



## Atorvastatin Calcium Tablets

<b>Type of Posting</b>	Notice of Intent to Revise
<b>Posting Date</b>	26-May-2023
<b>Targeted Official Date</b>	To Be Determined, Revision Bulletin
<b>Expert Committee</b>	Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts and the [Pending Monograph Guideline](#), this is to provide notice that the Small Molecules 2 Expert Committee intends to revise the Atorvastatin Calcium Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Atorvastatin Calcium Tablets monograph to widen the acceptance criteria of atorvastatin epoxy pyrrolooxazin 7-hydroxy analog in the test for *Organic impurities* from NMT 0.5% to NMT 1.0%.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.<sup>1</sup>

Should you have any questions, please contact Yanyin Yang, Senior Scientist II (301-692-3623 or [yanyin.yang@usp.org](mailto:yanyin.yang@usp.org)).

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<sup>1</sup> This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the [USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF](#).

## Atorvastatin Calcium Tablets

### DEFINITION

Atorvastatin Calcium Tablets contain an amount of atorvastatin calcium  $[(C_{33}H_{34}FN_2O_5)_2Ca]$ , equivalent to NLT 94.5% and NMT 105.0% of the labeled amount of atorvastatin.

### IDENTIFICATION

- **A.** The UV absorption spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **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

#### • PROCEDURE

**Buffer:** 0.05 M ammonium citrate buffer pH 4.0 prepared as follows. Dissolve 9.62 g of [anhydrous citric acid](#) in 950 mL of [water](#), adjust with [ammonium hydroxide](#) to a pH of 4.0, and dilute with [water](#) to 1000 mL.

**Mobile phase:** [Acetonitrile](#), [stabilizer-free tetrahydrofuran](#), and *Buffer* (27:20:53)

**Solution A:** Dissolve 9.62 g of [anhydrous citric acid](#) in 900 mL of [water](#), adjust with [ammonium hydroxide](#) to a pH of 7.4, and dilute with [water](#) to 1000 mL.

**Diluent:** [Acetonitrile](#) and *Solution A* (1:1)

**System suitability solution:** 0.1 mg/mL of [USP Atorvastatin Calcium RS](#) and 0.01 mg/mL of [USP Atorvastatin Related Compound H RS](#) in *Diluent*. Shake mechanically for 30 min or until dissolved.

**Standard solution:** 0.1 mg/mL of [USP Atorvastatin Calcium RS](#) in *Diluent*. Shake mechanically for 15 min or until dissolved.

**Sample stock solution:** Prepare a known nominal concentration of atorvastatin by transferring NLT 10 Tablets to an appropriate volumetric flask. Add *Diluent* to about 50% of the final volume of the flask, and shake the mixture mechanically for 15 min or until dissolved. Dilute with *Diluent* to volume. Centrifuge or pass through a suitable filter of 0.45- $\mu$ m pore size.

**Sample solution:** Nominally equivalent to 0.1 mg/mL of atorvastatin in *Diluent* from the *Sample stock solution*

#### Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

**Mode:** LC

**Detector**

**Assay:** UV 244 nm

**Identification A:** Diode array; UV 200–400 nm

**Column:** 4.6-mm  $\times$  25-cm; 5- $\mu$ m packing [L1](#)

**Column temperature:** 30°

**Flow rate:** 1.5 mL/min

**Injection volume:** 20  $\mu$ L

#### System suitability

**Samples:** *System suitability solution* and *Standard solution*

#### Suitability requirements

**Resolution:** NLT 5.0 between atorvastatin and atorvastatin related compound H, *System suitability solution*

**Tailing factor:** NMT 1.5 for atorvastatin, *System suitability solution*

**Relative standard deviation:** NMT 1.0%, *Standard solution*

## Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of atorvastatin ( $C_{33}H_{35}FN_2O_5$ ) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [M \times (M_{r1}/M_{r2})] \times 100$$

$r_U$  = peak response of atorvastatin from the *Sample solution*

$r_S$  = peak response of atorvastatin from the *Standard solution*

$C_S$  = concentration of [USP Atorvastatin Calcium RS](#) in the *Standard solution* (mg/mL)

$C_U$  = nominal concentration of atorvastatin in the *Sample solution* (mg/mL)

$M$  = number of moles of atorvastatin per mole of atorvastatin calcium, 2

$M_{r1}$  = molecular weight of atorvastatin, 558.64

$M_{r2}$  = molecular weight of atorvastatin calcium, 1155.34

**Acceptance criteria:** 94.5%–105.0%

## PERFORMANCE TESTS

### • **DISSOLUTION** (711)

#### Test 1

**Buffer:** 0.05 M phosphate buffer prepared as follows. Dissolve 6.8 g of [monobasic potassium phosphate](#) in 900 mL of [water](#). Adjust with 6 N [sodium hydroxide](#) to a pH of 6.8 and dilute with [water](#) to 1 L.

**Medium:** *Buffer*; 900 mL

**Apparatus 2:** 75 rpm

**Time:** 15 min

**Diluent:** [Acetonitrile](#) and [water](#) (50:50)

**Standard stock solution:** 1 mg/mL of [USP Atorvastatin Calcium RS](#) in *Diluent*. Shake mechanically for 10 min or until dissolved.

**Standard solution:** ( $L/900$ ) mg/mL in *Medium* from *Standard stock solution*, where  $L$  is the label claim in mg/Tablet

**Sample solution:** Pass a portion of the solution under test through a suitable filter or centrifuge prior to analysis.

#### Instrumental conditions

(See [Ultraviolet-Visible Spectroscopy](#) (857).)

**Mode:** UV

**Analytical wavelength:** 244 nm

**Cell:** See [Table 1](#) or make appropriate dilutions of the solutions with *Medium* to be within the validated linearity range of the suitable spectrophotometer.

**Table 1**

Label Claim (mg/Tablet)	Cell (cm)
10	1.0
20 and 40	0.5
80	0.2

**Blank:** *Medium*

#### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of atorvastatin ( $C_{33}H_{35}FN_2O_5$ ) dissolved:

$$(A_U/A_S) \times C_S \times V \times D \times [M \times (M_{r1}/M_{r2})] \times (1/L) \times 100$$

$A_U$  = absorbance of the *Sample solution*

$A_S$  = absorbance of the *Standard solution*

$C_S$  = concentration of [USP Atorvastatin Calcium RS](#) in the *Standard solution* (mg/mL)

$V$  = volume of *Medium*, 900 mL

$D$  = dilution factor for the *Sample solution*, if applicable

$M$  = number of moles of atorvastatin per mole of atorvastatin calcium, 2

$M_{r1}$  = molecular weight of atorvastatin, 558.64

$M_{r2}$  = molecular weight of atorvastatin calcium, 1155.34

$L$  = label claim (mg/Tablet)

**Tolerances:** NLT 80% (Q) of the labeled amount of atorvastatin ( $C_{33}H_{35}FN_2O_5$ ) is dissolved.

**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

*Dissolution Test 2* is suitable for products labeled to contain 80 mg of atorvastatin.

**Medium and Apparatus 2:** Proceed as directed in *Test 1*.

**Time:** 30 min

**Diluent, Standard solution, Sample solution, Instrumental conditions, and Blank:** Proceed as directed in *Test 1*.

**Tolerances:** NLT 85% (Q) of the labeled amount of atorvastatin ( $C_{33}H_{35}FN_2O_5$ ) is dissolved.

**Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

**Buffer:** Combine 250 mL of 0.2 M monobasic potassium phosphate, 112 mL of [0.2 N sodium hydroxide](#), and 638 mL of water. Adjust with either [0.02 N sodium hydroxide](#) or [phosphoric acid](#) to a pH of 6.8.

**Solution A:** [Acetonitrile](#), [methanol](#), and [0.1% trifluoroacetic acid](#) (5:5:90)

**Solution B:** [Acetonitrile](#), [methanol](#), and [0.1% trifluoroacetic acid](#) (45:45:10)

**Solution C:** Dissolve 50 g of Tween 80 in 1 L of *Buffer*.

**Mobile phase:** See [Table 2](#).

**Table 2**

Time (min)	Solution A (%)	Solution B (%)
0.00	30	70
0.69	30	70
0.74	0	100
2.73	0	100
2.77	30	70
5.00	30	70

**Medium:** *Solution C* and *Buffer* (6:94); 900 mL

**Apparatus 2:** 75 rpm

**Time:** 30 min

**Standard stock solution:** 0.96 mg/mL of [USP Atorvastatin Calcium RS](#) in [methanol](#)

**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- $\mu$ m pore size.

#### Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

**Mode:** LC

**Detector:** UV 248 nm

**Column:** 2.1-mm  $\times$  5-cm; 2.6- $\mu$ m packing [L1](#)

**Column temperature:** 40°

**Flow rate:** 0.7 mL/min

**Injection volume:** 2  $\mu$ L

#### System suitability

**Sample:** *Standard solution*

#### Suitability requirements

**Tailing factor:** NMT 1.5

**Relative standard deviation:** NMT 2.0%

#### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of atorvastatin ( $C_{33}H_{35}FN_2O_5$ ) dissolved:

$$(r_U/r_S) \times C_S \times V \times [M \times (M_{r1}/M_{r2})] \times (1/L) \times 100$$

$r_U$  = peak response of atorvastatin from the *Sample solution*

$r_S$  = peak response of atorvastatin from the *Standard solution*

$C_S$  = concentration of [USP Atorvastatin Calcium RS](#) in the *Standard solution* (mg/mL)

$V$  = volume of *Medium*, 900 mL

$M$  = number of moles of atorvastatin per mole of atorvastatin calcium, 2

$M_{r1}$  = molecular weight of atorvastatin, 558.64

$M_{r2}$  = molecular weight of atorvastatin calcium, 1155.34

$L$  = label claim (mg/Tablet)

**Tolerances:** NLT 80% ( $Q$ ) of the labeled amount of atorvastatin ( $C_{33}H_{35}FN_2O_5$ ) is dissolved.

**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

**Medium:** Dissolve 6.8 g of [monobasic potassium phosphate](#) and 0.89 g of [sodium hydroxide](#) in 1 L of water.

Adjust with either [1 N sodium hydroxide](#) or [phosphoric acid](#) to a pH of 6.8; 900 mL.

**Apparatus 2:** 75 rpm

**Time:** 15 min

**Buffer:** Dissolve about 6.8 g of [monobasic potassium phosphate](#) in 1000 mL of [water](#). Adjust with 0.5 N [potassium hydroxide](#) solution to a pH of 6.0.

**Mobile phase:** [Acetonitrile](#) and *Buffer* (55:45)

**Standard stock solution:** 0.225 mg/mL of atorvastatin from [USP Atorvastatin Calcium RS](#) prepared as follows.

To a suitable amount of [USP Atorvastatin Calcium RS](#), add 5% of total volume of [methanol](#), sonicate to dissolve, and cool. Dilute with *Medium* to volume.

**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- $\mu$ m pore size.

#### Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

**Mode:** LC

**Detector:** UV 248 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing [L1](#)

**Column temperature:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 20 µL

#### System suitability

**Sample:** *Standard solution*

#### Suitability requirements

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

#### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of atorvastatin (C<sub>33</sub>H<sub>35</sub>FN<sub>2</sub>O<sub>5</sub>) dissolved:

$$(r_U/r_S) \times C_S \times V \times [M \times (M_{r1}/M_{r2})] \times (1/L) \times 100$$

$r_U$  = peak response of atorvastatin from the *Sample solution*

$r_S$  = peak response of atorvastatin from the *Standard solution*

$C_S$  = concentration of [USP Atorvastatin Calcium RS](#) in the *Standard solution* (mg/mL)

$V$  = volume of *Medium*, 900 mL

$M$  = number of moles of atorvastatin per mole of atorvastatin calcium, 2

$M_{r1}$  = molecular weight of atorvastatin, 558.64

$M_{r2}$  = molecular weight of atorvastatin calcium, 1155.34

$L$  = label claim (mg/Tablet)

**Tolerances:** NLT 80% (Q) of the labeled amount of atorvastatin (C<sub>33</sub>H<sub>35</sub>FN<sub>2</sub>O<sub>5</sub>) is dissolved.

**Test 5:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

**Medium:** Dissolve 6.8 g of [monobasic potassium phosphate](#) and 0.9 g of [sodium hydroxide](#) in 1 L of water.

Adjust with either [sodium hydroxide](#) or [phosphoric acid](#) to a pH of 6.8; 900 mL.

**Apparatus 2:** 75 rpm

**Time:** 20 min

**Buffer:** Dissolve 10.5 g of [citric acid](#) in 1000 mL of [water](#). Adjust with [ammonium hydroxide](#) to a pH of 4.0.

**Mobile phase:** [Acetonitrile](#), [tetrahydrofuran](#), and *Buffer* (50:10:40)

**Diluent:** [Acetonitrile](#) and [water](#) (50:50)

**Standard stock solution:** 0.925 mg/mL of [USP Atorvastatin Calcium RS](#) in *Diluent*. Sonicate to dissolve.

**Standard solution:** (L/900) mg/mL in *Medium* from *Standard stock solution*, where L is the label claim in mg/Tablet. Pass the solution through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate.

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate.

#### Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

**Mode:** LC

**Detector:** UV 244 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing [L1](#)

#### Temperatures

**Autosampler:** 10°

**Column:** 30°

**Flow rate:** 1.5 mL/min

**Injection volume:** 50 µL

**Run time:** NLT 2 times the retention time of atorvastatin

### System suitability

**Sample:** *Standard solution*

#### Suitability requirements

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of atorvastatin ( $C_{33}H_{35}FN_2O_5$ ) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times [M \times (M_{r1}/M_{r2})] \times (1/L) \times 100$$

$r_U$  = peak response of atorvastatin from the *Sample solution*

$r_S$  = peak response of atorvastatin from the *Standard solution*

$C_S$  = concentration of [USP Atorvastatin Calcium RS](#) in the *Standard solution* (mg/mL)

$V$  = volume of *Medium*, 900 mL

$M$  = number of moles of atorvastatin per mole of atorvastatin calcium, 2

$M_{r1}$  = molecular weight of atorvastatin, 558.64

$M_{r2}$  = molecular weight of atorvastatin calcium, 1155.34

$L$  = label claim (mg/Tablet)

**Tolerances:** NLT 80% (Q) of the labeled amount of atorvastatin ( $C_{33}H_{35}FN_2O_5$ ) is dissolved.

**Test 6:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

**Medium:** 0.05 M phosphate buffer, pH 6.8, prepared as follows. Dissolve 6.8 g of [monobasic potassium phosphate](#) and 0.89 g of [sodium hydroxide](#) in 1 L of [water](#). Adjust with 1 N [sodium hydroxide](#) to a pH of 6.8; 900 mL.

**Apparatus 2:** 100 rpm

**Time:** 20 min

**Buffer:** 1.36 g/L of [monobasic potassium phosphate](#) in [water](#)

**Mobile phase:** [Acetonitrile](#) and *Buffer* (50:50). Adjust with [phosphoric acid](#) solution to a pH of 2.8.

**Diluent:** [Acetonitrile](#) and [water](#) (50:50)

**Standard stock solution:** 0.461 mg/mL of [USP Atorvastatin Calcium RS](#) in *Diluent*. Sonicate to dissolve.

**Standard solution:** ( $L/900$ ) mg/mL in *Medium* from *Standard stock solution*, 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, and discard the first few milliliters of the filtrate.

### Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

**Mode:** LC

**Detector:** UV 238 nm

**Column:** 4.6-mm × 5-cm; 5-µm packing [L1](#)

#### Temperatures

**Autosampler:** 10°

**Column:** 30°

**Flow rate:** 0.8 mL/min

**Injection volume:** 20 µL

**Run time:** NLT 2 times the retention time of atorvastatin

### System suitability

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of atorvastatin ( $C_{33}H_{35}FN_2O_5$ ) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times [M \times (M_{r1}/M_{r2})] \times (1/L) \times 100$$

$r_U$  = peak response of atorvastatin from the *Sample solution*

$r_S$  = peak response of atorvastatin from the *Standard solution*

$C_S$  = concentration of [USP Atorvastatin Calcium RS](#) in the *Standard solution* (mg/mL)

$V$  = volume of *Medium*, 900 mL

$M$  = number of moles of atorvastatin per mole of atorvastatin calcium, 2

$M_{r1}$  = molecular weight of atorvastatin, 558.64

$M_{r2}$  = molecular weight of atorvastatin calcium, 1155.34

$L$  = label claim (mg/Tablet)

**Tolerances:** NLT 80% (Q) of the labeled amount of atorvastatin ( $C_{33}H_{35}FN_2O_5$ ) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

**IMPURITIES**

**Change to read:**

• **ORGANIC IMPURITIES**

Rinse glassware with *Diluent* before preparing solutions containing atorvastatin calcium.

**Buffer:** 5.75 g/L of [monobasic ammonium phosphate](#) in [water](#). Adjust with dilute [acetic acid](#) (10% v/v) or dilute [ammonium hydroxide](#) (10% v/v) to a pH of  $4.3 \pm 0.05$ .

**Solution A:** [Acetonitrile](#) and [stabilizer-free tetrahydrofuran](#) (925:75)

**Solution B:** *Solution A* and *Buffer* (42:58)

**Solution C:** [Methanol](#), *Solution A*, and *Buffer* (60:20:20)

**Diluent:** [N,N-Dimethylformamide](#)

**System suitability solution:** 60 µg/mL of [USP Atorvastatin Calcium RS](#), 50 µg/mL of [USP Atorvastatin Related Compound B RS](#), 10 µg/mL of [USP Atorvastatin Related Compound H RS](#), and 0.5 µg/mL of [USP Atorvastatin Related Compound D RS](#) in *Diluent*

**Standard solution:** 5 µg/mL of [USP Atorvastatin Calcium RS](#) in *Diluent*. Sonication may be necessary for complete dissolution.

**Sample solution:** Nominally equivalent to 1 mg/mL of atorvastatin, prepared as follows. Crush and finely powder NLT 20 Tablets. Transfer the amount of powder, equivalent to about 50 mg of atorvastatin, to a 50-mL volumetric flask. Add 30 mL of *Diluent* and shake mechanically for 15 min. Dilute with *Diluent* to volume and pass the solution through a suitable filter of 0.45-µm pore size, discarding the first few mL of the filtrate.

**Mobile phase:** See [Table 3](#).

**Table 3**

Time (min)	Solution B (%)	Solution C (%)	Flow Rate (mL/min)
0	100	0	1.8



Time (min)	Solution B (%)	Solution C (%)	Flow Rate (mL/min)
30	100	0	1.8
45	25	75	1.5
50	25	75	1.5
55	20	80	1.5
58	100	0	1.8
65	100	0	1.8

For the *Standard solution*, the run time is only 30 min. For the *System suitability solution* and *Sample solution*, the run time is 65 min.

### Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

**Mode:** LC

**Detector:** UV 244 nm

**Column:** 4.6-mm × 25-cm; 5-μm packing [L1](#)

#### Temperatures

**Autosampler:** 10°

**Column:** 30°

**Flow rate:** See [Table 3](#).

**Injection volume:** 20 μL

### System suitability

**Sample:** *System suitability solution*

[NOTE—The relative retention times of all peaks eluting before atorvastatin related compound H as given in [Table 4](#) are calculated with respect to the atorvastatin peak. The relative retention times for all peaks eluting after atorvastatin related compound H are calculated with respect to atorvastatin related compound H.]

#### Suitability requirements

**Resolution:** NLT 1.4 between atorvastatin related compound B and atorvastatin

**Tailing factor:** NMT 1.5 for the atorvastatin peak

**Relative standard deviation:** NMT 5% for the atorvastatin peak

**Signal-to-noise ratio:** NLT 10 for atorvastatin related compound D

### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [M \times (M_{r1}/M_{r2})] \times (1/F) \times 100$$

$r_U$  = peak response of each impurity from the *Sample solution*

$r_S$  = peak response of atorvastatin from the *Standard solution*

$C_S$  = concentration of [USP Atorvastatin Calcium RS](#) in the *Standard solution* (mg/mL)

$C_U$  = nominal concentration of atorvastatin in the *Sample solution* (mg/mL)

$M$  = number of moles of atorvastatin per mole of atorvastatin calcium, 2

$M_{r1}$  = molecular weight of atorvastatin, 558.64

$M_{r2}$  = molecular weight of atorvastatin calcium, 1155.34

$F$  = relative response factor (see [Table 4](#))

Acceptance criteria: See [Table 4](#).

**Table 4**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Atorvastatin amide <sup>a,b</sup>	0.44	—	—
Atorvastatin related compound A <sup>b,c</sup>	0.84	—	—
Atorvastatin pyrrolidone analog <sup>d</sup>	0.88	0.68	0.5
Atorvastatin related compound B <sup>b,e</sup>	0.94	—	—
Atorvastatin	1.00	—	—
Atorvastatin related compound C <sup>b,f</sup>	1.09	—	—
Atorvastatin pyrrolidone lactone <sup>b,g</sup>	1.62	—	—
Atorvastatin related compound H <sup>h</sup>	1.00	1.18	1.0
Atorvastatin epoxy pyrrolooxazin 6-hydroxy analog <sup>i</sup>	1.06	0.53	0.5
Atorvastatin methyl ester <sup>b,j</sup>	1.12	—	—
Atorvastatin epoxy pyrrolooxazin 7-hydroxy analog, if present <sup>k</sup>	1.14	0.53	▲1.0▲ (TBD)
Atorvastatin epoxy THF analog <sup>l,m</sup>	1.20	1.12	1.0
Atorvastatin related compound D <sup>n</sup>	1.27	1.12	0.5
Atorvastatin <i>tert</i> -butyl ester <sup>b,o</sup>	1.49	—	—
Any other unspecified degradation product	—	1.00	0.2
Total degradation products	—	—	4.0

<sup>a</sup> (3*R*,5*R*)-7-[(3*R*,5*R*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanamido]-3,5-dihydroxyheptanoic acid.

- <sup>b</sup> Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.
- <sup>c</sup> (3*R*,5*R*)-7-[2-Isopropyl-4,5-diphenyl-3-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.
- <sup>d</sup> (3*R*,5*R*)-7-[5-(4-Fluorophenyl)-3-isopropyl-2-oxo-4-phenyl-3-(phenylcarbamoyl)-2,3-dihydro-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.
- <sup>e</sup> (3*S*,5*R*)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.
- <sup>f</sup> (3*R*,5*R*)-7-[2,3-Bis(4-fluorophenyl)-5-isopropyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.
- <sup>g</sup> 5-(4-Fluorophenyl)-1-{2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl}-3-isopropyl-2-oxo-*N*,4-diphenyl-2,3-dihydro-1*H*-pyrrole-3-carboxamide.
- <sup>h</sup> 5-(4-Fluorophenyl)-1-{2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl}-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide.
- <sup>i</sup> 4-{6-(4-Fluorophenyl)-7,8-epoxy-6-hydroxy-8*a*-isopropyl-7-phenyl-8-(phenylcarbamoyl)hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-2-yl}-3-hydroxybutanoic acid.
- <sup>j</sup> (3*R*,5*R*)-Methyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoate.
- <sup>k</sup> (3*R*)-4-(1*b*-(4-Fluorophenyl)-7-hydroxy-7-isopropyl-1*a*-phenyl-7*a*-(phenylcarbamoyl)hexahydro-1*aH*-oxireno[2',3':3,4]pyrrolo[2,1-*b*][1,3]oxazin-3-yl)-3-hydroxybutanoic acid.
- <sup>l</sup> 4-(4-Fluorophenyl)-2,4-dihydroxy-2-isopropyl-*N*,5-diphenyl-3,6-dioxabicyclo[3.1.0]hexane-1-carboxamide.
- <sup>m</sup> Atorvastatin related compound D can undergo transformation equilibrium to the atorvastatin epoxy THF analog. The equilibrium can be shifted under slightly acidic conditions and therefore some products could have a combined specification reported under atorvastatin related compound D.
- <sup>n</sup> 3-(4-Fluorobenzoyl)-2-isobutyryl-*N*,3-diphenyloxirane-2-carboxamide.
- <sup>o</sup> (3*R*,5*R*)-*tert*-Butyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoate.

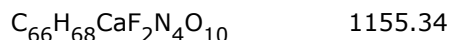
## ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** (11).

### [USP Atorvastatin Calcium RS](#)

### [USP Atorvastatin Related Compound B RS](#)

Calcium (3*S*,5*R*)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate (1:2).



### [USP Atorvastatin Related Compound D RS](#)

3-(4-Fluorobenzoyl)-2-isobutyryl-*N*,3-diphenyloxirane-2-carboxamide.



### [USP Atorvastatin Related Compound H RS](#)

5-(4-Fluorophenyl)-1-{2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl}-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide.



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Not Applicable

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