official monograph and will become official on September 1, 2020. A similar Revision Bulletin is also posted for *Dehydrated Alcohol*.

Should you have any questions, please contact Methanol-ID@usp.org.

Revision Bulletin
Official: September 1, 2020

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.

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C_2H_6O 46.07
Ethanol;
Ethyl alcohol [64-17-5]; UNII: 3K9958V90M.

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.

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*.

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)

M_{r1} = molecular weight of acetaldehyde, 44.05

M_{r2} = molecular weight of acetal, 118.2

Benzene calculation

$$\text{Result} = [B_E/(B_T - B_E)] \times C_B$$

B_E = peak area of benzene from *Sample solution A*

B_T = peak area of benzene from *Standard solution D*

C_B = concentration of benzene in *Standard solution D* (µL/L)

[NOTE—If necessary, the identity of benzene can be confirmed using another suitable chromatographic system (stationary phase with a different polarity).]

Any other impurity calculation

$$\text{Result} = (r_U/r_M) \times C_M$$

r_U = peak area of each impurity in *Sample solution B*

r_M = peak area of 4-methylpentan-2-ol in *Sample solution B*

C_M = concentration of 4-methylpentan-2-ol in *Sample solution B* (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 stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.

Opalescence standard: Transfer 15.0 mL of the *Primary opalescent suspension* to a 1000-mL volumetric flask, and dilute with water to volume. This suspension should not be used beyond 24 h after preparation.

Standard suspension A: *Opalescence standard* and water (1 in 20)

Standard suspension B: *Opalescence standard* and water (1 in 10)

Sample solution A: Substance to be examined

Sample solution B: Dilute 1.0 mL of *Sample solution A* with water to 20 mL, and allow to stand for 5 min before testing.

Blank: Water

Analysis: Transfer a sufficient portion of *Sample solution A* and *Sample solution B* to separate test tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Standard suspension A, Standard suspension B*, and *Blank* to separate matching test tubes. Compare *Sample solution A*, *Sample solution B*, *Standard suspension A*, *Standard suspension B*, and *Blank* in diffused daylight, viewing vertically against a black background (see *Visual Comparison* ⟨630⟩). The diffusion of light must be such that *Standard suspension A* can readily be distinguished from water, and *Standard suspension B* can readily be distinguished from *Standard suspension A*.

Acceptance criteria: *Sample solution A* and *Sample solution B* show the same clarity as that of water or their opalescence is not more pronounced than that of *Standardsuspension A*.◆

- **Acidity or Alkalinity**

Phenolphthalein solution: Dissolve 0.1 g of phenolphthalein in 80 mL of alcohol, and dilute with water to 100 mL.

Sample: 20 mL of Alcohol

Analysis: To the *Sample* add 20 mL of freshly boiled and cooled water and 0.1 mL of *Phenolphthalein solution*. The solution is colorless. Add 1.0 mL of 0.01 N sodium hydroxide.

Acceptance criteria: The solution is pink (30 µL/L, expressed as acetic acid).

- ◆**Color of Solution**

Standard stock solution: Combine 3.0 mL of ferric chloride CS, 3.0 mL of cobaltous chloride CS, 2.4 mL of cupric sulfate CS, and 1.6 mL of dilute hydrochloric acid (10 g/L).

Standard solution: Transfer 1.0 mL of *Standard stock solution* to a 100-mL volumetric flask, and dilute with dilute hydrochloric acid (10 g/L). Prepare the *Standard solution* immediately before use.

Sample solution: Substance to be examined

Blank: Water

Analysis: Transfer a sufficient portion of the *Sample solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm to obtain a depth of 40 mm. Similarly transfer portions of the *Standard solution* and *Blank* to separate, matching test tubes. Compare

the *Sample solution, Standard solution*, and *Blank* in diffused daylight, viewing vertically against a white background (see *Visual Comparison* ⟨630⟩).

Acceptance criteria: The *Sample solution* has the appearance of water or is not more intensely colored than the *Standard solution*. ◆

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, protected from light.
- **USP Reference Standards** ⟨11⟩

  USP Alcohol RS

Alcohol—*see Alcohol General Monographs*

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