BRIEFING

Benzyl Alcohol, *NF 22* page 2830 and page 879 of *PF* 28(3) [May–July 2002]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for *Benzyl Alcohol*, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following draft monograph represents the **ADOPTION STAGE 6** draft, which has been accepted by the members of the Pharmacopeial Discussion Group.

Pharmacopeial Discussion Group Sign-Off Document

Attributes	EP	JP	USP
Definition	+	+	+
Identification	+	+	+
Appearance of solution	+	+	+
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, Labeling, Storage.

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

Proposed changes to the current *NF* monograph include the following:

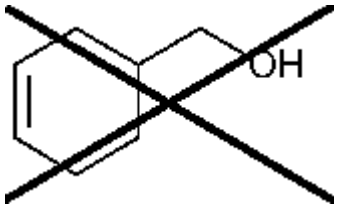
1. Definition — The lower limit is changed from 97.0 percent to 98.0 percent based on the argument that this quality is easily obtainable and that the tight limits of the *Related compounds* test justify a tighter limit for the *Assay*.
2. *Packaging* — No change.
3. *Labeling* — Requirements for injectable dosage forms are added.
4. *USP Reference standards* — A new reference standard for benzyl alcohol is added to comply with the proposed IR test.
5. *Clarity of solution* — This test is added because of the possible use of benzyl alcohol in parenteral dosage forms.
6. *Color of solution* — This test is added because of the possible use of benzyl alcohol in parenteral dosage forms.
7. *Identification* — In light of comments received, the use of infrared absorption spectrophotometry is adopted for this test.

8. *Specific gravity* — This test has been deleted from the monograph and added to the *Benzyl Alcohol* entry under *Description and Solubility*.
9. *Peroxide value* — This test is added to conform to EP standards.
10. *Refractive index* — The lower limit is changed to reflect EP standards.
11. *Acidity* — Minor editorial changes are made.
12. *Residue on ignition* — This test is deleted. Inorganic compounds are not likely to be present because distillation procedures are used during the production of this substance.
13. *Limit of nonvolatile residue* — The sample weight is increased from 2 g to 10 g to ensure greater accuracy.
14. *Halogenated compounds and halides* — This test is deleted. The GC method adequately controls benzyl chloride, and inorganic halogenated compounds are not likely to be present because distillation procedures are used during the production of this substance.
15. *Related compounds* — The *Benzaldehyde* test is renamed as a *Related compounds* test. The test is revised to specify a G16 column based on analyses performed with a DB-Wax column, to reduce solution volumes and to widen the limits for the impurities under test.
16. *Organic volatile impurities* — This test is deleted, as it is not necessary.
17. *Assay* — The phenolphthalein solution preparation is changed to conform to EP methods.

(EMC: J. Lane) RTS—40773-8

Change to read:

~~**Benzyl Alcohol**~~



~~C_7H_8O 108.14~~

~~Benzenemethanol.~~
~~Benzyl alcohol [*100-51-6*].~~

~~» Benzyl Alcohol contains not less than 97.0 percent and not more than 100.5 percent of C_7H_8O.~~

~~**Packaging and storage—** Preserve in tight containers, and prevent exposure to light.~~

~~**Identification—** Add 2 or 3 drops of it to 5 mL of potassium permanganate solution (1 in 20), and acidify with 2 N sulfuric acid: the odor of benzaldehyde is perceptible.~~

~~**Specific gravity** ⟨841⟩ **:** between 1.042 and 1.047.~~

~~**Refractive index** ⟨831⟩ **:** between 1.539 and 1.541 at 20°.~~

~~**Acidity —** Neutralize 50 mL of alcohol containing 1 mL of phenolphthalein TS with 0.10 N sodium hydroxide. Dissolve 10 mL of Benzyl Alcohol in 10 mL of the neutralized alcohol, and titrate with 0.10 N sodium hydroxide: not more than 1.0 mL is consumed.~~

~~**Residue on ignition** ⟨281⟩ **—** Evaporate 25 mL in a suitable crucible, and ignite to constant weight: not more than 0.005% is found.~~

~~**Nonvolatile residue—** Evaporate 2.0 g of it to dryness on a water bath, and dry the residue at 105° for one hour. Cool in a desiccator, and weigh: not more than 1 mg is found.~~

~~**Halogenated compounds and halides—** [NOTE — All glassware used for this procedure must be chloride-free and may be prepared by soaking overnight in a mixture consisting of water and nitric acid (1:1), rinsing with water, and storing full of water.]~~

~~*Standard preparation* — Dissolve an accurately weighed quantity of sodium chloride in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of 0.0132 mg of NaCl per mL.~~

~~*Test preparation* — Dissolve 6.7 g in 50 mL of alcohol, dilute with water to 100.0 mL, and mix. To 10.0 mL of this solution add 7.5 mL of 2 N sodium hydroxide and 0.125 g of nickel-aluminum catalyst, and heat this mixture in a conical flask on a water bath for 10 minutes. Allow to cool to room temperature and filter, collecting the filtrate in a 25-mL volumetric flask. Wash with three 2-mL portions of alcohol, dilute the combined filtrate and washings with water to volume, and mix.~~

~~*Blank preparation* — Prepare as directed for *Test preparation* , omitting the Benzyl Alcohol.~~

~~*Ferric ammonium sulfate solution—* Shake 30.0 g of ferric ammonium sulfate with 40 mL of nitric acid, dilute with water to 100 mL, and mix. Centrifuge or filter, if necessary, to obtain a clear solution.~~

~~*Procedure—* To four 25-mL volumetric flasks separately transfer 10.0 mL of the *Test preparation* , 10.0 mL of the *Standard preparation* , 10.0 mL of the *Blank preparation* , and 10.0 mL of water. To each flask add 5.0 mL of *Ferric ammonium sulfate solution* , mix, and add dropwise and with swirling 2 mL of nitric acid and 5.0 mL of a solution of mercuric thiocyanate in anhydrous alcohol (0.3 in 100). Shake, dilute the contents of each flask with water to volume, and let the solutions stand in a water bath at 20° for 15 minutes. Measure the absorbance at 460 nm of the solution made from the *Test preparation* against the solution from the *Blank preparation* , and measure the absorbance at 460 nm of the solution from the *Standard preparation* against the solution from water. The former is not greater than the latter (0.03% as Cl).~~

~~**Benzaldehyde—**~~

~~*Internal standard solution—* Prepare a solution in acetonitrile containing about 0.2 mg of methylparaben per mL.~~

~~*Mobile phase* — Prepare a suitable degassed and filtered mixture of water and acetonitrile (62:38). Make adjustments if necessary (see *Chromatography* ⟨621⟩).~~

~~*Standard solution* — Prepare a solution in acetonitrile containing 0.200 mg of benzaldehyde per mL.~~

~~*Standard preparation* — Transfer 5.0 mL of *Standard solution* and 5.0 mL of *Internal standard solution* to a 50-mL volumetric flask, add acetonitrile to volume, and mix.~~

~~*Test preparation*— Pipet 2 mL of Benzyl Alcohol and 10 mL of *Internal standard solution* into a 100-mL volumetric flask, dilute with acetonitrile to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)— The liquid chromatograph is equipped with a 282-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the *Test preparation* , and record the peak responses as directed under *Procedure:* the resolution, *R* , between the benzyl alcohol and methylparaben peaks is not less than 2.0. Chromatograph the *Standard preparation* , and record the peak responses as directed under *Procedure:* the relative standard deviation of the ratio of the peak responses for replicate injections is not more than 2.0%.~~

~~*Procedure*— Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Test preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.6 for benzyl alcohol, 0.7 for methylparaben, and 1.0 for benzaldehyde. Calculate the percentage of benzaldehyde taken by the formula:~~

$$0.1(R_U/R_S),$$

~~in which R_U and R_S are the response ratios of benzaldehyde to methylparaben obtained for the *Test preparation* and the *Standard preparation* , respectively: not more than 0.20% is found.~~

~~**Organic volatile impurities,** *Method V* ⟨467⟩ **:** meets the requirements.~~

~~**Assay** — To about 900 mg of Benzyl Alcohol, accurately weighed, add 15.0 mL of a mixture of pyridine and acetic anhydride (7:1), and heat on a water bath under reflux for 30 minutes. Cool, add 25 mL of water, add 5 drops of a 1 in 100 solution of phenolphthalein in pyridine, and titrate with 1 N sodium hydroxide VS. Perform a blank determination. Calculate the percentage of C_7H_8O taken by the formula:~~

$$10.81\,N\,(V_B - V_U)/W,$$

~~in which V_U and V_B are the number of mL of 1 N sodium hydroxide used for the Benzyl Alcohol and the blank, respectively; and W is the weight, in g, of Benzyl Alcohol taken.~~

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Expert Committee : (EMC) Excipients: Monograph Content
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Add the following:

▲ Benzyl Alcohol
20024-26 C_7H_8O 108.14

Benzenemethanol.
Benzyl alcohol [*100-51-6*].

» Benzyl Alcohol contains not less than 98.0 percent and not more than 100.5 percent of C_7H_8O.

Packaging ~~and storage~~ — Preserve in tight containers, and prevent exposure to light.

Labeling— Where Benzyl Alcohol is intended for use in the manufacture of injectable dosage forms, it is so labeled.

USP Reference standards ⟨11⟩ **—** *USP Benzyl Alcohol RS.*

Clarity of solution— [NOTE — The *Test solution* is to be compared to *Reference suspension 1* in diffused daylight 5 minutes 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 to 6 hours 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 hours.

Opalescence standard— [NOTE — This suspension should not be used beyond 24 hours 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 suspensions— Transfer 5.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension 1*. Transfer 10.0 mL of the *Opalescence standard* to a second 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension 2*.

Test solution— Dissolve 2.0 g of Benzyl Alcohol in 60 mL of water, and mix.

Procedure— Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 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 *Test solution*, *Reference suspension 1*, *Reference suspension 2*, and water in diffused daylight, viewing vertically against a black background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). [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*.] The *Test 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—

Test solution— Use the *Test solution* prepared in the test for *Clarity of solution*.

Procedure— Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 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 *Test solution* with that of water in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). The *Test solution* has the color of water.

Identification— *Infrared Absorption* ⟨197F⟩ , on undried specimen.

Peroxide value ⟨401⟩ **:** not more than 5.

Refractive index ⟨831⟩ **:** between 1.538 and 1.541 at 20°.

Acidity— Neutralize 50 mL of alcohol containing 1 mL of phenolphthalein TS with 0.10 N sodium hydroxide. Dissolve 10 mL of Benzyl Alcohol in 10 mL of the neutralized alcohol, and titrate with 0.10 N sodium hydroxide to the first appearance of a pink color that persists for not less than 30 seconds: not more than 1.0 mL is consumed.

Limit of nonvolatile residue— [NOTE — Ensure that the Benzyl Alcohol to be examined complies with the test for *Peroxide value* ⟨401⟩ before performing this test.] Evaporate 10.0 g of Benzyl Alcohol on a water bath to dryness, and dry the residue at 105° for 1 hour. Cool in a desiccator, and weigh. The residue weighs not more than 5 mg: not more than 0.05% of nonvolatile residue is found.

Related compounds—

Test solution— Use the Benzyl Alcohol specimen under examination.

Ethylbenzene solution— Transfer 100 mg of ethylbenzene, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Test solution* to volume, and mix. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with *Test solution* to volume, and mix.

Dicyclohexyl solution— Transfer 2.0 g of dicyclohexyl to a 10-mL volumetric flask, dissolve in and dilute with *Test solution* to volume, and mix. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with *Test solution* to volume, and mix.

Standard solution 1— Transfer 750 mg of benzaldehyde, accurately weighed, and 500 mg of cyclohexylmethanol, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Test solution* to volume, and mix. Transfer 0.5 mL of this solution to a 10-mL volumetric flask, add 1.0 mL of *Ethylbenzene solution* and 1.5 mL of *Dicyclohexyl solution*, dilute with *Test solution* to volume, and mix.

Standard solution 2 (where the Benzyl Alcohol under test is intended for use in the manufacture of injectable dosage forms)— Transfer about 250 mg of benzaldehyde, accurately weighed, and about 500 mg of cyclohexylmethanol, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Test solution* to volume, and mix. Transfer 0.5 mL of this solution to a 10-mL volumetric flask, add 1.0 mL of *Ethylbenzene solution* and 1.0 mL of *Dicyclohexyl solution*, dilute with *Test solution* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)— The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 30-m column coated with a 0.5-µm film of G16. Helium is used as the carrier gas flowing at a rate of 1.2 mL per minute at 50°. The injection port and detector temperatures are maintained at about 200° and 310°, respectively. The column temperature is programmed to increase linearly from 50° to 220° at a rate of 5° per minute, and is maintained at 220° for 35 minutes. Chromatograph the appropriate *Standard solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.28 for ethylbenzene, 0.59 for dicyclohexyl, 0.68 for benzaldehyde, 0.71 for cyclohexylmethanol, and 1.0 for benzyl alcohol; and the resolution, *R*, between benzaldehyde and cyclohexylmethanol is not less than 3.0.

Procedure— Separately inject equal volumes (about 0.1 µL) of the appropriate *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. [NOTE — Disregard any peak having an area less than 0.01 times the area of the ethylbenzene peak in the chromatogram of the appropriate *Standard solution*. In the chromatogram of the *Test solution*, verify that there are no peaks with the same retention times as those of ethylbenzene or dicyclohexyl.]

In the chromatogram of the *Test 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 of *Standard solution 1* (0.15%) or in the chromatogram of *Standard solution 2* (0.05%) and the area of the peak due to benzaldehyde in the chromatogram of the *Test solution*.

In the chromatogram of the *Test 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 of *Standard solution 1* (0.10%) or in the chromatogram of *Standard solution 2* (0.10%) and the area of the peak due to cyclohexylmethanol in the chromatogram of the *Test solution*.

In the chromatogram of the *Test solution*, the sum of the areas of any peaks with retention times less than that of benzyl alcohol, excluding the peaks due to benzaldehyde and cyclohexylmethanol, is not greater than four times the area of the ethylbenzene peak in the chromatogram of *Standard solution 1* (0.04%) or is not greater than two times the area of the ethylbenzene peak in the chromatogram of *Standard solution 2* (0.02%).

In the chromatogram of the *Test solution*, the sum of the areas of any peaks with retention times greater than that of benzyl alcohol is not greater than the area of the dicyclohexyl peak in the chromatogram of *Standard solution 1* (0.3%) or in the chromatogram of *Standard solution 2* (0.2%).

~~**Organic volatile impurities,** *Method V* ⟨467⟩ **:** meets the requirements.~~

Assay— To about 900 mg of Benzyl Alcohol, accurately weighed, add 15.0 mL of a freshly prepared mixture of pyridine and acetic anhydride (7:1), and boil under reflux for 30 minutes. Cool, add 25 mL of water, add 0.25 mL of a phenolphthalein solution prepared by dissolving 100 mg of phenolphthalein in 80 mL of alcohol and diluting with water to 100 mL, and titrate with 1 N sodium hydroxide VS. Perform a blank determination (see *Titrimetry* ⟨541⟩). Calculate the percentage of C_7H_8O taken by the formula:

$$10.81N\,(V_B - V_U)/W,$$

in which V_U and V_B are the number of mL of 1 N sodium hydroxide used for the Benzyl Alcohol and the blank, respectively; and *W* is the weight, in g, of Benzyl Alcohol taken. ▲ *NF23*

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