BRIEFING

Benzyl Alcohol. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Benzyl Alcohol monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADOPTION STAGE 6** document, includes a minor change to *Procedure: Benzaldehyde and Other Related Substances* (previously labeled *Related compounds*). The procedure has been changed to address the instance in which the substance contains peaks that overlap with peaks due to ethylbenzene or dicyclohexyl. Instruction has been added to correct for this additional peak when calculating the sum, disregard any limit that is 0.01 times the area of ethylbenzene.

(EM1: K. Moore.)
RTS—C58790

Change to read:

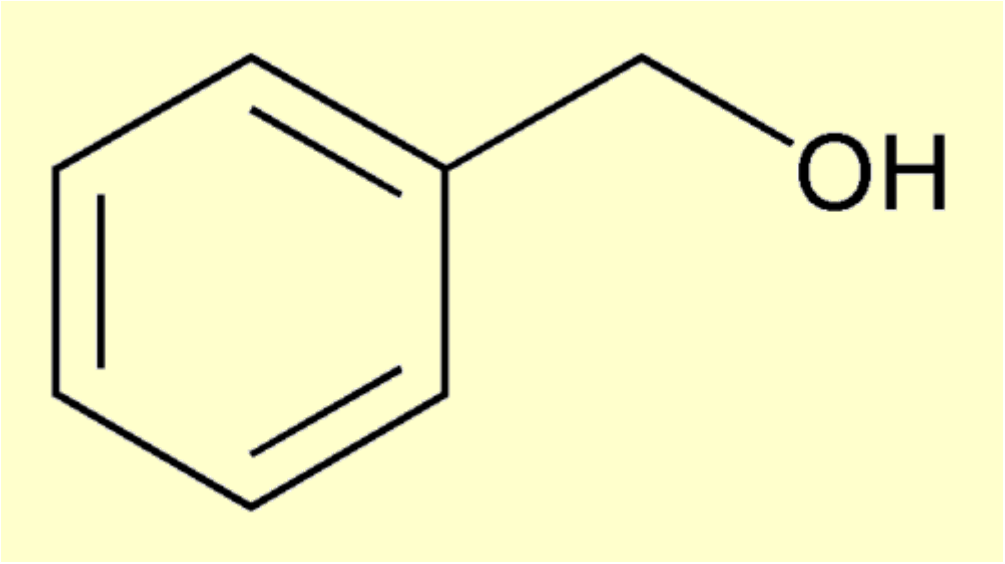
▲ **Benzyl Alcohol**

Attributes	EP	JP	USP
Definition	+	+	+
Refractive Index	+	+	+
Acidity	+	+	+
Benzaldehyde and Other Related Substances	+	+	+
Peroxide Value	+	+	+
Residue on Evaporation	+	+	+
Assay	+	+	+

Legend: + will adopt and implement; − will not stipulate.

Nonharmonized attributes: *Characters, Clarity of Solution, Color of Solution, Labeling,* and *Packaging and Storage*

Reagents and Reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.



C_7H_8O 108.1

Phenylmethanol [100-51-6].

DEFINITION

Benzyl Alcohol contains NLT 98.0% and NMT the equivalent of 100.5% of phenylmethanol (C_7H_8O).

IDENTIFICATION

- **Infrared Absorption** ⟨197F⟩ **:** On undried specimen

ASSAY

- **Procedure**

Phenolphthalein solution: Dissolve 0.1 g of phenolphthalein in 80 mL of ethanol (96%), and dilute with water to 100.0 mL. To test for sensitivity, add 100 mL of carbon dioxide-free water to 0.1 mL of the *Phenolphthalein solution*. The solution is colorless. NMT 0.2 mL of 0.02 M sodium hydroxide is required to change the color to pink.

Sample: 0.900 g

Analysis: To the *Sample*, add 15 mL of a freshly prepared mixture of pyridine and acetic anhydride (7:1), and boil under a reflux condenser on a water bath for 30 min. Cool, and add 25 mL of water. Using 0.25 mL of *Phenolphthalein solution* as the indicator, titrate with 1 M sodium hydroxide VS. Carry out a blank titration. Calculate the percentage content of C_7H_8O from the formula:

$$\text{Result} = 10.81 \times (n_2 - n_1)/m$$

n_2 = amount of 1 M sodium hydroxide used for the sample (mL)

n_1 = amount of 1 M sodium hydroxide used for the blank (mL)

m = amount of sample taken (g)

Acceptance criteria: 98.0%–100.5%

IMPURITIES

Inorganic Impurities

- **Fats and Fixed Oils,** *Peroxide Value* ⟨ 401 ⟩ **:** NMT 5
- **Residue on Evaporation**

  Analysis: After ensuring that the Benzyl Alcohol complies with the test for *Fats and Fixed Oils, Peroxide Value*, evaporate 10.0 g to dryness in a tared quartz or porcelain crucible or platinum dish on a hot plate at a temperature not exceeding 200°. Ensure that the Benzyl Alcohol does not boil during evaporation. Dry the residue on the hot plate for 1 h, and allow to cool in a desiccator.

  Acceptance criteria: The residue weighs NMT 5 mg, corresponding to NMT 0.05%.

Organic Impurities

- **Procedure: Benzaldehyde and Other Related Substances**

  Sample solution: Use the Benzyl Alcohol specimen under examination.

  Standard solution A: Dissolve 0.100 g of ethylbenzene in 10.0 mL of the *Sample solution*. Dilute 2.0 mL of this solution to 20.0 mL with the *Sample solution*.

  Standard solution B: Dissolve 2.000 g of dicyclohexyl in 10.0 mL of the *Sample solution*. Dilute 2.0 mL of this solution to 20.0 mL with the *Sample solution*.

  Reference solution A: (for use in nonparenteral applications)

  Dissolve 0.750 g of benzaldehyde and 0.500 g of cyclohexylmethanol in the *Sample solution*, and dilute to 25.0 mL with the *Sample solution*. Add 1.0 mL of this solution to a mixture of 2.0 mL of *Standard solution A* and 3.0 mL of *Standard solution B*, and dilute with the *Sample solution* to 20.0 mL.

  Reference solution B: (for use in parenteral applications) Dissolve 0.250 g of benzaldehyde and 0.500 g of cyclohexylmethanol in the *Sample solution*, and dilute to 25.0 mL with the *Sample solution*. Add 1.0 mL of this solution to a mixture of 2.0 mL of *Standard solution A* and 2.0 mL of *Standard solution B*, and dilute with the *Sample solution* to 20.0 mL.

  Chromatographic system

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

  Mode: GC

  Detector: Flame ionization

Carrier: Helium, chromatography grade

Carrier linear velocity: 25 cm/s, at 50°

Detector temperature: 310°

Column: 30-m × 0.32-mm, 0.5-µm film thickness, G16.

Column temperature

Time (min)	Temperature (°)
0	50
34	220
69	220

Injection port temperature: 200°

System suitability

Sample: For nonparenteral applications, use *Reference solution A*. For parenteral applications, use *Reference solution B*.

[NOTE—The retention time of benzyl alcohol is about 26 min. The relative retention times for ethylbenzene, dicyclohexyl, benzaldehyde, cyclohexylmethanol and benzyl alcohol are about 0.28, 0.59, 0.68, 0.71, 1.0, respectively.]

Injection volume: 0.1 µL without air plug

Suitability requirements

Sensitivity: Adjust the sensitivity of the detector so that the height of the peak due to ethylbenzene is NLT 30% of the full scale of the recorder.

Resolution: NLT 3.0 between the peaks corresponding to benzaldehyde and cyclohexylmethanol

Analysis

Samples: *Sample solution* and *Reference solution A* for non-parenteral applications and *Reference solution B* for parenteral applications

Acceptance criteria: (non-parenteral applications)

If any peaks are present in the chromatogram obtained with the *Sample solution* that have the same retention times as the peaks due to ethyl benzene and dicyclohexyl, subtract the areas of any such peaks from the peak areas at these retention times in the chromatograms of *Reference solution A* or *Reference solution B* (corrected peak areas of ethylbenzene and dicyclohexyl). Any such peaks in the *Sample solution* should be included in the assessments for the total of other peaks.

In the chromatogram obtained with the *Sample solution*, the area of any peak corresponding to benzaldehyde is not greater than the difference between the area of the peak due to benzaldehyde in the chromatogram obtained with *Reference solution A* (0.15%) and

the area of the peak due to benzaldehyde in the chromatogram obtained with the *Sample solution*.

In the chromatogram obtained with the *Sample solution*, the area of any peak corresponding to cyclohexylmethanol is not greater than the difference between the area of the peak due to cyclohexylmethanol in the chromatogram obtained with *Reference solution A* (0.10%) and the area of the peak due to cyclohexylmethanol in the chromatogram obtained with the *Sample solution*.

In the chromatogram obtained with the *Sample solution*, the sum of the areas of any peak with a relative retention time less than that of benzyl alcohol and apart from the peaks due to benzaldehyde and cyclohexylmethanol is not greater than four times the area of ethylbenzene in *Reference solution A*, corrected if necessary as described above (0.04%).

In the chromatogram obtained with the *Sample solution*, the sum of the areas of any peak with a relative retention time greater than that of benzyl alcohol is not greater than the area of dicyclohexyl in *Reference solution A*, corrected if necessary as described above (0.3%).

Disregard any peak with an area less than 0.01 times that of the peak due to ethylbenzene in the chromatogram of *Reference solution A*, corrected if necessary as described above.

Acceptance criteria: (parenteral applications)

If any peaks are present in the chromatogram obtained with the *Sample solution* that have the same retention times as the peaks due to ethyl benzene and dicyclohexyl, subtract the areas of any such peaks from the peak areas at these retention times in the chromatograms of *Reference solution A* or *Reference solution B* (corrected peak areas of ethylbenzene and dicyclohexyl). Any such peaks in the *Sample solution* should be included in the assessments for the total of other peaks.

In the chromatogram obtained with the *Sample solution*, the area of any peak corresponding to benzaldehyde is not greater than the difference between the area of the peak due to benzaldehyde in the chromatogram obtained with *Reference solution B* (0.05%) and the area of the peak due to benzaldehyde in the chromatogram obtained with the *Sample solution*.

In the chromatogram obtained with the *Sample solution*, the area of any peak corresponding to cyclohexylmethanol is not greater than the difference between the area of the peak due to cyclohexylmethanol in the chromatogram obtained with *Reference solution B* (0.10%) and the area of the peak due to cyclohexylmethanol in the chromatogram obtained with the *Sample solution*.

In the chromatogram obtained with the *Sample solution*, the sum of the areas of any peak with a relative retention time less than that of benzyl alcohol and apart from the peaks due to benzaldehyde and cyclohexylmethanol is not greater than two times the area of ethylbenzene in *Reference solution B*, corrected if necessary as described above (0.02%).

In the chromatogram obtained with the *Sample solution*, the sum of the areas of any peak with a relative retention time greater than that of benzyl alcohol is not greater than the area of dicyclohexyl in *Reference solution B*, corrected if necessary as described above (0.2%).

Disregard any peak with an area less than 0.01 times that of the peak due to ethylbenzene in the chromatogram of *Reference solution B*, corrected if necessary as described above.

SPECIFIC TESTS

- **Acidity**

  Phenolphthalein solution: Prepare as directed in the *Assay*.

  Analysis: To 10 mL of Benzyl Alcohol add 10 mL of ethanol (96%) and 1 mL of *Phenolphthalein solution*.

  Acceptance criteria: NMT 1 mL of 0.1 M sodium hydroxide is required to change the color of the indicator to pink.

- ✦ **Clarity of Solution:** [Note— The *Sample solution* is to be compared to *Reference suspension 1* in diffused daylight 5 min after preparation of *Reference suspension 1*.]

  Hydrazine solution: Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand 4–6 h before use.

  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: [Note— 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.]

  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.

  Opalescence standard: [Note— This suspension should not be used beyond 24 h after preparation.]

  Transfer 15.0 mL of the *Primary opalescent suspension* to a 1000-mL volumetric flask, dilute with water to volume, and mix.

  Reference suspension 1: Transfer 5.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, and dilute with water to volume.

  Reference suspension 2: Transfer 10.0 mL of the *Opalescence standard* to a second 100-mL volumetric flask, and dilute with water to volume.

  Sample solution: Dissolve 2.0 g of Benzyl Alcohol in 60 mL of 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 *Reference suspension 1*, *Reference suspension 2*, and water to separate matching test tubes. Compare the *Sample solution*, *Reference suspension 1*, *Reference suspension 2*, and water in diffused daylight, viewing vertically against a black background (see *Spectrophotometry and Light-Scattering* ⟨ 851 ⟩ *, Visual Comparison*). [Note— The diffusion of light must be such that *Reference suspension 1* can readily be distinguished from water, and that *Reference suspension 2* can readily be distinguished from *Reference suspension 1*.]

  Acceptance criteria: The *Sample solution* shows the same clarity as that of water, or its opalescence is not more pronounced than that of *Reference suspension 1*. ✦

- ✦ **Color of Solution**

Sample solution: Use the *Sample solution* prepared in the test for *Clarity of Solution*.

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 a portion of water to a separate matching test tube. Compare the color of the *Sample solution* with that of water in diffused daylight, viewing vertically against a white background (see *Spectrophotometry and Light-Scattering* ⟨ 851 ⟩ *, Visual Comparison*).

Acceptance criteria: The *Sample solution* has the color of water. ✦

- **Refractive Index** ⟨ 831 ⟩ **:** 1.538 to 1.541 at 20°

ADDITIONAL REQUIREMENTS

- ✦**Labeling:** Where Benzyl Alcohol is intended for use in the manufacture of parenteral applications, it is so labeled. ✦
- ✦**Packaging and Storage:** Preserve in tight containers, protected from light. ✦
- ✦**USP Reference Standards**

  USP Benzyl Alcohol RS ✦

▲ *NF28*

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
Monograph	Kevin T. Moore, Ph.D. Senior Scientist 1-301-816-8369	(EM105) Excipient Monographs 1

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