Table 2

		3 h	9 h	12 h	21 h
L1	Individual Tablets	10%–27%	35%–70%	44%–92%	NLT 87%
L2	Average	10%–27%	35%–70%	44%–92%	NLT 87%
L2	Individual Tablets	0%–37%	25%–80%	34%–102%	NLT 77%
L3	Average	10%–27%	35%–70%	44%–92%	NLT 87%
L3	Individual Tablets	NMT 2 Tablets are outside the range of 0%–37% and no individual Tablet is outside the range of 0%–47%	NMT 2 Tablets are outside the range of 25%–80% and no individual Tablet is outside the range of 15%–90%	NMT 2 Tablets are outside the range of 34%–102% and no individual Tablet is outside the range of 24%–112%	NMT 2 Tablets release less than 77% and no individual Tablet releases less than 67%

Tolerances: See *Table 3*.

Table 3

Time (h)	Amount Dissolved (Tablets labeled to contain 500 mg of valproic acid)	Amount Dissolved (Tablets labeled to contain 250 mg of valproic acid)
1	NMT 10%	NMT 10%
2	5%–25%	5%–25%
12	55%–75%	65%–85%
24	NLT 80%	NLT 80%

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at the times specified conforms to *Acceptance Table 2* in *Dissolution* ⟨711⟩.●(RB 1-Sep-2011)

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS ⟨11⟩**
  USP Valproic Acid RS

Donepezil Hydrochloride Tablets

DEFINITION

Change to read:

Donepezil Hydrochloride Tablets contain NLT •90.0%●(RB 1-Aug-2011) and NMT •110.0%●(RB 1-Aug-2011) of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$).

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION ⟨197U⟩**
  Wavelength range: 220–360 nm
  Sample solution: Crush a suitable number of Tablets, and transfer an amount of powder, equivalent to 10 mg of donepezil hydrochloride, to a 100-mL volumetric flask. Add 80 mL of 0.1 N hydrochloric acid, and sonicate for 5 min. Cool the solution to room temperature, and dilute with 0.1 N hydrochloric acid to volume. Transfer a portion of this solution to a centrifuge tube, and centrifuge for 15 min. Transfer 5 mL of the clear supernatant to a 25-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume.
  Analysis: Using a 1-cm cell, record the UV spectrum of the *Sample solution*.
  Acceptance criteria: The solution exhibits absorption maxima at 230, 271, and 315 nm.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **PROCEDURE**
  Diluent: Methanol and 0.1 N hydrochloric acid (3:1)
  Mobile phase: Dissolve 2.5 g of sodium decanesulfonate in 650 mL of water, and add 1.0 mL of perchloric acid and 350 mL of acetonitrile. If necessary, adjust with an additional 0.5 mL of perchloric acid to a pH of about 1.8.
  System suitability solution: 0.2 mg/mL of USP Donepezil Hydrochloride RS and 0.008 mg/mL of USP Donepezil Related Compound A RS. [NOTE—Dissolve in 40% of the flask volume of methanol, swirl, and dilute with water to volume.]
  Standard solution: 0.4 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*. [NOTE—Dissolve in 60% of the flask volume of *Diluent*, swirl, and dilute with *Diluent* to volume.]
  Sample solution: Nominally, 0.4 mg/mL of donepezil hydrochloride prepared as follows. Dissolve a suitable number of Tablets in 75% of the flask volume of *Diluent*, and sonicate in an ultrasonic bath for 20 min. Swirl the mixture for 30 s, allow to cool to room temperature, and dilute with *Diluent* to volume. •[NOTE—If necessary, add a magnetic stirring bar to the flask, and mix for 10 min on the magnetic stirrer, to aid in dissolution.]●(RB 1-Aug-2011) Allow a few min for the solids to settle. Pass through a suitable filter, discarding the first 2–3 mL of the filtrate.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 271 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L1
  Column temperature: 35°
  Flow rate: 1.4 mL/min
  Injection size: 20 µL
  System suitability
  Samples: *System suitability solution* and *Standard solution*
  [NOTE—The relative retention times for donepezil related compound A and donepezil are about 0.92 and 1.0, respectively.]
  Suitability requirements
  Resolution: NLT 1.5 between donepezil related compound A and donepezil, *System suitability solution*
  Tailing factor: NMT 1.5 for the donepezil peak, *System suitability solution*
  Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) in the portion of Tablets taken:

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

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

Acceptance criteria: •90.0%–110.0%•(RB 1-Aug-2011)

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨**711**⟩
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
•Determine the amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved, by using one of the following methods.
Chromatographic method•(RB 1-Aug-2011)
Diluent: Methanol and 0.1 N hydrochloric acid (3:1)
Mobile phase: Acetonitrile, water, and perchloric acid (350:650:1)
Standard stock solution: 1.1 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*. Dilute this solution with *Medium* to obtain a final concentration of 0.11 mg/mL.
Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of (*L*/1000) mg/mL, where *L* is the label claim in mg/Tablet.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first few mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 271 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1.0 mL/min
Injection size: 50 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Column efficiency: NLT 5000 theoretical plates
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) 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*, 900 mL

•**Spectrometric method**
Standard solution: 0.11 mg/mL of USP Donepezil Hydrochloride RS in water
Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of (*L*/900) mg/mL, where *L* is the label claim in mg/Tablet.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Instrumental conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: 230 nm
Blank: *Medium*
Calculate the percentage of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*
A_U = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL•(RB 1-Aug-2011)

Tolerances: NLT 80% (*Q*) of the labeled amount of donepezil hydrochloride is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** ⟨**905**⟩**:** Meet the requirements

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES,** •**PROCEDURE 1**
[NOTE—On the basis of the synthetic route, perform either *Procedure 1* or *Procedure 2*. *Procedure 2* is recommended if any of the impurities included in *Table 3* are potential degradation products.]•(RB 1-Aug-2011)
Diluent, Mobile phase, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Standard solution: 0.8 µg/mL of USP Donepezil Hydrochloride RS in *Diluent*
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for donepezil related compound A and donepezil are about 0.92 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 1.5 between donepezil related compound A and donepezil, *System suitability solution*
Relative standard deviation: NMT 8.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
[NOTE—Identify the impurities using the relative retention times given in *Table 1*.]
Calculate the percentage of any individual impurity in the portion of Tablets taken:

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

r_U = peak response of each individual impurity from the *Sample solution*
r_S = peak response of donepezil hydrochloride from the *Standard solution*
C_S = concentration of USP Donepezil Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of donepezil hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desbenzyl donepezil[a]	0.33	1.0	0.5
Donepezil open ring[b]	0.70	0.6	0.5
Donepezil hydrochloride	1.0	—	—
Donepezil *N*-oxide[c]	1.2	1.0	0.5
Any individual unspecified degradation product	—	—	0.2

[a] 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.
[b] 2-(3-(1-Benzylpiperidin-4-yl)-2-oxopropyl)-4,5-dimethoxybenzoic acid.
[c] 2-[(1-Benzylpiperidin-4-yl)methyl]-5,6-dimethoxyindan-1-one *N*-oxide.

Add the following:

•• **ORGANIC IMPURITIES, PROCEDURE 2**
Diluent: Acetonitrile and water (25:75)
Solution A: Add 1 mL of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 6.5. Pass through a filter of 0.45-µm or finer pore size.
Solution B: Acetonitrile
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	75	25
10	40	60
40	40	60
41	75	25
50	75	25

Standard solution: 0.01 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*. Sonication may be used to aid the dissolution.
Sample solution: 1.0 mg/mL of donepezil hydrochloride in *Diluent*. Sonication may be used to aid the dissolution.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 286 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 50°
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%, for five replicate injections
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each specified impurity or any individual degradation product in the portion of Tablets taken:

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

r_U = peak response of each individual impurity from the *Sample solution*
r_S = peak response of donepezil hydrochloride from the *Standard solution*
C_S = concentration of USP Donepezil Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of donepezil hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor for the corresponding impurity peak from *Table 3*
Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time*	Relative Response Factor	Acceptance Criteria, NMT (%)
Desbenzyl donepezil[a]	0.23	1.5	0.15
Donepezil pyridine analog (DPMI)[b]	0.49	1.9	0.15
Donepezil benzyl bromide[c]	0.68	0.73	0.15
Donepezil hydrochloride	1.0	1.0	—
Dehydrodeoxy donepezil[d]	1.72	2.0	0.15
Deoxydonepezil[e]	2.12	0.67	0.15
Any individual degradation product	—	1.0	0.1
Total impurities	—	—	0.75

* Relative retention times are based on 1-mL gradient delay volume.
[a] 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one hydrochloride.
[b] 5,6-Dimethoxy-2-(pyridin-4-ylmethyl)indan-1-one.
[c] 1,1-Dibenzyl-4-[(5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidinium bromide.
[d] 1-Benzyl-4-[(5,6-dimethoxyinden-2-yl)methyl]piperidine hydrochloride.
[e] 1-Benzyl-4-[(5,6-dimethoxyindan-2-yl)methyl]piperidine hydrochloride.

•(RB 1-Aug-2011)

ADDITIONAL REQUIREMENTS
• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

Add the following:

•• **LABELING:** If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.•(RB 1-Aug-2011)
• **USP REFERENCE STANDARDS** ⟨11⟩
USP Donepezil Hydrochloride RS
USP Donepezil Related Compound A RS
(*E*)-2-[(1-Benzylpiperidin-4-yl)methylene]-5,6-dimethoxyindan-1-one.
$C_{24}H_{27}NO_3$ 377.48

Doxycycline Hyclate Delayed-Release Tablets

DEFINITION
Doxycycline Hyclate Delayed-Release Tablets contain an amount of Doxycycline Hyclate equivalent to NLT 90.0% and NMT 120.0% of the labeled amount of doxycycline ($C_{22}H_{24}N_2O_8$).

IDENTIFICATION
A. 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**
[NOTE—Throughout the following procedure, protect the *Standard solution* and *Sample solution* from light.]
Mobile phase: Transfer 0.77 g of ammonium acetate, 0.75 g of sodium hydroxide, 0.50 g of tetrabutylammonium hydrogen sulfate, and 0.40 g of edetate disodium to a 1000-mL volumetric flask. Add 850 mL of water,