Isopropyl Alcohol

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Expert Committee	Simple Excipients Expert Committee

In accordance with the Rules and Procedures of the Council of Experts, the Simple Excipients Expert Committee has revised the Isopropyl Alcohol monograph. The purpose of the revision is to strengthen the Identification (ID) section of the monograph by including the Limit of Methanol test as an additional ID test.

To address the serious hazards associated with the use of methanol-containing isopropyl alcohol, the Simple Excipients Expert Committee (SE) has revised the Isopropyl Alcohol monograph. These revisions are consistent with a letter (Feb. 25, 2021) from, and a recent FDA Guidance (January 2021) issued by the U.S. Food and Drug Administration (FDA). USP previously revised the *USP* Alcohol and *USP* Dehydrated Alcohol monographs by including an Identification C Test for "*Limit of Methanol*." Additional information about that topic can be found in the Frequently Asked Questions for Alcohol and Dehydrated Alcohol.

As mentioned in the *Notice of Intent to Revise* posted on Apr. 30, 2021, the purpose of these revisions is to strengthen the *ID* section of the monograph by including the test for *Limit of Methanol* as an additional *ID* test. The new *Limit of Methanol* test utilizes a gas-chromatography (GC) method similar to the *Limit of Volatile Impurities* test in the *USP* Isopropyl Alcohol monograph. The limit for methanol (200 µL/L) is the same as that in the *USP* Alcohol monograph, consistent with what is recommended in the FDA Guidance (January 2021). The *Limit of Volatile Impurities* GC method is also updated by including the methanol as a specified impurity. Additionally, external reference standards are used for quantitative analysis of each individual impurity.

The changes to the current *USP* Isopropyl Alcohol monograph include:

1. *Identification C.* A new *Limit of Methanol* test is added to the *Identification* section. The test is referring to the *Assay* and *Limit of Volatile Impurities* tests in the same monograph with a limit for methanol (200 µL/L).

   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.]

2. *Assay.* Updated to align with the *Limit of Methanol* and *Limit of Volatile Impurities* methods because the same GC method is applied for these tests.
   - System suitability solution is updated to include 200 µL/L of methanol and 1000 µL/L of ethyl acetate in USP 2-Propanol System Suitability RS.
   - Clarified that Sample solution is the Isopropyl Alcohol substance under the test.
   - The hold time at final temperature of 100° is extended from 1 min to 5 min to elute late-eluting unknown impurities in some Isopropyl Alcohol samples. As such, the run time was extended to 26 min.
   - Under *System Suitability*,
     - Methanol and ethyl acetate are added to Table 2 to indicate their relative retention times (RRT), respectively. The RRTs for other impurities are also adjusted according to the method validation results. Please note the RRTs may vary a little bit depending on the instrument and column used.
     - A note is added to Table 2 to clarify that ethyl acetate is not considered as a known impurity, but to be used as a reference standard to calculate unspecified impurities.

    - For *Suitability requirements*, the number of replicate injections is specified for *Relative standard deviation*. Methanol and ethyl acetate are added to the *Signal-to-noise ratio requirements.*
- The calculation and acceptance criteria for *Assay* remain unchanged by using the area normalization procedure because Isopropyl Alcohol sample is analyzed.

3. *Limit of Volatile Impurities.*
    - Updated the GC method to include the new impurity: Methanol.
    - Utilized the same testing procedure as described in the *Assay*.
    - Standard solution A and Standard solution B are added for quantitative analysis of each known and unspecified impurity.
    - Individual impurities are quantitatively determined against their respective reference standards with known concentrations. Ethyl acetate is used as a reference standard for calculation of unspecified impurities.
    - The area normalization procedure (% of total detected area) for impurity analysis is deleted. The calculations for methanol, individual known impurities, and individual unspecified impurities are added.
    - Updated Table 3 to include the acceptance criteria for methanol (NMT 0.02%, corresponding to 200 µL/L). The limit of NMT 0.1% remained the same for individual known impurities (ethyl ether, acetone, diisopropyl ether, 1-propanol, and 2-butanol), and any unspecified impurity. The limit for total impurities (NMT 1.0%) also remained unchanged.

As a note to stakeholders, USP Reference Standards (RS) are qualified and suitable for use in the *Limit of Methanol* and *Limit of Volatile Impurities* tests, including USP 2-Propanol System Suitability RS (Cat# 1570439), USP Methyl Alcohol RS (Cat# 1424109), USP Acetone RS (Cat# 1006801), USP 1-Propanol RS (Cat# 1570406), USP 2-Butanol RS (Cat# 1081829). In addition, USP Ethyl Acetate RS (Cat# 1265402) is qualified and suitable for use as an RS for calculations of unspecified impurities.

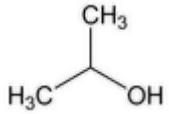
The Isopropyl Alcohol Revision Bulletin will supersede the currently official monograph and become official on Feb.1, 2022. USP encourages early adoption by stakeholders as outlined in the *USP General Notices 3.10. Applicability of Standards*.

A similar Revision Bulletin will also be posted for the *USP* Azeotropic Isopropyl Alcohol monograph.

Should you have any questions, please contact Jenny Liu, Principal Scientist (240-221-2072 or jyl@usp.org).

Revision Bulletin
Official: February 1, 2022

Isopropyl Alcohol
To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click *https://www.uspnf.com/rb-isopropyl-alcohol-20210730*.



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C_3H_8O 60.10
2-Propanol;
Isopropanol [67-63-0].

DEFINITION
Isopropyl Alcohol contains NLT 99.0% of isopropyl alcohol (C_3H_8O).

IDENTIFICATION
- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197F
- **B.** The retention time of the major peak of the *Sample solution* corresponds to the 2-propanol peak of the *System suitability solution*, as obtained in the *Assay*.

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.]

System suitability solution, Sample solution, Standard solution A, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay* and *Limit of Volatile Impurities* test.

Analysis: Proceed as directed in the *Limit of Volatile Impurities* test, *Methanol calculation*.

Acceptance criteria: Meets the requirements in *Table 3* for methanol ▲ (RB 1-Feb-2022)

ASSAY

Change to read:

● **Procedure**

System suitability solution: ▲200 µL/L of methanol and 1000 µL/L of ethyl acetate in ▲ (RB 1-Feb-2022) USP 2-Propanol System Suitability RS

Sample solution: Isopropyl Alcohol

▲(substance under test) ▲ (RB 1-Feb-2022)

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.25-mm × 60-m fused silica column, coated with a 1.4-µm film of phase G43

Temperatures

Detector: 200°

Injection port: 150°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
35	—	35	5
35	1	45	—
45	10	100	▲5▲ (RB 1-Feb-2022)

Carrier gas: Helium

Flow rate: 2.3 mL/min

Injection volume: 1 µL

Injection type: Split injection; split ratio is about 50:1. [NOTE—A 4-mm straight liner is suitable.]

Run time: ▲26▲ (RB 1-Feb-2022) min

System suitability

Sample: *System suitability solution*

[NOTE—See *Table 2*.]

Table 2

Name	Relative Retention Time
▲Methanol	0.5▲ (RB 1-Feb-2022)
Ethyl ether	▲0.8▲ (RB 1-Feb-2022)
Acetone	0.9
Isopropyl alcohol	1.0
Diisopropyl ether	▲1.3▲ (RB 1-Feb-2022)
n-Propyl alcohol (1-propanol)	▲1.4▲ (RB 1-Feb-2022)
▲Ethyl acetate[a]	1.6▲ (RB 1-Feb-2022)
2-Butanol	▲1.7▲ (RB 1-Feb-2022)

[a] Ethyl acetate Reference Standard is not a known impurity. It is used for calculation of unspecified impurities only.

Suitability requirements

Resolution: NLT 1.5 between acetone and isopropyl alcohol

Relative standard deviation: NMT 2.0% for the isopropyl alcohol peak ▲of 6 replicate injections of *System suitability solution*▲ (RB 1-Feb-2022)

Tailing factor: NMT 2.0 for the isopropyl alcohol peak

Signal-to-noise ratio: NLT 10 for any of the following peaks: ▲methanol,▲ (RB 1-Feb-2022) ethyl ether, acetone, isopropyl alcohol, diisopropyl ether, 1-propanol, 2-butanol, ▲and ethyl acetate▲ (RB 1-Feb-2022)

Analysis

Sample: *Sample solution*

Calculate the percentage of isopropyl alcohol (C_3H_8O) in the portion of Isopropyl Alcohol taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of isopropyl alcohol

r_T = sum of all the peak responses

Acceptance criteria: NLT 99.0%

IMPURITIES

Change to read:

• **Limit of Volatile Impurities**

System suitability solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

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

[Note—To be performed as a part of *Identification C*.]

Standard solution B: 1000 µL/L each of acetone, diisopropyl ether, ethyl ether, 1-propanol, 2-butanol, and ethyl acetate in *Sample solution*▲ (RB 1-Feb-2022)

Analysis

Samples: *Sample solution*, ▲*Standard solution A*, and *Standard solution B*

Methanol calculation

[Note—To be performed as a part of *Identification C*.]

$$\text{Result (\% v/v)} = \{[M_U/(M_S - M_U)] \times C_M\}/10{,}000$$

M_U = peak area of methanol in the *Sample solution*

M_S = peak area of methanol in *Standard solution A*

C_M = concentration of spiked methanol in *Standard solution A* (µL/L)

Individual known impurity (ethyl ether, acetone, diisopropyl ether, 1-propanol, 2-butanol) calculation

$$\text{Result (\% v/v)} = \{[K_U/(K_S - K_U)] \times C_K\}/10{,}000$$

K_U = peak area of individual known impurity in the *Sample solution*

K_S = peak area of individual known impurity in *Standard solution B*

C_K = concentration of spiked individual known impurity in *Standard solution B* (µL/L)

Individual unspecified impurity calculation

$$\text{Result (\% v/v)} = [(r_U/r_S) \times C_S]/10{,}000$$

r_U = peak area of each unspecified impurity in the *Sample solution*

r_S = peak area of ethyl acetate in *Standard solution B*

C_S = concentration of ethyl acetate in *Standard solution B* (µL/L) ▲ (RB 1-Feb-2022)

Acceptance criteria: See *Table 3*.

Table 3

Impurity	Percentage (% ▲v/v)
Methanol[a]	NMT 0.02[a] ▲ (RB 1-Feb-2022)
Each ▲other▲ (RB 1-Feb-2022) individual ▲known impurity (ethyl ether, acetone, diisopropyl ether, 1-propanol, 2-butanol)▲ (RB 1-Feb-2022)	NMT 0.1
▲Individual unspecified impurity	NMT 0.1 ▲ (RB 1-Feb-2022)
Total ▲impurities▲ (RB 1-Feb-2022)	NMT 1.0

[a] To be performed as a part of *Identification C*.

- **Limit of Nonvolatile Residue**

  Sample: 50 mL

  Analysis: Evaporate the *Sample* in a tared porcelain dish on a steam bath to dryness, and heat at 105° for 1 h.

  Acceptance criteria: NMT 2.5 mg (0.005%)

SPECIFIC TESTS

- **Specific Gravity** ⟨841⟩**:** 0.783–0.787
- **Refractive Index** ⟨831⟩**:** 1.376–1.378 at 20°
- **Acidity**

  Sample solution: To 50 mL of Isopropyl Alcohol add 100 mL of carbon dioxide-free water.

  Analysis: To the *Sample solution* add 2 drops of phenolphthalein TS, and titrate with 0.020 N sodium hydroxide to a pink color that persists for 30 s.

  Acceptance criteria: NMT 0.70 mL of 0.020 N sodium hydroxide is required for neutralization.
- **Water Determination** ⟨921⟩, *Method I*

  Sample: 5.0 g

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, and prevent exposure to excessive heat. Protect from light.
- **USP Reference Standards** ⟨11⟩

  USP 2-Propanol RS

  USP 2-Propanol System Suitability RS

  It contains isopropyl alcohol with 0.1% each of ethyl ether, acetone, diisopropyl ether, 1-propanol, and 2-butanol.

Isopropyl Alcohol—*see Isopropyl Alcohol General Monographs*

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