Estradiol Transdermal System

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Expert Committee	Chemical Medicines Monographs 5

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 5 Expert Committee intends to revise the Estradiol Transdermal System monograph.

Based on the supporting documentation received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Test 7* in the *Drug Release* section of the monograph.

- *Drug Release Test 7* was validated using the ZORBAX Eclipse Plus C18 brand of column with L1 packing. The typical retention time for estradiol is about 6.3 min.

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.[1]

Should you have any questions, please contact Gerald J. Hsu, Senior Scientific Liaison to the Chemical Medicines Monographs 5 Expert Committee (240-221-2097 or gdh@usp.org).

[1] 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.

Estradiol Transdermal System

DEFINITION

Estradiol Transdermal System contains NLT 85.0% and NMT 120.0% of the labeled amount of estradiol ($C_{18}H_{24}O_2$).

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**

Diluent: Acetonitrile and water (1:1)

Mobile phase: Acetonitrile and water (55:45)

Standard solution: 0.1 mg/mL of USP Estradiol RS in *Diluent*

Sample solutions: Equivalent to 0.1 mg/mL of estradiol in *Diluent*, prepared as follows. Cut 10 Transdermal Systems into pieces, and keep the pieces from each system separate. Remove and discard the protective liners, if present, from the strips. Transfer the pieces of each system into separate stoppered flasks of suitable size, and add a measured volume of *Diluent* to each flask to provide the target estradiol concentration. Shake by mechanical means for about 3 h, and sonicate for 15 min.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 15-cm; packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection size: 25 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.9–1.6

Relative standard deviation: NMT 2.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of estradiol ($C_{18}H_{24}O_2$) in each Transdermal System taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Estradiol RS in the *Standard solution* (mg/mL)

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

Use the individual assays to determine *Uniformity of Dosage Units*.

Acceptance criteria: 85.0%–120.0%

OTHER COMPONENTS

- **Alcohol Content** (if present)

Diluent: Acetonitrile and water (1:1)

Internal standard solution: Prepare by diluting 4.0 mL of dehydrated methanol with water to 100 mL.

Standard stock solution: 5.0 mg/mL of ethanol in *Diluent*. Prepare by weighing by difference 1.6 mL of dehydrated alcohol into a tared 50-mL volumetric flask containing 15 mL of water, and dilute with *Diluent* to volume. Pipet 10.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Standard solution: 2.5 mg/mL of ethanol. Prepare by pipeting 25.0 mL of the *Standard stock solution* into a 50-mL volumetric flask. Add 5.0 mL of the *Internal standard solution*, and dilute with water to volume.

Sample solutions: Prepare as directed for the *Sample solutions* in the *Assay*, with the following changes. Pipet 25.0 mL of each solution into individual 50-mL volumetric flasks. Add 5.0 mL of the *Internal standard solution*, and dilute with water to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 2-mm × 2-m glass; support S2

Temperature

Column: 100°

Injection port: 200°

Detector: 200°

Carrier gas: Helium

Flow rate: 30 mL/min

Injection size: 2 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for the methanol and alcohol peaks are 0.4 and 1.0, respectively.]

Suitability requirements

Relative standard deviation: NMT 1.5% from the peak response ratio of alcohol to methanol

Analysis

Samples: *Standard solution* and *Sample solutions*

Calculate the percentage of alcohol (C_2H_5OH) in each Transdermal System taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of alcohol to methanol from the *Sample solution*

R_S = peak response ratio of alcohol to methanol from the *Standard solution*

C_S = concentration of dehydrated alcohol in the *Standard solution* (mg/mL)

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

Average the percentage of alcohol found in the Transdermal Systems analyzed.

Acceptance criteria: 80%–120% of the labeled amount of C_2H_5OH

PERFORMANCE TESTS

Change to read:

- **Drug Release ⟨724⟩**

Test 1: For products labeled for dosing every 84 h

Medium: Water; 900 mL, deaerated

Apparatus 5: 50 rpm

Times: 24, 48, and 96 h

Mobile phase: Water and acetonitrile (3:2)

Standard solution: 9 µg/mL of USP Estradiol RS in dehydrated alcohol. Dilute this solution with *Medium* to obtain solutions having concentrations of about 0.9, 0.45, and 0.045 µg/mL.

Sample solution: At each sampling time interval, withdraw a 10-mL aliquot of the solution under test.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: Fluorimetric, with excitation at 220 nm and emission at 270 nm

Column: 4.6-mm × 3-cm; packing L1

Temperature: 40°

Flow rate: 1.0 mL/min

Injection size: 50 µL

System suitability

Sample: *Standard solution*

Tailing factor: 0.9–2.5

Relative standard deviation: NMT 3.0%, using 0.45 µg/mL of the *Standard solution*

Analysis: Plot the peak responses of the *Standard solutions* versus concentration, in µg/mL, of estradiol. From the graph determine the amount, in µg/mL, of estradiol released. Calculate the cumulative release rate as percentage of the labeled amount of estradiol:

At 24 h:

$$\text{Result} = \{[900(A_1 - b)]/(1000 \times m \times L)\} \times 100$$

At 48 h:

$$\text{Result} = \{[890(A_2 - b) + 10(A_1 - b]/(1000 \times m \times L)\} \times 100$$

At 96 h:

$$\text{Result} = \{[880(A_3 - b) + 10(A_2 - b) + 10(A_1 - b)]/(1000 \times m \times L)\} \times 100$$

A_1 = peak area of estradiol in the *Sample solution* at the first time interval

A_n = peak area of estradiol in the *Sample solution* at the release interval n

m = slope of the calibration curve

b = y-intercept of the calibration curve

L = Transdermal System label claim (mg)

Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved (release rate)
24	1.2%–6.0%
48	3.0%–11.4%
96	5.0%–16.3%

The percentages of the labeled amount of estradiol ($C_{18}H_{24}O_2$) released at the times specified conform to *Drug Release ⟨724⟩*, *Acceptance Table 1*.

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

Medium: 0.005 M phosphate buffer, pH 5.5, containing 0.3% sodium lauryl sulfate; 500 mL

Apparatus 5: 100 rpm. Use a 76-mm stainless steel disk assembly. Adhere the patch to the disk assembly using transfer tape. [Note—A suitable tape is available as 3M adhesive transfer tape 927, www.mmm.com.]

Times: 1, 4, 8, and 24 h

Mobile phase: Acetonitrile and water (1:1)

Standard stock solution: 800 µg/mL of USP Estradiol RS in acetone

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a solution having a known concentration close to that expected in the solution under test, assuming 100% drug release.

Sample solution: At each sampling time interval, withdraw a known volume aliquot of the solution under test.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 205 nm

Column: 3.9-mm × 30-cm; packing L1

Flow rate: 1.0 mL/min

Injection size: 100 µL

System suitability

Sample: *Standard solution*

Tailing factor: NMT 2.0

Relative standard deviation: NMT 3.0%

Analysis: Calculate the amount of estradiol released at each sampling time:

$$M_i = (r_U/r_S) \times C_S \times V_i$$

$$m_1 = M_1$$

$$m_2 = M_2 + M_1(V_a/V_1)$$

$$m_3 = M_3 + M_2(V_a/V_2) + M_1(V_a/V_1)$$

$$m_4 = M_4 + M_3(V_a/V_3) + M_2(V_a/V_2) + M_1(V_a/V_1)$$

Calculate the percentage of the labeled amount of estradiol released at each sampling time:

$$\text{Result} = (m_i/L) \times 100$$

M_i	= amount of estradiol released into the *Medium* at a given sampling time (mg)
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)
V_i	= corrected volume of the *Medium* at a given sampling time (mL)
m_1, m_2, m_3,	= total amounts of estradiol released from the patch at given sampling times (mg)

m_4

M_1, M_2, M_3, M_4 = amounts of estradiol released into the *Medium* at given sampling times (mg)

V_a = volume of the aliquot taken from the dissolution vessel at each sampling time (mL)

V_1, V_2, V_3 = volumes of *Medium* at given sampling times (mL)

L = Transdermal System label claim (mg)

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved (release rate)
1	15%–40%
4	45%–70%
8	70%–90%
24	NLT 80%

The percentages of the labeled amount of estradiol ($C_{18}H_{24}O_2$) released at the times specified conform to *Drug Release ⟨724⟩*, *Acceptance Table 1*.

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

Medium: 1% (v/v) polysorbate 40 in water; 900 mL

Apparatus 5: 50 rpm

Times: 4, 8, and 24 h

Standard stock solution: Known concentration (mg/mL) of USP Estradiol RS in methanol

Standard solution: Five different concentrations within the range of the expected release amounts of estradiol, prepared as follows. Add 1.0 mL of polysorbate 40 into a 100-mL volumetric flask, and then add the required amount of *Standard stock solution*. Mix well to dissolve the polysorbate 40, and dilute with water to volume.

Sample solution: At each sampling time interval, withdraw a known volume aliquot of the solution under test.

Mobile phase: Acetonitrile and water (2:3)

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 15-cm, 5-µm packing L1 for 9-cm^2 systems; 4.6-mm × 12.5-cm, 5-µm packing L1 for 18-, 27-, or 36-cm^2 systems. In any case, a guard column containing packing L1 is used.

Flow rate: 1.0 mL/min

Injection size: 50 µL

System suitability

Sample: *Standard solution*

Relative standard deviation: NMT 2.0%

Analysis: Calculate the cumulative release rate as a percentage of the labeled amount of estradiol:

$$\text{Result} = \{[900(A - b)]/(1000 \times m \times L)\} \times 100$$

A = peak area of estradiol in the *Sample solution* at each time interval

b = y-intercept of the calibration curve

m = slope of the calibration curve

L = Transdermal System label claim (mg)

Tolerances: The percentages of the labeled amount of estradiol ($C_{18}H_{24}O_2$) released at the times specified conform to *Table 3*, *Table 4*, and *Table 5*.

L1 (6 units)

Table 3

Time (h)	Amount Dissolved (individual values)
4	40%–71%
8	58%–94%
24	NLT 75%

L2 (12 units)

Table 4

Time (h)	Amount Dissolved (average of 12)	Amount Dissolved (individual values)
4	40%–71%	34%–77%
8	58%–94%	50%–102%
24	NLT 75%	NLT 68%

L3 (24 units)

Table 5

Time (h)	Amount Dissolved (average of 24)	Amount Dissolved (individual for 22 units of 24)	Amount Dissolved (individual for 24)
4	40%–71%	34%–77%	29%–82%
8	58%–94%	50%–102%	43%–109%
24	NLT 75%	NLT 68%	NLT 60%

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

Medium: Water; 500 mL for 0.025 mg/day and 0.0375 mg/day dosage; 900 mL for 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day dosage

Apparatus 6: 50 rpm. Use a stainless steel cylinder assembly. Adhere the Transdermal System to the cylinder assembly using a strip of suitable double-sided transfer tape.

Times: 2, 6, and 12 h

Buffer solution: 25 mM of monobasic sodium phosphate, adjusted with phosphoric acid to a pH of 3.0

Mobile phase: Acetonitrile and *Buffer solution* (40:60)

Standard stock solution: 0.2 mg/mL of USP Estradiol RS in methanol

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a solution having a known concentration that is approximately 90% of the concentration expected from complete release in the solution under test.

Sample solution: At each sampling time interval, withdraw about 1.5 mL of the solution under test. Place each sample aliquot into an amber HPLC vial.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 3.0-mm × 10-cm; 3.5-µm packing L1

Flow rate: 0.5 mL/min

Injection volume: 15 µL

Run time: 2.5 times the retention time of estradiol

System suitability

Sample: *Standard solution*

Tailing factor: NMT 1.8

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of estradiol ($C_{18}H_{24}O_2$) in the sample withdrawn from the vessel at time point *i*:

$$C_i = (r_i/r_S) \times C_S$$

r_i = peak response of estradiol from the *Sample solution* at time point *i*

r_S = peak response of estradiol from the *Standard solution*

C_S = concentration of USP Estradiol RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of estradiol ($C_{18}H_{24}O_2$) released at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of estradiol in the portion of the sample withdrawn at each time point (*i*) (mg/mL)

V = volume of *Medium*, 900 or 500 mL

L = Transdermal System label claim (mg)

V_S = volume of *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 6*.

Table 6

Time (h)	Amount Dissolved (release rate, %)
2	20–40
6	48–68
12	70–90

The percentages of the labeled amount of estradiol ($C_{18}H_{24}O_2$) released at the times specified conform to *Dissolution ⟨711⟩*, *Acceptance Table 2*.

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

Medium: Water; 500 mL for 0.025 and 0.0375 mg/day dosages; 900 mL for 0.05, 0.075, and 0.1 mg/day dosages

Apparatus 6: 50 rpm. Use a stainless steel cylinder assembly. Adhere the Transdermal System to the bottom of the cylinder by using a suitable adhesive.

Times: 1, 4, 8, and 12 h

Mobile phase: Acetonitrile and water (60:40)

Diluent: Absolute alcohol and water (50:50)

Standard stock solution: 500 µg/mL of USP Estradiol RS in absolute alcohol prepared as follows. Transfer a suitable amount of USP Estradiol RS to a suitable volumetric flask, add absolute alcohol to 50% of the flask volume, and sonicate to dissolve. Dilute with absolute alcohol to volume.

Standard solution: Dilute the *Standard stock solution* with *Diluent* to obtain a solution with a known concentration that is approximately 80% of the concentration expected from complete release in the solution under test.

Sample solution: Accurately transfer 4.0 mL of absolute alcohol as a stabilizer to each sample tube prior to sampling. At each sampling time interval, withdraw about 4.0 mL of the solution under test, and pass through a suitable filter of 10-µm pore size. Mix 4.0 mL of the filtered test solution with 4.0 mL of absolute alcohol in the sample tube.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Flow rate: 1.0 mL/min

Injection volume: 50 µL

Run time: 4.5 times the retention time of estradiol

System suitability

Sample: *Standard solution*

Tailing factor: NMT 2.0

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of estradiol ($C_{18}H_{24}O_2$) in the sample withdrawn from the vessel at time point *i*:

$$C_i = (r_i/r_S) \times C_S \times D$$

r_i = peak response of estradiol from the *Sample solution* at time point *i*

= peak response of estradiol from the *Standard solution*

r_S

C_S = concentration of USP Estradiol RS in the *Standard solution* (mg/mL)

D = dilution factor, 2

Calculate the percentage of the labeled amount of estradiol ($C_{18}H_{24}O_2$) released at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of estradiol in the portion of the sample withdrawn at each time point (i) (mg/mL)

V = volume of *Medium*, 900 mL

L = Transdermal System label claim (mg)

V_S = volume of *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 7*.

Table 7

Time Point (i)	Time (h)	Amount Dissolved (release rate, %)
1	1	10–30
2	4	38–58
3	8	63–83
4	12	NLT 80

The percentages of the labeled amount of estradiol ($C_{18}H_{24}O_2$) released at the times specified conform to *Drug Release ⟨724⟩*, *Acceptance Table 1*.

▲**Test 7:** If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 7*.

Medium: 0.1% hydroxypropyl-ß-cyclodextrin; 900 mL

Apparatus 5: 50 rpm.

Times: 1, 2, 4, and 8 h

Mobile phase: Acetonitrile and water (40:60)

Standard stock solution 1: 10.4 µg/mL of USP Estradiol RS in methanol prepared as follows. Transfer a suitable amount of USP Estradiol RS to a suitable volumetric flask, add 50% of the flask volume of methanol to dissolve. Dilute with methanol to volume.

Standard stock solution 2: 13.5 µg/mL of USP Estradiol RS in methanol prepared as follows. Transfer a suitable amount of USP Estradiol RS to a suitable volumetric flask, add 50% of the flask volume of methanol to dissolve. Dilute with methanol to volume.

Standard solutions: Dilute *Standard stock solution 1* or *Standard stock solution 2* with *Medium* to obtain five solutions with known concentrations approximately from 15% to 120% of the concentration expected from complete release in the solution under test.

Sample solution: At each sampling time interval, withdraw about 1.5 mL of the solution under test.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: Fluorescence with excitation at 280 nm and emission at 310 nm

Column: 4.6-mm × 10-cm; 1.8-µm packing L1

Column temperature: 40°

Flow rate: 0.8 mL/min

Injection volume: 50 µL

Run time: NLT 1.2 times the retention time of estradiol

System suitability

Sample: Middle point *Standard solution*

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solutions* and *Sample solution*

Use the standard concentrations and their respective peak areas in a linear regression with a $1/x$ weighting to calculate the slope (m), y-intercept (b), and the correlation coefficient (r). The correlation coefficient (r) for the standard curve must be NLT 0.99. No individual point may deviate from the curve by greater than 7%.

Calculate the concentration (C_i), in µg/mL, of estradiol ($C_{18}H_{24}O_2$) in the sample withdrawn from the vessel at time point i:

$$C_i = (r_i - b)/m$$

r_i = peak area of estradiol from the *Sample solution* at time point i

b = y-intercept of the linear regression

m = slope of the linear regression

Calculate the percentage of the labeled amount of estradiol ($C_{18}H_{24}O_2$) released at each time point (i):

$$\text{Result}_i = C_i \times V \times F \times (1/L) \times 100$$

C_i = concentration of estradiol in the portion of the sample withdrawn at each time point (i) (µg/mL)

V = volume of *Medium*, 900 mL

F = conversion factor for converting µg to mg, 0.001

L = Transdermal System label claim (mg)

Tolerances: See *Table 8*.

Table 8

Time Point (*i*)	Time (h)	Amount Dissolved (release rate, %)
1	1	15–40
2	2	28–53
3	4	55–80

Time Point (*i*)	Time (h)	Amount Dissolved (release rate, %)
4	8	NLT 80

The percentages of the labeled amount of estradiol ($C_{18}H_{24}O_2$) released at the times specified conform to *Drug Release* ⟨724⟩, *Acceptance Table 1*.▲ (TBD)

- **Uniformity of Dosage Units** ⟨905⟩**:** The results from the Transdermal Systems used in the *Assay* meet the requirements.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in hermetic, light-resistant, unit-dose pouches.
- **Labeling:** The label states the total amount of estradiol in the Transdermal System and the release rate, in mg/day, for the duration of application of one system. When more than one *Drug Release* test is given, the labeling states the *Drug Release* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

  USP Estradiol RS

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