Table 1

Peak Identfication	Approximate Relative Retention Time *(RRT)*	Relative Response Factor *(R)*	Limit of Impurity
Bicyclorisperidone[1]	0.68	0.81	Not more than 0.5%
Risperidone	1.0	1.0	—
Risperidone *trans-N*-oxide[2]	1.65	—	Not quantified. Used for identification and system suitability check only.
Risperidone *cis-N*-oxide[3]	1.81	0.95	Not more than 0.5%
Any other unspecified degradation product	—	1.0	Not more than 0.3%
Total impurities	—	—	Not more than 1.0%

[1]3-(4-fluoro-2-hydroxyphenyl)-1-[2-(6,7,8,9-tetrahydro-2-methyl-4-oxo-*4H*-pyrido-[1,2-a]pyrimidin-3-yl)ethyl]-2-aza-1-azoniabicyclo[2.2.2]oct-2-ene iodide.

[2]*trans*-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-*4H*-pyrido[1,2-a]pyrimidin-4-one, *N*-oxide monohydrate.

[3]*cis*-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-*4H*-pyrido[1,2-a]pyrimidin-4-one, *N*-oxide monohydrate.

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the responses for all of the peaks. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(1/R)(r_i / r_S)$$

in which R is the appropriate relative response factor as listed in *Table 1;* r_i is the peak response for each impurity in the *Test solution;* and r_S is the peak response of risperidone in the *Test solution:* not more than 0.3% of any individual unidentified impurity is found, not more than 0.5% of any individual specified impurity is found, and not more than 1.0% of total impurities is found.

Assay—

Diluent—Prepare a degassed mixture of methanol and water (80:20).

Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and trifluroacetic acid (80:19.5:0.1). Adjust with ammonium hydroxide to a pH of 3.0.

Solution B—Prepare a filtered and degassed mixture of water, methanol, and trifluoroacetic acid (61:39:0.1). Adjust with ammonium hydroxide to a pH of 3.0.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer an accurately weighed quantity of USP Risperidone RS to a suitable volumetric flask, and dissolve in and dilute quantitatively with *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Transfer an accurately weighed portion of not fewer than 10 Tablets to a volumetric flask that can accommodate a final concentration of 0.1 mg of risperidone per mL. Add an appropriate amount of water equivalent to 20% of the total volume of the volumetric flask, and mechanically shake for about 30 minutes. Add a volume of methanol equivalent to 60% of the total volume of the volumetric flask, and mechanically shake for about 30 minutes. Dilute with methanol to volume, and mix to obtain the final 0.1 mg per mL concentration. Pass a portion of this solution through a suitable filter having a 0.45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 275-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 2.5 mL per minute. The column is maintained at room temperature. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–8	100	0	isocratic
8–16	100→0	0→100	linear gradient
16–20	0	100	isocratic
20–21	0→100	100→0	linear gradient
21–30	100	0	re-equilbration

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor of risperidone is not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the risperidone peak. Calculate the quantity, in mg, of risperidone ($C_{23}H_{27}FN_4O_2$) in the portion of Tablets taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Risperidone RS in the *Standard preparation;* C_U is the concentration, in mg per mL, of risperidone in the *Assay preparation;* and r_U and r_S are the peak responses of risperidone obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Add the following:

▲Risperidone Orally Disintegrating Tablets

DEFINITION

Risperidone Orally Disintegrating Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of risperidone ($C_{23}H_{27}FN_4O_2$).

IDENTIFICATION

- The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Mobile phase: Acetonitrile, trifluoroacetic acid, and water (200: 1.5: 800). Adjust with ammonium hydroxide to a pH of 3.0.

Diluent: Methanol and 0.1 N HCl (40:60)

System suitability solution: 0.1 mg/mL of USP Risperidone Related Compounds Mixture RS prepared as follows: Dis-

solve first in 20% of the flask volume of methanol. Dilute with *Diluent* to volume.
Standard solution: 0.1 mg/mL of USP Risperidone RS in *Diluent*
Sample solution: 0.1 mg/mL of risperidone in *Diluent* from NLT 13 Tablets. [NOTE—Sonicate for 30 min.]
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 275 nm
Column: 3.0-mm × 15-cm; 3.5-µm packing L1
Flow rate: 0.8 mL/min
Injection size: 10 µL
Run time: 2.2 times the retention time of risperidone
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—For relative retention times, see *Impurity Table 1* under *Organic Impurities*.]
Suitability requirements
Resolution: NLT 1.8 between *Z*-oxime and bicyclorisperidone, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_{23}H_{27}FN_4O_2$ in the portion of Tablets taken:

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

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

PERFORMANCE TESTS

• **DISINTEGRATION ⟨701⟩**
Test 1: NMT 30 s
Test 2: NMT 60 s. [NOTE—If the product complies with this test, the labeling indicates that the product meets USP *Disintegration Test 2*.]

• **DISSOLUTION ⟨711⟩**
Medium: 0.1 N HCl; 500 mL
Apparatus 2: 50 rpm
Time: 10 min
Buffer: 8.7 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 7.8.
Mobile phase: Acetonitrile and *Buffer* (45:55)
Standard solution: (L/500) mg/mL of USP Risperidone RS in *Medium*, where L is the label claim in mg/Tablet.
Sample solution: Pass 10 mL of the solution under test through a suitable nylon filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 10-cm; 5-µm packing L1
Column temperature: 28 ± 3°
Flow rate: 2 mL/min
Injection size: 20 µL. [NOTE—Use 40 µL for Tablets labeled to contain 0.5 mg of risperidone.]
Run time: 2 times the retention time of risperidone
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_{23}H_{27}FN_4O_2$ dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 500 mL
Tolerances: NLT 80% (Q) of the labeled amount of risperidone is dissolved.

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements
Procedure for content uniformity
Mobile phase: Proceed as directed in the *Dissolution* test.
Standard solution: (L/100) mg/mL of USP Risperidone RS in 0.1 N HCl, where L is the Tablet label claim in mg
Sample solution: Transfer 1 Tablet to a 100-mL volumetric flask, and dilute with 0.1 N HCl to volume to obtain a nominal concentration of (L/100) mg/mL of risperidone, where L is the label claim in mg/Tablet. Sonicate for 30 min at 40°.
Chromatographic system: Proceed as directed in the *Dissolution* test.
Injection size: 20 µL
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_{23}H_{27}FN_4O_2$ in the portion of Tablets taken:

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

r_U = peak response of risperidone from the *Sample solution*
r_S = peak response of risperidone from the *Standard solution*
C_S = concentration of USP Risperidone RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of risperidone in the *Sample solution* (mg/mL)

IMPURITIES

Organic Impurities

• **PROCEDURE**
Mobile phase, Diluent, System suitability solution, Standard solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.
Analysis
Sample: *Sample solution*
Calculate the percentage of any individual impurity in the portion of Tablets taken:

$$\text{Result} = (r_{U1}/r_{U2}) \times (1/F) \times 100$$

r_{U1} = peak response of any individual impurity from the *Sample solution*
r_{U2} = peak response of risperidone from the *Sample solution*
F = relative response factor (see *Impurity Table 1*)

Acceptance criteria
Individual impurities: See *Impurity Table 1*.
Total impurities: NMT 1.0%

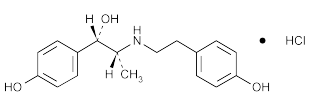
Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Z-oxime*,[a]	0.59	1.0	—
Bicyclorisperidone[b]	0.66	0.86	0.3
Risperidone	1.0	1.0	—
Risperidone *cis*-*N*-oxide[c]	1.7	0.97	0.5
Any unspecified degradation product	—	1.0	0.2

* Process impurity; it is used to establish system suitability only.
[a] (*Z*)-3-[2-[4-(2,4-Difluorophenyl)(hydroxyimino)methyl]-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one.
[b] 3-(4-Fluoro-2-hydroxyphenyl)-1-[2-(6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido-[1,2-a]pyrimidin-3-yl)ethyl]-2-aza-1-azoniabicyclo[2.2.2]oct-2-ene.
[c] *cis*-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one,*N*-oxide.

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers. Store at controlled room temperature.
- **LABELING:** When more than one *Disintegration* test is given, the labeling states the *Disintegration* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Risperidone RS
  4*H*-Pyrido[1,2-*a*]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-.
  3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.
  $C_{23}H_{27}FN_4O_2$ 410.48
  USP Risperidone Related Compounds Mixture RS
  Contains a 98.9/0.5/0.3/0.3 (area %) mixture of the following four compounds:
  Risperidone (98.9%)
  Risperidone *cis*-*N*-oxide (0.5%): *cis*-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, *N*-oxide monohydrate.
  $C_{23}H_{29}FN_4O_4$ 444.50
  Bicyclorisperidone (0.3%): 3-(4-fluoro-2-hydroxyphenyl)-1-[2-(6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidin-3-yl)ethyl]-2-aza-1-azoniabicyclo[2.2.2]oct-2-ene iodide.
  $C_{23}H_{28}FIN_4O_4$ 538.40
  Z-oxime (0.3%): (*Z*)-3-[2-[4-(2,4-Difluorophenyl)(hydroxyimino)methyl]-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.
  $C_{23}H_{28}F_2N_4O_2$ 430.29 ▲*USP35*

Ritodrine Hydrochloride



$C_{17}H_{21}NO_3 \cdot HCl$ 323.81

Benzenemethanol, 4-hydroxy-α-[1-[[2-(4-hydroxyphenyl)ethyl]amino]ethyl]-, hydrochloride, (*R**, *S**)-.
erythro-*p*-Hydroxy-α-[1-[(*p*-hydroxyphenethyl)amino]ethyl]benzyl alcohol hydrochloride [23239-51-2].

» Ritodrine Hydrochloride contains not less than 97.0 percent and not more than 103.0 percent of $C_{17}H_{21}NO_3 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩**—**
USP Ritodrine Hydrochloride RS

Identification—

A: The IR absorption spectrum of a potassium bromide dispersion of it exhibits maxima only at the same wavelengths as that of a similar preparation of USP Ritodrine Hydrochloride RS.

B: The retention time of the ritodrine hydrochloride in the *Assay preparation* obtained in the *Assay* corresponds to that of the *Standard preparation* obtained in the *Assay.*

C: A solution (1 in 100) responds to the tests for *Chloride* ⟨191⟩.

pH ⟨791⟩**:** between 4.5 and 6.0, in a solution (1 in 50).

Loss on drying ⟨731⟩**:** Dry it at 105° for 2 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.2%.

Heavy metals, *Method II* ⟨231⟩**:** not more than 0.002%.

Related compounds—

Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay.*

Test preparation—Prepare a solution containing about 1 mg of Ritodrine Hydrochloride in each mL of *Mobile phase.*

Diluted test preparation—Quantitatively dilute a suitable volume of the *Test preparation* with *Mobile phase* to obtain a solution having a known concentration of 0.01 mg per mL of ritodrine hydrochloride.

Procedure—Chromatograph the *Test preparation* and the *Diluted test preparation,* as directed in the *Assay.* The relative retention times are about 0.3 for tyramine, 0.65 for *erythro*-1-(4-ketocyclohexyl)-2-[(1-hydroxyphenethyl)amino]propanol-1, 0.85 for *erythro*-*p*-hydroxy-[1-(4-ketocyclohexylethyl)amino]ethyl benzyl alcohol, 1.0 for ritodrine, 1.15 for *threo* diastereomer of ritodrine, and 2.3 for *p*-hydroxy-β-(*p*-hydroxyphenethyl)amino] propiophenone. Determine the peak responses for ritodrine and for the related compounds from the chromatograms obtained from the *Diluted test preparation* and the *Test preparation,* respectively. Calculate the percentage of related compounds found: not more than 0.5% of any individual impurity and not more than 2.0% of total impurities is found.

Assay—

Mobile phase—Dissolve 6.6 g of dibasic ammonium phosphate and 1.1 g of sodium 1-heptanesulfonate in 700 mL of water, and mix with 300 mL of methanol. Adjust by the addition of phosphoric acid to a pH of 3.0, mix, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Ritodrine Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.2 mg per mL.

Assay preparation—Transfer about 200 mg of Ritodrine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in *Mobile phase,* dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

System suitability preparation—Dissolve about 20 mg of Ritodrine Hydrochloride in about 50 mL of *Mobile phase.* Add 5.6 mL of sulfuric acid, dilute with *Mobile phase* to 100 mL, and mix. Heat a portion of this solution for about 2 hours at about 85°, and then cool to room temperature. Cautiously mix 10.0