BRIEFING

Ethylparaben, *NF 22* page 2866 and page 1968 of *PF* 28(6) [Nov.–Dec. 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.

Pharmacopeial Discussion Group Sign-Off Document

Attributes	EP	JP	USP
Definition	+	+	+
Identification A	+	+	+
Appearance of solution	+	+	+
Acidity	+	+	+
Related substances*	+	+	+
Sulphated ash	+	+	+
Assay	+	+	+

* 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 pharmacopeia 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:

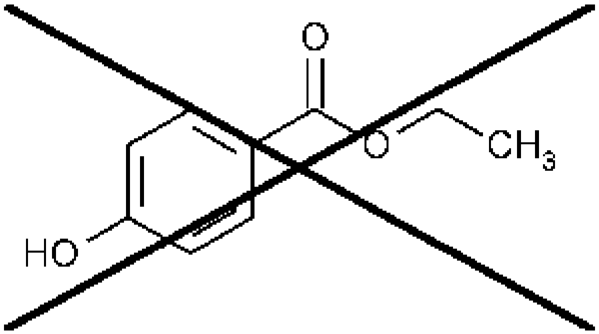
1. In the opening paragraph (the Definition)—Calculations using the dried substance are deleted, as the *Loss on drying* test is deleted. The acceptance range has been widened.
2. *Packaging and storage*— No change.
3. *USP Reference standards*— The reference standard for Methylparaben has been added for the *Related substances* test.
4. *Identification*— The test for *Melting range* has been moved under *Identification*.

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.
8. *Loss on drying*— Deleted.
9. *Residue on ignition*— The limits are increased to not more than 0.1% to comply with EP standards.
10. *Organic volatile impurities*— No change.
11. *Related substances*— This test is added to comply with EP standards.
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—41235-9

Change to read:

~~Ethylparaben~~



~~$C_9H_{10}O_3$ 166.17~~

~~Benzoic acid, 4-hydroxy-, ethyl ester.~~
~~Ethyl *p* -hydroxybenzoate [*120-47-8*].~~

~~» Ethylparaben contains not less than 99.0 percent and not more than 100.5 percent of $C_9H_{10}O_3$, calculated on the dried basis.~~

~~**Packaging and storage—** Preserve in well-closed containers.~~

~~**USP Reference standards** ⟨11⟩ — *USP Ethylparaben RS* .~~

~~**Identification,** *Infrared Absorption* ⟨197M⟩ .~~

~~**Melting range** ⟨741⟩ **:** between 115° and 118°.~~

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

~~**Other requirements—** It meets the requirements for *Acidity* , *Loss on drying* , and *Residue on ignition* under *Butylparaben* .~~

~~**Assay—** Proceed with Ethylparaben as directed in the *Assay* under *Butylparaben.* Each mL of 1 N sodium hydroxide is equivalent to 166.2 mg of~~ ~~$C_9H_{10}O_3$.~~

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:

■ Ethylparaben

$C_9H_{10}O_3$ 166.17

Benzoic acid, 4-hydroxy-, ethyl ester.
Ethyl *p*-hydroxybenzoate [*120-47-8*].

» Ethylparaben contains not less than 98.0 percent and not more than 102.0 percent of $C_9H_{10}O_3$.

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 96° and 99°.

Color of solution— Dissolve 1 g in alcohol, dilute with alcohol to 10 mL, and mix *(Ethylparaben 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 *Ethylparaben 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 Ethylparaben 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 Methylparaben RS in 1 mL of the *Test solution,* and dilute with acetone to 10 mL *(Standard solution B)*.

Procedure— Separately apply 2 µL of the *Test solution* and 2 µL 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— Transfer about 1.000 g of Ethylparaben, accurately weighed, to a flask fitted with a ground-glass stopper. 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 of 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 166.2 mg of $C_9H_{10}O_3$. ■1S (*NF23*)

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