Add the following:

▪Hydrochlorothiazide Capsules

DEFINITION
Hydrochlorothiazide Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

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**

Buffer: 13.8 g/L of monobasic sodium phosphate
Mobile phase: Acetonitrile and *Buffer* (10:90). Adjust with 10% (v/v) phosphoric acid to a pH of 3.0 ± 0.1. Pass through a filter of 0.45-µm pore size.
System suitability solution: 0.15 mg/mL each of USP Hydrochlorothiazide RS and USP Chlorothiazide RS in *Mobile phase*. Sonicate to completely dissolve.
Standard stock solution: 0.50-mg/mL solution prepared as follows: Dissolve a quantity of USP Hydrochlorothiazide RS in acetonitrile (10% of the volume of the flask), and dilute with *Mobile phase*. Sonicate to completely dissolve.
Standard solution: 50-µg/mL solution in *Mobile phase* from the *Standard stock solution*. Sonicate to completely dissolve.
Sample stock solution: 0.25 mg/mL of hydrochlorothiazide solution prepared as follows: Transfer a number of Capsules into a suitable volumetric flask. Add water, 10% of the volume of the flask, and sonicate for 10 min with vigorous shaking. Add *Buffer*, 20% of the volume of the flask, and again sonicate for 10 min. Add acetonitrile up to 40% of the volume of the flask, and sonicate for 30 min. Dilute with *Buffer* to volume, and pass through a suitable filter of 0.45-µm pore size.
Sample solution: 50 µg/mL of hydrochlorothiazide in *Mobile phase* from the *Sample stock solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 272 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 2.0 mL/min
Injection volume: 20 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between chlorothiazide and hydrochlorothiazide, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*
Column efficiency: NLT 4000 theoretical plates, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Capsules taken:

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

r_U = peak response of hydrochlorothiazide from the *Sample solution*
r_S = peak response of hydrochlorothiazide from the *Standard solution*
C_S = concentration of hydrochlorothiazide in the *Standard solution* (µg/mL)
C_U = nominal concentration of hydrochlorothiazide in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

•**Test 1**• (RB 1-Sep-2011)
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Time: 30 min
Standard solution: 6.75-µg/mL solution prepared as follows: Dissolve a quantity of USP Hydrochlorothiazide RS in acetonitrile (10% of the volume of the flask), and dilute with *Medium*. Sonicate to completely dissolve.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute with *Medium* to a concentration similar to the *Standard solution*.
Analytical wavelength: UV 272 nm
Pathlength: 1 cm
Blank: *Medium*
Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of hydrochlorothiazide in the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
D = dilution for the *Sample solution*
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

•**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: 0.01 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Time: 30 min
Standard stock solution: 0.35 mg/mL of USP Hydrochlorothiazide RS in *Medium*. An amount of acetonitrile, not exceeding 25% of the final volume, may be used to help solubilize hydrochlorothiazide.
Standard solution: (L/900) mg/mL of hydrochlorothiazide in *Medium*, from the *Standard stock solution*, where L is the Capsule label claim in mg.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Empty capsules solution: Place 10 Capsules into a 900-mL volumetric flask. Slowly add 800 mL of *Medium* pre-heated to 37°, and stir until dissolved. Cool to room temperature, and dilute with *Medium* to volume.
Analytical wavelength: UV 272 nm
Pathlength: 1 cm
Blank: *Medium*
Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = [(A_U - A_{EC})/A_S] \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*
A_{EC} = absorbance of the *Empty capsules solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of hydrochlorothiazide in the *Standard solution* (mg/mL)
L = label claim (mg/Capsule)
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.● (RB 1-Sep-2011)

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

IMPURITIES

• **ORGANIC IMPURITIES**

Buffer, Mobile phase, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard stock solution: 0.25-mg/mL solution prepared as follows: Dissolve a quantity of USP Hydrochlorothiazide RS in acetonitrile (10% of the volume of the flask), and dilute with *Mobile phase*.

Standard solution: 0.25 µg/mL of USP Hydrochlorothiazide RS in *Mobile phase* from the *Standard stock solution*

Sample solution: Use the *Sample stock solution* as prepared in the *Assay*.

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between chlorothiazide and hydrochlorothiazide, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Column efficiency: NLT 4000 theoretical plates, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Capsules 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 hydrochlorothiazide from the *Standard solution*
C_S = concentration of hydrochlorothiazide in the *Standard solution* (µg/mL)
C_U = nominal concentration of hydrochlorothiazide in the *Sample solution* (µg/mL)
F = relative response factor (see *Table 1*)

Acceptance criteria

Individual impurities: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A	0.65	0.61	1.0
Chlorothiazide	0.80	—	—[a]
Hydrochlorothiazide	1.0	1.0	—
5-Chlorohydrochlorothiazide	2.88	—	—[a]
Any other individual unspecifed degradant	—	1.0	0.2
Total impurities[b]	—	—	1.5

[a] Process related impurity. The relative retention time is given for identification.

[b] Total impurities include benzothiadiazine related compound A and all unknown degradation impurities. Disregard any peak less than 0.05%.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.

Add the following:

●• **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.● (RB 1-Sep-2011)

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Chlorothiazide RS

2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-, 1,1-dioxide.

$C_7H_6ClN_3O_4S_2$ 295.72

USP Hydrochlorothiazide RS■1S (*USP34*)