In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 6 Expert Committee has revised the Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to widen the acceptance criteria for any unspecified impurity related both to naproxen sodium and pseudoephedrine hydrochloride from NMT 0.15% to NMT 0.2% in the test for Organic Impurities to accommodate the manufacturer’s FDA-approved specification.

Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Richard Nguyen, Scientific Liaison (301-816-8170 or rbn@usp.org) or Tsion Billilign, Scientific Liaison (301-816-8286 or tb@usp.org).
Add the following:

**Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets**

**DEFINITION**
Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of naproxen sodium \((C_{13}H_{15}NaO_3)\) and pseudoephedrine hydrochloride \((C_{10}H_{12}NO \cdot HCl)\).

**IDENTIFICATION**
- **A.** The retention times of the naproxen and pseudoephedrine peaks of the Sample solution correspond to those of the Standard solution, as obtained in the Assay.
- **B.** The UV absorption spectra of the naproxen and pseudoephedrine peaks of the Sample solution exhibit maxima and minima at the same wavelengths as those of the corresponding peaks of the Standard solution, as obtained in the Assay.

**ASSAY**
- **PROCEDURE**
  - **Buffer:** Dissolve 400 mg of sodium lauryl sulfate in 1 L of water. Add 5 mL of triethylamine and adjust with glacial acetic acid to a pH of 4.1.
  - **Mobile phase:** Acetonitrile, methanol, and Buffer (25:25:50)
  - **Standard solution:** 0.22 mg/mL of USP Naproxen Sodium RS and 0.12 mg/mL of USP Pseudoephedrine Hydrochloride RS in methanol
  - **Sample stock solution:** Nominally 2.2 mg/mL of naproxen sodium and 1.2 mg/mL of pseudoephedrine hydrochloride in methanol prepared as follows. Transfer NLT 5 whole Tablets to an appropriate volumetric flask, add 70% of the final volume of methanol, and shake to disintegrate the Tablets. Sonicate for 30 min with intermittent shaking. Allow the solution to cool to room temperature and dilute with methanol to volume. Centrifuge 10 mL of the solution for 10 min, and use the clear supernatant to prepare the Sample solution.
  - **Sample solution:** Nominally 0.22 mg/mL of naproxen sodium and 0.12 mg/mL of pseudoephedrine hydrochloride in methanol from the Sample stock solution. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.
  - **Chromatographic system** (See Chromatography (621), System Suitability.)
    - **Mode:** LC
    - **Detector:** UV 257 nm
    - **Column:** 4.6-mm × 25-cm; 5-µm packing L1
    - **Flow rate:** 1.0 mL/min
    - **Injection volume:** 10 µL
    - **Run time:** NLT 6 times the retention time of pseudoephedrine
  - **System suitability**
    - **Sample:** Standard solution
    - **Suitability requirements**
      - **Tailing factor:** NMT 2.0 for the naproxen and pseudoephedrine peaks
      - **Relative standard deviation:** NMT 2.0% for the naproxen and pseudoephedrine peaks
  - **Analysis**
    - **Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of naproxen sodium \((C_{13}H_{15}NaO_3)\) and pseudoephedrine hydrochloride \((C_{10}H_{12}NO \cdot HCl)\) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_u}{r_S} \right) \times \left( \frac{C_j}{C_0} \right) \times 100
\]

- **r_u** = peak response of naproxen or pseudoephedrine from the Sample solution
- **r_S** = peak response of naproxen or pseudoephedrine from the Standard solution
- **C_j** = concentration of USP Naproxen Sodium RS or USP Pseudoephedrine Hydrochloride RS in the Standard solution (mg/mL)
- **C_u** = nominal concentration of naproxen sodium or pseudoephedrine hydrochloride in the Sample solution (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**
- **Dissolution** (711)
  - **Test 1**
    - **Medium:** 0.01% sodium lauryl sulfate in water, degassed; 900 mL
    - **Apparatus 1:** 75 rpm
    - **Times**
      - **Naproxen sodium:** 1 h
      - **Pseudoephedrine hydrochloride:** 1, 3, and 8 h
    - **Buffer:** Add 5 mL of triethylamine to 1 L of 0.4 g/L of sodium lauryl sulfate in water. Adjust with glacial acetic acid to a pH of 4.1.
    - **Mobile phase:** Acetonitrile, methanol, and Buffer (25:25:50)
  - **Standard stock solution:** 1.22 mg/mL of USP Naproxen Sodium RS and 0.66 mg/mL of USP Pseudoephedrine Hydrochloride RS in methanol
  - **Standard solution:** 0.24 mg/mL of USP Naproxen Sodium RS and 0.13 mg/mL of USP Pseudoephedrine Hydrochloride RS in Medium from the Standard stock solution
  - **Sample solution:** At the times specified, withdraw 10 mL of the solution under test, and pass through a suitable filter of 0.45-µm pore size. Replace the aliquots withdrawn for analysis with equal volumes of fresh portions of Medium maintained at 37°C.

**Chromatographic system** (See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 257 nm
- **Column:** 4.6-mm × 25-cm; 5-µm packing L1
- **Flow rate:** 1.5 mL/min
- **Injection volume:** 40 µL
- **Run time:** NLT 2.5 times the retention time of pseudoephedrine

**System suitability**
- **Sample:** Standard solution
  - **Suitability requirements**
    - **Tailing factor:** NMT 2.0 for the naproxen and pseudoephedrine peaks
    - **Relative standard deviation:** NMT 2.0% for the naproxen and pseudoephedrine peaks

**Analysis**
- **Samples:** Standard solution and Sample solution

Calculate the percentage \((Q)\) of the labeled amount of naproxen sodium \((C_{13}H_{15}NaO_3)\) dissolved:

\[
Q = \left( \frac{r_u}{r_S} \right) \times \left( \frac{C_j}{C_0} \right) \times 100
\]

**Acceptance criteria:** 90.0%–110.0%
If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Solution A: Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water. Adjust with phosphoric acid to a pH of 4.0.

Solution B: Acetonitrile

Mobile phase: See Table 2.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>1.0</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>1.1</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>1.3</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

Standard solution: 0.24 mg/mL of USP Naproxen Sodium RS and 0.13 mg/mL of USP Pseudoephedrine Hydrochloride RS prepared as follows. Dissolve suitable quantities of USP Naproxen Sodium RS and USP Pseudoephedrine Hydrochloride RS with 2% of the final volume of methanol and sonicate if necessary. Dilute with Medium to volume. Sample solution: At the times specified, withdraw 10 mL of the solution under test, and pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See Chromatography (621), System Suitability.) Mode: LC Detector: UV 254 nm for the pseudoephedrine peak (before relative retention time of 0.5 in relation to the naproxen peak); UV 290 nm for the naproxen peak (at relative retention time of 0.5 and after relative retention time of 0.5 in relation to the naproxen peak) Column: 4.6-mm x 15-cm; 5-µm packing L1 Column temperature: 30° Flow rate: 1.6 mL/min Injection volume: 30 µL System suitability Sample: Standard solution Suitability requirements Tailing factor: NMT 2.0 for the naproxen and pseudoephedrine peaks Relative standard deviation: NMT 2.0% for the naproxen and pseudoephedrine peaks Analysis Samples: Standard solution and Sample solution Calculate the percentage (Q) of the labeled amount of naproxen sodium (C₁₃H₁₈NO₂) dissolved:

\[ \text{Result} = \frac{r_s}{r_u} \times C_s \times V \times (1/L) \times 100 \]  

\[ r_u = \text{peak response of naproxen from the Sample solution} \]  
\[ r_s = \text{peak response of naproxen from the Standard solution} \]  
\[ C_s = \text{concentration of USP Naproxen Sodium RS in the Standard solution (mg/mL)} \]  
\[ V = \text{volume of Medium, 900 mL} \]  
\[ L = \text{label claim of naproxen sodium (mg/Tablet)} \]  

The percentages of the labeled amount of pseudoephedrine hydrochloride (C₁₀H₁₃NO.HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

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

Medium: 0.01% sodium lauryl sulfate in water; 900 mL Apparatus 1: 75 rpm

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Naproxen sodium related impurities

**Sample solution:** Nominally 3.1 mg/mL of naproxen sodium from NLT 20 finely powdered Tablets to an appropriate volumetric flask, add 70% of the final volume of Diluent, and sonicate for 20 min with intermittent shaking. Allow the solution to cool to room temperature and dilute with Diluent to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 260 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing L1

**Flow rate:** 1.0 mL/min

**Injection volume:** 10 µL

**Run time:** NLT 5.6 times the retention time of naproxen

**System suitability**

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

**Suitability requirements**

**Resolution:** NLT 2 between naproxen related compound K and naproxen; NLT 2 between naproxen and naproxen related compound L, System suitability solution

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

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of each naproxen sodium related impurity in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_U}{C_S} \right) \times \left( \frac{1}{F} \right) \times 100
\]

\( r_U \) = peak response of each naproxen related impurity from the Sample solution

\( r_S \) = peak response of naproxen from the Standard solution

\( C_U \) = concentration of USP Naproxen Sodium RS in the Sample solution (mg/mL)

\( C_S \) = nominal concentration of naproxen sodium in the Sample solution (mg/mL)

\( F \) = relative response factor (see Table 4)

**Acceptance criteria:** See Table 4.

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**Organic impurities**

**Naproxen sodium related impurities**

**Mobile phase:** Acetonitrile, water, and glacial acetic acid (50:50:0.1)

**Diluent:** Acetonitrile and water (90:10)

**System suitability solution:** 3.1 mg/mL of USP Naproxen Sodium RS and 8 µg/mL of each of USP Naproxen Related Compound K RS and USP Naproxen Related Compound L RS in Diluent

**Standard solution:** 0.006 mg/mL of USP Naproxen Sodium RS in Diluent

**Sample solution:** Nominally 3.1 mg/mL of naproxen sodium in Diluent prepared as follows. Transfer a suitable amount of naproxen sodium from NLT 20 finely

**Suitability Requirements**

1. **Resolution:** NLT 2 between naproxen related compound K and naproxen; NLT 2 between naproxen and naproxen related compound L, System suitability solution

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

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of each naproxen sodium related impurity in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_U}{C_S} \right) \times \left( \frac{1}{F} \right) \times 100
\]

\( r_U \) = peak response of each naproxen related impurity from the Sample solution

\( r_S \) = peak response of naproxen from the Standard solution

\( C_U \) = concentration of USP Naproxen Sodium RS in the Sample solution (mg/mL)

\( C_S \) = nominal concentration of naproxen sodium in the Sample solution (mg/mL)

\( F \) = relative response factor (see Table 4)

**Acceptance criteria:** See Table 4.

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**Table 3**

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount of Pseudoephedrine Hydrochloride Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40–65</td>
</tr>
<tr>
<td>2</td>
<td>75–100</td>
</tr>
<tr>
<td>3</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of pseudoephedrine hydrochloride (C₆H₁₂N₂O · HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Uniformity of Dosage Units** (905): Meet the requirements

**IMPURITIES**

**Organic impurities**

**Naproxen sodium related impurities**

**Mobile phase:** Acetonitrile, water, and glacial acetic acid (50:50:0.1)

**Diluent:** Acetonitrile and water (90:10)

**System suitability solution:** 3.1 mg/mL of USP Naproxen Sodium RS and 8 µg/mL of each of USP Naproxen Related Compound K RS and USP Naproxen Related Compound L RS in Diluent

**Standard solution:** 0.006 mg/mL of USP Naproxen Sodium RS in Diluent

**Sample solution:** Nominally 3.1 mg/mL of naproxen sodium in Diluent prepared as follows. Transfer a suitable amount of naproxen sodium from NLT 20 finely

**Suitability Requirements**

1. **Resolution:** NLT 2 between naproxen related compound K and naproxen; NLT 2 between naproxen and naproxen related compound L, System suitability solution

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

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of each naproxen sodium related impurity in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_U}{C_S} \right) \times \left( \frac{1}{F} \right) \times 100
\]

\( r_U \) = peak response of each naproxen related impurity from the Sample solution

\( r_S \) = peak response of naproxen from the Standard solution

\( C_U \) = concentration of USP Naproxen Sodium RS in the Sample solution (mg/mL)

\( C_S \) = nominal concentration of naproxen sodium in the Sample solution (mg/mL)

\( F \) = relative response factor (see Table 4)

**Acceptance criteria:** See Table 4.
Solution B: Acetonitrile and water (90:10)
Mobile phase: See Table 5.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>50</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>55</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Diluent: 5 mL/L of triethylamine in water. Adjust with phosphoric acid to a pH of 6.8.

System suitability solution: 0.5 mg/mL of USP Pseudoephedrine Hydrochloride RS and 1.5 µg/mL of USP Ephedrine Hydrochloride RS in Diluent
Standard solution: 0.001 mg/mL of USP Pseudoephedrine Hydrochloride RS in Diluent
Sample solution: Nominally 0.5 mg/mL of pseudoephedrine hydrochloride in Diluent prepared as follows. Transfer a suitable amount of pseudoephedrine hydrochloride from NLT 20 finely powdered Tablets to an appropriate volumetric flask, add 70% of the total volume of Diluent, and sonicate for 30 min with intermittent shaking. Allow the solution to cool to room temperature and dilute with Diluent to volume. Centrifuge a portion of the solution for 10 min. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm x 25-cm; 5-µm packing L1
Flow rate: 1.0 mL/min
Injection volume: 20 µL
System suitability
Samples: System suitability solution and Standard solution

Suitability requirements
Resolution: NLT 1.5 between ephedrine and pseudoephedrine, System suitability solution
Relative standard deviation: NMT 5.0%, Standard solution

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each pseudoephedrine hydrochloride related impurity in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_U}{r_V} \right) \times \left( \frac{C_U}{C_V} \right) \times (1/F) \times 100 \]

\[ r_U = \text{peak response of pseudoephedrine hydrochloride from Standard solution} \]
\[ r_V = \text{peak response of pseudoephedrine hydrochloride related impurity from Sample solution} \]
\[ C_U = \text{concentration of USP Pseudoephedrine Hydrochloride RS in Standard solution (mg/mL)} \]
\[ C_V = \text{nominal concentration of pseudoephedrine hydrochloride in Sample solution (mg/mL)} \]
\[ F = \text{relative response factor (see Table 6)} \]

Acceptance criteria: See Table 6.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norephedrine hydrochloride(a)</td>
<td>0.62</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Norpseudoephedrine hydrochloride(b)</td>
<td>0.72</td>
<td>1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Ephedrine hydrochloride</td>
<td>0.90</td>
<td>0.94</td>
<td>0.2</td>
</tr>
<tr>
<td>Pseudoephedrine hydrochloride</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified impurity</td>
<td>—</td>
<td>1.0</td>
<td>(\geq 0.2) (Feb 1-Mar-2019)</td>
</tr>
<tr>
<td>Total impurities(c)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(a\) \((1\,R,2\,S)-2\text{-Amino-1-phenylpropan-1-ol hydrochloride.}\)
\(b\) \((1\,S,2\,S)-2\text{-Amino-1-phenylpropan-1-ol hydrochloride.}\)
\(c\) Exclude naproxen related peaks after a relative retention time of 1.8 and blank peaks before a relative retention time of 0.2.

ADDITIONAL REQUIREMENTS
• Packaging and Storage: Preserve in a dry place. Store 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 Ephedrine Hydrochloride RS (1\,R,2\,S)-(Methylamino)-1-phenylpropan-1-ol hydrochloride.
  \(C_{16}H_{25}NO \cdot HCl\) 201.69
  USP Naproxen Sodium RS
  USP Naproxen Related Compound K RS 1-(6-Methoxynaphthalen-2-yl)ethanol.
  \(C_{13}H_{14}O_2\) 202.25
  USP Naproxen Related Compound L RS 1-(6-Methoxynaphthalen-2-yl)ethanone.
  \(C_{13}H_{12}O_2\) 200.23
  USP Pseudoephedrine Hydrochloride RS \(\geq 25\) (USP41)