Analysis 2: Shake 1 mL with 20 mL of water and allow the liquids to separate. To 10 mL of the water layer add 1 drop of ferric chloride TS.
Acceptance criteria 2: The mixture develops no violet color.

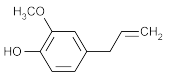
SPECIFIC TESTS
- **SPECIFIC GRAVITY ⟨841⟩:** 0.921–0.924
- **CONGEALING TEMPERATURE ⟨651⟩:** NLT 0°
- **OPTICAL ROTATION,** *Angular Rotation* **⟨781A⟩:** –0.5° to +0.5°
- **DISTILLING RANGE,** *Method I* **⟨721⟩:** 174°–177°
- **REFRACTIVE INDEX ⟨831⟩:** 1.455–1.460 at 20°

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in tight containers.

Add the following:

■• **USP REFERENCE STANDARDS ⟨11⟩**
USP Eucalyptol RS■1S *(USP35)*

Eugenol



$C_{10}H_{12}O_2$ 164.20
Phenol, 2-methoxy-4-(2-propenyl)-;
4-Allyl-2-methoxyphenol [97-53-0].

DEFINITION
Eugenol is obtained from clove oil and from other sources.

IDENTIFICATION

Add the following:

■• **A. INFRARED ABSORPTION ⟨197F⟩**■1S *(USP35)*

IMPURITIES
- **HEAVY METALS,** *Method II* **⟨231⟩:** NMT 40 ppm
- **HYDROCARBONS**
Analysis: Dissolve 1 mL in 20 mL of 0.5 N sodium hydroxide in a 50-mL stoppered tube, add 18 mL of water, and mix.
Acceptance criteria: A clear mixture results immediately, but it may become turbid when exposed to air.
- **LIMIT OF PHENOL**
Analysis: Shake 1 mL with 20 mL of water. Filter, and add 1 drop of ferric chloride TS to 5 mL of the clear filtrate.
Acceptance criteria: The mixture exhibits a transient grayish-green color but not a blue or violet color.

SPECIFIC TESTS
- **SPECIFIC GRAVITY ⟨841⟩:** 1.064–1.070
- **DISTILLING RANGE,** *Method II* **⟨721⟩:** NLT 95% distills from 250°–255°
- **REFRACTIVE INDEX ⟨831⟩:** 1.540–1.542 at 20°
- **SOLUBILITY IN 70% ALCOHOL:** One volume dissolves in 2 volumes of 70% alcohol.

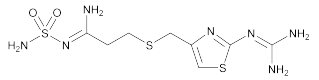
ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

Add the following:

■• **USP REFERENCE STANDARDS ⟨11⟩**
USP Eugenol RS■1S *(USP35)*

Famotidine

Change to read:



$C_8H_{15}N_7O_2S_3$ 337.45
Propanimidamide, *N'*-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-;
[1-Amino-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propylidene]sulfamide;
■3-[[2-(Diaminomethyleneamino)thiazol-4-yl]methylthio]-*N'*-sulfamoylpropanimidamide■1S *(USP35)* [76824-35-6].

DEFINITION
Famotidine contains NLT 98.5% and NMT 101.0% of famotidine ($C_8H_{15}N_7O_2S_3$), calculated on the dried basis.

IDENTIFICATION
- **A. INFRARED ABSORPTION ⟨197K⟩**

Delete the following:

■• **B. ULTRAVIOLET ABSORPTION ⟨197U⟩**
Analytical wavelength: 265 nm
Buffer: Adjust 250 mL of 0.02 M phosphoric acid with a 100 mg/mL sodium hydroxide solution to a pH of 2.5, and dilute with water to 500 mL.
Sample solution: 25 µg/mL in *Buffer*
Acceptance criteria: The absorptivities, calculated on the dried basis, do not differ by more than 3.0%.■1S *(USP35)*

ASSAY

Change to read:

- **PROCEDURE**
Sample: Dissolve 250 mg of Famotidine in 80 mL of glacial acetic acid.
Analysis: Titrate with 0.1 N perchloric acid VS (see *Titrimetry* ⟨541⟩), using a suitable anhydrous electrode system.■■1S *(USP35)* Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 16.87 mg of $C_8H_{15}N_7O_2S_3$.
Acceptance criteria: 98.5%–101.0% on the dried basis

IMPURITIES
- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%
- **HEAVY METALS,** *Method II* **⟨231⟩:** NMT 10 ppm

Delete the following:

■• **CHROMATOGRAPHIC PURITY**
Adsorbent: 0.25-mm layer of chromatographic silica gel mixture
Sample solution: Transfer 200 mg of Famotidine to a 10-mL volumetric flask. Add 2 mL of methanol, and shake for 10 min. Add 0.1 mL of glacial acetic acid, stir until dissolved, and dilute with methanol to volume.
Standard solution A: 0.2 mg/mL of USP Famotidine RS in methanol and glacial acetic acid (100:1)

Standard solution B: 65 µg/mL from *Standard solution A* in methanol and glacial acetic acid (100:1)
Application volume: 5 µL
Developing solvent system: Ethyl acetate, methanol, toluene, and ammonium hydroxide (40:25:20:2)
Visualization: Short-wave UV
Analysis
Samples: *Sample solution, Standard solution A*, and *Standard solution B*
Separately apply to a plate, and dry under a stream of nitrogen. Proceed as directed for *Chromatography* ⟨621⟩, *Thin-Layer Chromatography*. Compare the intensities of any secondary spots from the *Sample solution* with those of the principal spots from the *Standard solutions*.
Acceptance criteria: No secondary spot from the *Sample solution* is larger in size or more intense than the principal spot from *Standard solution B* (0.3%); and the sum of the intensities of the secondary spots from the *Sample solution* corresponds to NMT 1.0% (*Standard solution A*).■1S (*USP35*)

Add the following:

■• **ORGANIC IMPURITIES**
Buffer: 1.882 g/L of sodium 1-hexanesulfonate in water, adjusted with acetic acid to a pH of 3.5
Solution A: Acetonitrile, methanol, and *Buffer* (94:6:900)
Solution B: Acetonitrile
Mobile phase: See *Table 1*. [NOTE—If necessary, adjust the *Mobile phase* to achieve a retention time of 19–23 min for the famotidine peak and a maximum of 48 min for the famotidine related compound E peak.]

Table 1

Time (min)	Solution A (%)	Solution B (%)	Flow Rate (mL/min)
0	100	0	1
23	96	4	1
27	96	4	2
47	78	22	2
48	100	0	2
54	100	0	1

Standard solution: 0.5 µg/mL of USP Famotidine RS in *Solution A*
System suitability stock solution: 0.25 mg/mL of USP Famotidine Related Compound D RS in methanol
System suitability solution: Transfer 1 mL of the *System suitability stock solution* and 0.5 mL of the *Standard solution* into a 100-mL volumetric flask, and dilute with *Solution A* to volume.
Sample solution: 0.5 mg/mL of Famotidine in *Solution A*
Identification solution: 0.5 mg/mL of USP Famotidine RS and 1.5 µg/mL of each of USP Famotidine Related Compound B RS, USP Famotidine Related Compound C RS, USP Famotidine Related Compound D RS, USP Famotidine Related Compound E RS, and USP Famotidine Related Compound F RS in *Solution A*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 265 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 50°
Flow rate: See *Table 1*.
Injection volume: 20 µL
System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 3.5 between famotidine and famotidine related compound D
Analysis
Samples: *Standard solution*, *Sample solution*, and *Identification solution*
Chromatograph the *Identification solution*, and identify the components on the basis of their relative retention times, given in *Table 2*.
Calculate the percentage of each impurity in the portion of Famotidine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of famotidine from the *Standard solution*
C_S = concentration of USP Famotidine RS in the *Standard solution* (mg/mL)
C_U = concentration of Famotidine in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 2*)
Acceptance criteria
Individual impurities: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Famotidine	1.0	—	—
Famotidine related compound D[a]	1.1	1.0	0.3
Famotidine related compound C[b]	1.2	0.53	0.3
Famotidine cyanoamidine[c]	1.4	0.71	0.2
Famotidine related compound F[d]	1.5	0.59	0.1
Famotidine amidine[e]	1.6	1.0	0.2
Famotidine related compound B[f]	2.0	0.40	0.3
Famotidine related compound E[g]	2.1	1.0	0.3
Any other individual impurity	—	1.0	0.1
Total impurities	—	—	1.0

[a] Famotidine propanamide.
[b] Famotidine sulfamoyl propanamide.
[c] *N*-Cyano-3-[[2-(diaminomethyleneamino)thiazol-4-yl]methylthio] propanimidamide.
[d] Famotidine propionic acid.
[e] 3-[[2-(Diaminomethyleneamino)thiazol-4-yl]methylthio]propanimidamide.
[f] Famotidine dimer.
[g] Famotidine disulfide.

■1S (*USP35*)

SPECIFIC TESTS

Change to read:

• **LOSS ON DRYING** ⟨731⟩**:** Dry a sample at a pressure ■not exceeding■1S (*USP35*) 5 mm of mercury at 80° for 5 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light. ■Store at room temperature.■1S *(USP35)*

Change to read:

• **USP REFERENCE STANDARDS** ⟨11⟩
USP Famotidine RS
■USP Famotidine Related Compound B RS
3,5-Bis[2-[[2-[(diaminomethylene)amino]thiazol-4-yl]methylthio]ethyl]-4*H*-1,2,4,6-thiatriazine 1,1-dioxide.
$C_{16}H_{23}N_{11}O_2S_5$ 561.73
USP Famotidine Related Compound C RS
3-[[2-(Diaminomethyleneamino)thiazol-4-yl]methylthio]-*N*-sulfamoylpropanamide hydrochloride.
$C_8H_{15}ClN_6O_3S_3$ 374.88
USP Famotidine Related Compound D RS
3-[[2-(Diaminomethyleneamino)thiazol-4-yl]methylthio]propanamide.
$C_8H_{13}N_5OS_2$ 259.35
USP Famotidine Related Compound E RS
2,2′-[4,4′-Disulfanediylbis(methylene)bis(thiazole-4,2-diyl)]diguanidine.
$C_{10}H_{14}N_8S_4$ 374.53
USP Famotidine Related Compound F RS
3-[[2-(Diaminomethyleneamino)thiazol-4-yl]methylthio]propanoic acid.
$C_8H_{12}N_4O_2S_2$ 260.34■1S *(USP35)*

Famotidine Injection

DEFINITION
Famotidine Injection is a sterile, concentrated solution of Famotidine. It contains NLT 90.0% and NMT 110.0% of the labeled amount of famotidine ($C_8H_{15}N_7O_2S_3$). It may contain suitable preservatives.

IDENTIFICATION
• **A.** The retention time of the famotidine peak from the *Sample solution* corresponds to that from the *Standard solution*, as obtained in the *Assay*.

ASSAY
• **PROCEDURE**
Buffer: 13.8 g/L of monobasic sodium phosphate
Mobile phase: Methanol, water, and *Buffer* (5:32:3). Adjust with 1 N sodium hydroxide to a pH of 5.3.
Diluent: Dissolve 1.36 g of monobasic potassium phosphate in 800 mL of water, adjust with 1 N sodium hydroxide to a pH of 7.0, and dilute with water to 1 L.
Standard solution
If benzyl alcohol is present: 0.1 mg/mL of USP Famotidine RS and 0.09 mg/mL of USP Benzyl Alcohol RS in *Diluent*
If benzyl alcohol is not present: 0.1 mg/mL of USP Famotidine RS in *Diluent*
Sample solution: Transfer a volume of Injection, equivalent to 20 mg of famotidine based on the label claim, to a 200-mL volumetric flask, and dilute with *Diluent* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm; 5-µm packing L3
Flow rate: 1 mL/min
Injection size: 30 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0% for the famotidine peak
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of famotidine ($C_8H_{15}N_7O_2S_3$) in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of famotidine from the *Sample solution*
r_S = peak response of famotidine from the *Standard solution*
C_S = concentration of USP Famotidine RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of famotidine in the *Sample solution* (mg/mL)
Acceptance criteria: 90.0%–110.0%

OTHER COMPONENTS

Change to read:

• **CONTENT OF BENZYL ALCOHOL** (if present)
Buffer, Mobile phase, Diluent, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability stock solution: Proceed as directed in the *Organic Impurities* test.
System suitability solution: Transfer 25 mL of *System suitability stock solution* to a 50-mL volumetric flask. Add 1 drop (approximately 20 mg) of USP Benzyl Alcohol RS, and dilute with *Diluent* to volume.
System suitability
Samples: *Standard solution* and *System suitability solution*
[NOTE—See *Table 1* for the relative retention times.]
Suitability requirements
Resolution: NLT 1.3 between adjacent peaks of benzyl alcohol and ■famotidine propionic acid;■1S *(USP35)* the benzyl alcohol peak is resolved from the solvent front, *System suitability solution*
Relative standard deviation: Less than 2.0% for each peak, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of benzyl alcohol in the portion of Injection taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area of benzyl alcohol from the *Sample solution*
r_S = peak area of benzyl alcohol from the *Standard solution*
C_S = concentration of USP Benzyl Alcohol RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of benzyl alcohol in the *Sample solution* (mg/mL)
Acceptance criteria: The content of benzyl alcohol meets the requirements under *Injections* ⟨1⟩, *Added Substances*.