**BRIEFING**

**Methylparaben, NF 22 page 2896 and page 575 of PF 28(2) [Mar.–Apr. 2002].** The European Pharmacopoeia, a member of the Pharmacopoeial Discussion Group, is the coordinating pharmacopoeia in the efforts toward the international harmonization of compendial standards for this monograph. The presented text represents the **ADOPTION STAGE 6** draft in the harmonization process.

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* JP will not include the system suitability requirement and consequently will not include reference solution (b).

**Legend:** + will adopt and implement; – will not stipulate.

**Nonharmonized attributes:** Characters, Identification by infrared spectrophotometry, Storage.

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

**Local requirements:** JP: Heavy metals (20 ppm); USP: Organic volatile impurities.

Differences between the **ADOPTION STAGE 6** document and the current *NF* monograph include the following:

1. In the opening paragraph (the Definition)—Calculations using the dried substance are deleted, as the *Loss on drying* test is deleted. The acceptance range has been widened.

2. **Packaging and storage**— No change.

3. **USP Reference standards**— No change.

4. **Identification**— The test for Melting range has been moved under Identification. Other Identification tests have been omitted, as they are not needed with the Infrared Absorption and Melting range tests.
5. Color of solution— This test is added to comply with EP standards.

6. Melting range— Moved under Identification.

7. Acidity— The EP test method has replaced the current USP method.


9. Residue on ignition— A sample weight of 1.0 g is added.

10. Organic volatile impurities— No change.

11. Related substances— This test is modified to include one related substance, ethylparaben, for system suitability requirements.

12. Assay— The sample amount and the amount of 1 N sodium hydroxide has changed, and the heating process has changed to a specific temperature and does not include refluxing.

(EMC: J. Lane ) RTS—41235-4

Change to read:

Methylparaben

\[ C_8H_8O_3 \] 152.15

Benzoic acid, 4-hydroxy, methyl ester.
Methyl \( \beta \)-hydroxybenzoate [ 99-76-3 ].

Methylparaben contains not less than 99.0 percent and not more than 100.5 percent of \( C_8H_8O_3 \).

Packaging and storage— Preserve in well-closed containers.

USP Reference standards (11) — USP Methylparaben RS . USP Ethylparaben RS .

Identification—

A: Infrared Absorption (197M).
The principal spot obtained in the chromatogram of Test-solution B prepared as directed in the test for Chromatographic-purity corresponds in size and \( R_f \) value to that of the principal spot obtained from Standard-solution B.

C: Transfer about 10 mg to a test tube, add 1 mL of sodium carbonate TS, mix, boil for 30 seconds, and cool (Test-solution A). Transfer about 10 mg to a second test tube, add 1 mL of sodium carbonate TS, and mix (Test-solution B). [NOTE—The Methylparaben partly dissolves in Test-solution B.] Prepare a solution of 4-aminoantipyrine in pH 9.0 alkaline borate buffer containing 1 mg per mL. Simultaneously add 5 mL of the 4-aminoantipyrine solution and 0.5 mL of potassium ferricyanide TS to Test-solution A and Test-solution B, and mix: Test-solution B becomes yellow to orange-brown and Test-solution A becomes orange to red, with the color of Test-solution A being clearly more intense than any similar color that may be obtained with Test-solution B.

**Color of solution**—Dissolve 1 g in alcohol, dilute with alcohol to 10 mL, and mix (Methylparaben-solution). This solution is clear and not more intensely colored than a solution prepared immediately before use by mixing 2.4 mL of ferric chloride CS, 1.0 mL of cobaltous chloride CS, and 0.4 mL of cupric sulfate CS with 0.3 N hydrochloric acid to make 10 mL, and diluting 5 mL of this solution with 0.3 N hydrochloric acid to make 100 mL. Make the comparison by viewing the solutions downward in matched color-comparison tubes against a white surface (see Color-and-Achromicity (631)).

**Acidity**—To 2 mL of Methylparaben-solution prepared in the Color of solution test add 3 mL of alcohol, 5 mL of carbon dioxide-free water, and 0.1 mL of bromocresol green TS, and titrate with 0.10 N sodium hydroxide: not more than 0.1 mL is required to produce a blue color.

**Residue on ignition** (281) : not more than 0.1%.

**Chromatographic purity**—

Prepare a solution of Methylparaben in acetone containing 10 mg per mL (Test-solution A). Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with acetone to volume, and mix (Test-solution B).

Dissolve an accurately weighed quantity of USP Methylparaben RS in acetone, and mix to obtain a solution having a known concentration of about 1 mg per mL (Standard-solution A). Transfer about 10 mg of USP Ethylparaben RS, accurately weighed, to a 10-mL volumetric flask, dissolve in 1 mL of Test-solution A, dilute with acetone to volume, and mix (Standard-solution C).

Separately apply 2 \( \mu L \) of each Test-solution and 2 \( \mu L \) of each Standard-solution to a thin-layer chromatographic plate (see Chromatography (621)) coated with a 0.25-mm layer of chromatographic octadecylsilanized silica gel mixture. Develop the chromatogram in a solvent system consisting of a mixture of methanol, water, and glacial acetic acid (70:30:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under short-wavelength UV light, and compare the intensities of any secondary spots observed in the chromatogram of Test-solution A with that of the principal spot in the chromatogram of Standard-solution A: the intensity of any individual secondary spot in the chromatogram of Test-solution A is not greater than that of the principal spot obtained in the chromatogram of Standard-solution A (0.5%). The test is not valid unless the chromatogram obtained with Standard-solution C shows two clearly separated principal spots.

**Melting range** (741) : between 125° and 128°.

**Organic volatile impurities, Method IV (467)**: meets the requirements.
Assay—Transfer about 2 g of Methylparaben, accurately weighed, to a flask fitted with a ground-glass stopper and equipped for refluxing under a water-cooled condenser. Add 40.0 mL of 1 N sodium hydroxide VS, and reflux for 1 hour. Cool to room temperature, and rinse the condenser with water. Titrate the excess sodium hydroxide with 1 N sulfuric acid VS, continuing the titration until the second point of inflection and determining the endpoint potentiometrically (see Titrimetry (541)). Perform a blank determination (see Residual Titrations under Titrimetry (541)). Each mL of 1 N sodium hydroxide is equivalent to 152.2 mg of C₈H₈O₃.

Auxiliary Information—Staff Liaison: Justin Lane, B.S., Scientific Associate
Expert Committee: (EMC) Excipients: Monograph Content
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Phone Number: 1-301-816-8323
Add the following:

- Methylparaben
  \[C_8H_8O_3\] 152.15

Benzoic acid, 4-hydroxy-\(\cdot\), methyl ester.
Methyl \(p\)-hydroxybenzoate [99-76-3].

» Methylparaben contains not less than 98.0 percent and not more than 102.0 percent of \(C_8H_8O_3\).

Packaging and storage—Preserve in well-closed containers.

USP Reference standards (11) — USP Ethylparaben RS. USP Methylparaben RS.

Identification—

A: Infrared Absorption (197M).

B: Melting range (741): between 125° and 128°.

Color of solution—Dissolve 1 g in alcohol, dilute with alcohol to 10 mL, and mix (Methylparaben solution). This solution is clear and not more intensely colored than alcohol or a solution prepared immediately before use by mixing 2.4 mL of ferric chloride CS, 1.0 mL of cobaltous chloride CS, and 0.4 mL of cupric sulfate CS with 0.3 N hydrochloric acid to make 10 mL, and diluting 5 mL of this solution with 0.3 N hydrochloric acid to make 100 mL. Make the comparison by viewing the solutions downward in matched color-comparison tubes against a white surface (see Color and Achromicity (631)).

Acidity—To 2 mL of Methylparaben solution prepared in the Color of solution test add 3 mL of alcohol, 5 mL of carbon dioxide-free water, and 0.1 mL of bromocresol green TS, and titrate with 0.10 N sodium hydroxide: not more than 0.1 mL is required to produce a blue color.

Residue on ignition (281): not more than 0.1%, determined on 1.0 g.

Related substances—

Test solution—Prepare a solution of Methylparaben in acetone containing 10 mg per mL.

Standard solutions—Transfer 0.5 mL of the Test solution to a 100-mL volumetric flask, dilute with acetone to volume, and mix (Standard solution A). Dissolve 10 mg, accurately weighed, of USP Ethylparaben RS in 1 mL of the Test solution, and dilute with acetone to 10 mL (Standard solution B).

Procedure—Separately apply 2 \(\mu\)L of the Test solution and 2 \(\mu\)L of each Standard solution to a thin-layer chromatographic plate (see Chromatography (621)), coated with a 0.25-mm layer of chromatographic octadecylsilanized silica gel mixture. Develop the chromatogram in a solvent system consisting of a mixture of methanol, water, and glacial acetic acid (70:30:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under short-wavelength UV light, and compare the intensities of any secondary spots observed in the chromatogram of
the Test solution with that of the principal spot in the chromatogram of Standard solution A: the intensity of any individual secondary spot in the chromatogram of the Test solution is not greater than that of the principal spot obtained in the chromatogram of Standard solution A (0.5%). The test is not valid unless the chromatogram obtained with Standard solution B shows two clearly separated principal spots.

**Organic volatile impurities, Method IV (467):** meets the requirements.

**Assay—** To about 1.000 g of Methylparaben, accurately weighed, add 20.0 mL of 1 N sodium hydroxide VS, and heat at about 70° for 1 hour. Cool rapidly in an ice bath. Carry out the titration on the solutions at room temperature. Titrate the excess sodium hydroxide with 1 N sulfuric acid VS, continuing the titration until the second point of inflection and determining the endpoint potentiometrically (see Titrimetry (541) ). Perform a blank determination (see Residual Titrations under Titrimetry (541) ). Each mL of 1 N sodium hydroxide is equivalent to 152.1 mg of \( C_8H_8O_3 \).-

**Auxiliary Information—Staff Liaison:** Justin Lane, B.S., Scientific Associate

**Expert Committee:** (EMC) Excipients: Monograph Content

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