0.5% of *Risperidone cis-N-oxide: 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].
0.3% of *Bicyclorisperidone:* 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]-1-aza-2-azoniabicyclo[2.2.2]oct-2-ene iodide.
0.3% of *Z-oxime:* (*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.

Risperidone Tablets

» Risperidone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of risperidone ($C_{23}H_{27}FN_4O_2$).

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩**—**
USP Risperidone RS
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 410.48 CAS-106266-06-2

Identification—

A: *Infrared Absorption*—

Test solution—Grind an appropriate number of Tablets to prepare a 550 ± 50 µg per mL solution of risperidone in ethyl acetate. Shake the solution for 30 minutes, and centrifuge for 20 minutes. Evaporate 5 mL of the supernatant with the aid of a stream of nitrogen to 2 mL on a warm water bath. Add 150 ± 50 mg of KBr powder, mix well, and evaporate to dryness. Grind the dried mixture, and press a small amount into a transparent pellet ⟨197K⟩.

Standard solution—Grind about 2 mg of USP Risperidone RS with about 200 mg of KBr powder, and press into a transparent pellet.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Dissolution ⟨711⟩**—**

Medium: 0.1 N hydrochloric acid; 500 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Determine the amount of $C_{23}H_{27}FN_4O_2$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (65:35), and add 1 mL of trifluoroacetic acid to each 1 L of the mixture. Adjust with ammonium hydroxide to a pH of 3.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Risperidone RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of about 0.006 mg per mL.

Test solution—Use portions of the solution under test, and pass through a suitable filter having a porosity of 35 µm.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 237-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution* and the *Test solution* as directed for *Procedure:* the retention time of risperidone is about 2.1 minutes, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of $C_{23}H_{27}FN_4O_2$ dissolved by the formula:

$$\frac{r_U \times C_S \times 500 \times 100}{r_S \times L}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of USP Risperidone RS in the *Standard solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *L* is the Tablet label claim in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{23}H_{27}FN_4O_2$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩**—**

Mobile phase and *Chromatographic system*—Proceed as directed for *Dissolution*.

Standard solution—Dissolve an accurately weighed quantity of USP Risperidone RS in a suitable volumetric flask, and dilute quantitatively with 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 0.03 mg of risperidone per mL.

Test solution—Transfer one Tablet into a 100-mL volumetric flask, add 50 mL of 0.1 N hydrochloric acid, and shake mechanically for about 30 minutes. Dilute with 0.1 N hydrochloric acid to volume, and mix. Pass a portion of this solution through a suitable filter having a 0.2-µm or finer porosity, and use the filtrate.

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

$$C(r_U / r_S)100$$

in which *C* is the concentration, in mg per mL, of USP Risperidone RS in the *Standard solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Related compounds—

Mobile phase and *Diluent*—Proceed as directed in the *Assay*.

Standard solution—Prepare as directed for the *Standard preparation* in the *Assay*.

Diluted sodium hydroxide—To 1 L of water in a beaker, add 0.1 N sodium hydroxide dropwise to obtain a pH of about 8.5.

Diluted hydrogen peroxide—Dilute 1 mL of hydrogen peroxide with water to 500 mL.

Peak identification solution—Suspend 10 mg of USP Risperidone RS in 10 mL of *Diluted sodium hydroxide* in a 100-mL volumetric flask. Store the flask at 90° for 24 hours. Cool the solution to room temperature. Add 10 mL of aqueous *Diluted hydrogen peroxide* to the flask, and store at 90° for an additional two hours. Cool the mixture to room temperature, and dilute with methanol to volume.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay*. Chromatograph about 20 µL of the *Peak identification solution,* record the peak responses as directed for *Procedure,* and identify the peaks using the relative retention times given in *Table 1:* the resolution, *R,* between the *trans-N*-oxide and *cis-N*-oxide is not less than 1.2. [NOTE—The approximate relative retention times given in *Table 1* are for identification purposes only.]

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-