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 3 Expert Committee intends to revise the Levothyroxine Sodium Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Levothyroxine Sodium Tablets monograph to add Dissolution Test 8. Existing references to reagents and reagent names have been updated for consistency with official reagent entry names.

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 Yanyin Yang, Senior Scientist II (301-692-3623 or yanyin.yang@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.
Levothyroxine Sodium Tablets

DEFINITION
Levothyroxine Sodium Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of levothyroxine sodium (C₁₅H₁₀I₄NNaO₄).

IDENTIFICATION
• A. The retention time of the major peak of the Sample solution corresponds to the levothyroxine peak of the Standard solution, as obtained in the Assay.

ASSAY
• Procedure
[Note—Use Sample solution 2 for Tablets labeled to meet the requirements of Dissolution Test 3. For all other products, use the Sample solution.]

Mobile phase: Acetonitrile and water (4:6) containing 0.5 mL of phosphoric acid per liter of mixture

Solution A: Dissolve 400 mg of sodium hydroxide in 500 mL of water. Cool, and add 500 mL of methanol.

Diluent: Methanol and water (6:4) containing 0.5 mL of phosphoric acid per liter of mixture

Levothyroxine stock solution: 0.4 mg/mL of USP Levothyroxine RS in Solution A

Liothyronine stock solution: 0.4 mg/mL of USP Liothyronine RS in Solution A. Make a 1:100 dilution of this solution using Mobile phase.

Standard solution: 10 µg/mL of levothyroxine from Levothyroxine stock solution and 0.2 µg/mL of liothyronine from Liothyronine stock solution, in Mobile phase

Sample solution: Transfer an equivalent to about 100 µg of levothyroxine sodium, from finely powdered Tablets (NLT 20), to a centrifuge tube, add two glass beads, pipet 10 mL of Mobile phase into the tube, and mix on a vortex mixer for 3 min. Centrifuge to obtain a clear supernatant, filtering if necessary.

Sample solution 2 (for Tablets labeled to meet the requirements of Dissolution Test 3): Place the appropriate number of Tablets (see Table 1) into a suitable container, add 100.0 mL of Diluent, and shake by mechanical means for at least 30 min, or until the Tablets are fully disintegrated. Pass through a PTFE filter of 0.45-µm pore size.

Table 1

<table>
<thead>
<tr>
<th>Tablet Strength (µg/Tablet of Levothyroxine Sodium)</th>
<th>Number of Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 100</td>
<td>20</td>
</tr>
<tr>
<td>At least 100 but less than 200</td>
<td>15</td>
</tr>
<tr>
<td>200 or more</td>
<td>10</td>
</tr>
</tbody>
</table>

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

Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 25-cm; packing L10
Flow rate: 1.5 mL/min
Injection volume: 100 µL

System suitability
Sample: Standard solution

Suitability requirements
Resolution: NLT 5.0 between liothyronine and levothyroxine
Relative standard deviation: NMT 2.0% for the levothyroxine peak

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of levothyroxine sodium (C_{15}H_{10}I_{4}NNaO_{4}) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_t}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_U}{M_t} \right) \times 100
\]

- \(r_t\) = peak response from the Sample solution
- \(r_S\) = peak response from the Standard solution
- \(C_S\) = concentration of USP Levothyroxine RS in the Standard solution (µg/mL)
- \(C_U\) = nominal concentration of levothyroxine sodium in the Sample solution (µg/mL)
- \(M_U\) = molecular weight of levothyroxine sodium, 798.85
- \(M_t\) = molecular weight of levothyroxine, 776.87

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

**Dissolution (711)**

[Note—All containers that are in contact with solutions containing levothyroxine sodium are to be made of glass.]

Test 1

Medium: **0.01 N hydrochloric acid** containing 0.2% sodium dodecyl sulfate (TBD); 500 mL

Apparatus 2: 50 rpm

Time: 45 min

Mobile phase: Methanol and 0.1% phosphoric acid (6:4)

Standard stock solution: 0.1 mg/mL of USP Levothyroxine RS in methanol

Standard solution: Dilute the Standard stock solution with Medium to obtain a solution having a concentration similar to that expected in the Sample solution.

Sample solution: Pass a portion of the solution under test through a suitable filter. [Note—Before use, check the filters for absorptive loss of drug.]

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 2 mL/min

Injection volume: 800 µL

System suitability
Sample: Standard solution
Suitability requirements

Tailing factor: NMT 1.5
Relative standard deviation: NMT 4.0% for levothyroxine

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of levothyroxine sodium \((C_{15}H_{10}I_{4}NNaO_{4})\) dissolved.

Tolerances: NLT 70% \((Q)\) of the labeled amount of levothyroxine sodium \((C_{15}H_{10}I_{4}NNaO_{4})\) is dissolved.

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

Medium, Apparatus 2, Mobile phase, Standard solution, Sample solution, Chromatographic system, and System suitability: Proceed as directed for Test 1.

Time: 15 min

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of levothyroxine sodium \((C_{15}H_{10}I_{4}NNaO_{4})\) dissolved.

Tolerances: NLT 80% \((Q)\) of the labeled amount of levothyroxine sodium \((C_{15}H_{10}I_{4}NNaO_{4})\) is dissolved.

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

Medium, Apparatus 2, Time, Standard solution, and Sample solution: Proceed as directed for Test 1.

[Note—Filter the Standard solution in a manner identical to that used for the Sample solution.]

Mobile phase: Acetonitrile and water \((35:65)\) that contains 0.5 mL of phosphoric acid per liter of mixture

Chromatographic system

(See Chromatography \((621)\), System Suitability.)

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 5-µm packing \(L10\)

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 100 µL

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 1.5
Relative standard deviation: NMT 4.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of levothyroxine sodium \((C_{15}H_{10}I_{4}NNaO_{4})\) dissolved.

Tolerances: NLT 80% \((Q)\) of the labeled amount of levothyroxine sodium \((C_{15}H_{10}I_{4}NNaO_{4})\) is dissolved.

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

[Note—Do not use paddle stirrers with synthetic coating.] 

Medium: 0.01 N hydrochloric acid; 500 mL for Tablets labeled to contain between 25 and 175 µg of levothyroxine sodium; and 900 mL for Tablets labeled to contain 200 or 300 µg of levothyroxine sodium

Apparatus 2: 75 rpm

Time: 45 min

Mobile phase: Acetonitrile, water, and phosphoric acid \((500:700:2)\)

Standard stock solution: Transfer about 100 mg of USP Levothyroxine RS to a 100-mL volumetric flask.

Add 80 mL of alcohol and 1 mL of 1 N hydrochloric acid, sonicate for 2 min, dilute with alcohol to volume,
and mix.

**Standard solution:** Dilute the *Standard stock solution* with a mixture of *alcohol* and *water* (1:1) to obtain a concentration of 0.01 mg/mL of levothyroxine. Dilute the resulting solution with *Medium* to obtain a final concentration similar to that expected in the *Sample solution*.

**Sample solution:** Sample per *Dissolution* (711). Centrifuge the solution under analysis.

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

- **Mode:** LC
- **Detector:** UV 225 nm
- **Column:** 4.0-mm × 12.5-cm; packing L7
- **Flow rate:** 1.5 mL/min
- **Injection volume:** 500 µL

**System suitability**
- **Sample:** *Standard solution*
- **Suitability requirements**
  - **Tailing factor:** NMT 1.5
  - **Relative standard deviation:** NMT 4.0% of levothyroxine

**Analysis**
- **Samples:** *Standard solution* and *Sample solution*
  - Calculate the percentage of the labeled amount of levothyroxine sodium \((C_{15}H_{10}I_{4}NNaO_{4})\) dissolved.

- **Tolerances:** NLT 80% (Q) of the labeled amount of levothyroxine sodium \((C_{15}H_{10}I_{4}NNaO_{4})\) is dissolved.

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

- **Medium:** *0.01 N hydrochloric acid* containing 0.2% ▲ *sodium dodecyl sulfate* ▲ (TBD); 500 mL
- **Apparatus 2:** 50 rpm
- **Time:** 30 min
- **Mobile phase:** *Acetonitrile*, *water*, and *phosphoric acid* (32: 68: 0.05)
- **Standard stock solution:** Transfer about 25 mg of *USP Levothyroxine RS* to a 250-mL volumetric flask.
  - Add 50 mL of *methanol*, sonicate to dissolve, and dilute with *methanol* to volume.
- **Standard solution:** 0.0004 mg/mL of *USP Levothyroxine RS* from *Standard stock solution* in *Medium*
- **Sample solution:** Collect the sample using a suitable glass syringe and cannula.

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

- **Mode:** LC
- **Detector:** UV 225 nm
- **Column:** 4.6-mm × 7.5-cm; 5-µm packing L10
- **Temperatures**
  - **Autosampler:** 10°
  - **Column:** 30°
- **Flow rate:** 1 mL/min
- **Injection volume:** 80 µL

**System suitability**
- **Sample:** *Standard solution*
- **Suitability requirements**
  - **Tailing factor:** NMT 1.5
  - **Relative standard deviation:** NMT 4.0% for levothyroxine
Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of levothyroxine sodium \( (\text{C}_{15}\text{H}_{10}\text{I}_4\text{NNaO}_4) \) dissolved.

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{M_{r1}}{M_{r2}} \right) \times \left( \frac{1}{L} \right) \times 100
\]

- \( r_U \): peak response of levothyroxine from the Sample solution
- \( r_S \): peak response of levothyroxine from the Standard solution
- \( C_S \): concentration of USP Levothyroxine RS in the Standard solution (mg/mL)
- \( V \): volume of Medium, 500 mL
- \( M_{r1} \): molecular weight of levothyroxine sodium, 798.85
- \( M_{r2} \): molecular weight of levothyroxine, 776.87
- \( L \): label claim (mg/Tablet)

Tolerances: NLT 80% \((Q)\) of the labeled amount of levothyroxine sodium \( (\text{C}_{15}\text{H}_{10}\text{I}_4\text{NNaO}_4) \) is dissolved.

Test 7: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 7.

Medium: 0.01 N hydrochloric acid containing 0.2% sodium dodecyl sulfate (TBD); 500 mL

Apparatus 2: 75 rpm

Time: 15 min

Solution A: 0.1% \((v/v)\) phosphoric acid in water

Mobile phase: Methanol and Solution A (63:37)

Sample solution: Pass a portion of the solution under test through a suitable filter, discarding the first few milliliters.

Standard stock solution: 0.1 mg/mL of USP Levothyroxine RS in methanol. Sonicate as needed to dissolve.

Standard solution: USP Levothyroxine RS in Medium, from the Standard stock solution at a concentration similar to that of the Sample solution

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 10-µm packing L1

Temperatures
- Autosampler: 12°
- Column: 25°

Flow rate: 2 mL/min

Injection volume: 800 µL

System suitability

Sample: Standard solution

Suitability requirements
- Tailing factor: NMT 1.5
- Relative standard deviation: NMT 4.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of levothyroxine sodium \( (\text{C}_{15}\text{H}_{10}\text{I}_4\text{NNaO}_4) \) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{M_{r1}}{M_{r2}} \right) \times \left( \frac{1}{L} \right) \times 100
\]
\[ r_U \text{ = peak response of levothyroxine from the Sample solution} \]
\[ r_S \text{ = peak response of levothyroxine from the Standard solution} \]
\[ C_S \text{ = concentration of USP Levothyroxine RS in the Standard solution (mg/mL)} \]
\[ V \text{ = volume of Medium, 500 mL} \]
\[ M_{r1} \text{ = molecular weight of levothyroxine sodium, 798.85} \]
\[ M_{r2} \text{ = molecular weight of levothyroxine, 776.87} \]
\[ L \text{ = label claim (mg/Tablet)} \]

**Tolerances:** NLT 80% (Q) of the labeled amount of levothyroxine sodium (C_{15}H_{10}I_{4}NaO_{4}) is dissolved.

**Test 8:** If the product complies with this test, the labeling indicates that it meets USP **Dissolution Test 8**.

Protect all solutions containing levothyroxine from light.

**Medium:** 0.01 N hydrochloric acid containing 0.2% sodium dodecyl sulfate; 500 mL

**Apparatus 2:** 50 rpm

**Time:** 60 min

**Solution A:** Add 1.0 mL of phosphoric acid into 1000 mL of water.

**Solution B:** Acetonitrile

**Mobile phase:** See Table 3.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>16</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>16.5</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>23</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

**Standard stock solution A:** 200 µg/mL of USP Levothyroxine RS in methanol. Sonicate to dissolve.

**Standard stock solution B:** 5 µg/mL of USP Levothyroxine RS from Standard stock solution A in Medium

**Standard solution:** USP Levothyroxine RS from Standard stock solution B in Medium at a concentration similar to that of levothyroxine in the Sample solution

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 225 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing L11

**Flow rate:** 1.2 mL/min

**Injection volume:** 100 µL

**System suitability**
Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0
Relative standard deviation: NMT 4.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of levothyroxine sodium \(\text{C}_{15}\text{H}_{11}\text{I}_{4}\text{NNaO}_{4}\) dissolved:

\[
\text{Result} = \left(\frac{r_U}{r_S}\right) \times C_S \times V \times \left(\frac{M_{r1}}{M_{r2}}\right) \times \left(\frac{1}{L}\right) \times 100
\]

- \(r_U\) = peak response of levothyroxine from the Sample solution
- \(r_S\) = peak response of levothyroxine from the Standard solution
- \(C_S\) = concentration of USP Levothyroxine RS in the Standard solution (mg/mL)
- \(V\) = volume of Medium, 500 mL
- \(M_{r1}\) = molecular weight of levothyroxine sodium, 798.85
- \(M_{r2}\) = molecular weight of levothyroxine, 776.87
- \(L\) = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of levothyroxine sodium \(\text{C}_{15}\text{H}_{11}\text{I}_{4}\text{NNaO}_{4}\) is dissolved.

(TBD)

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

Impurities

- Limit of Liothyronine Sodium

[Note—Use Sample solution 2 for Tablets labeled to meet the requirements of Dissolution Test 3. For all other products, use the Sample solution.]

Mobile phase, Liothyronine stock solution, Standard solution, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the Assay.

Liothyronine standard solution: 0.2 µg/mL of liothyronine from Liothyronine stock solution, in Mobile phase

Analysis

Samples: Sample solution and Liothyronine standard solution

Calculate the percentage of liothyronine sodium \(\text{C}_{15}\text{H}_{11}\text{I}_{3}\text{NNaO}_{3}\) in the portion of Tablets taken:

\[
\text{Result} = \left(\frac{r_U}{r_S}\right) \times \left(\frac{C_S}{C_U}\right) \times \left(\frac{M_{r1}}{M_{r2}}\right) \times 100
\]

- \(r_U\) = peak response of liothyronine from the Sample solution
- \(r_S\) = peak response of liothyronine from the Liothyronine standard solution
- \(C_S\) = concentration of USP Liothyronine RS in the Liothyronine standard solution (µg/mL)
- \(C_U\) = nominal concentration of liothyronine sodium in the Sample solution (µg/mL)
- \(M_{r1}\) = molecular weight of liothyronine sodium, 672.96
- \(M_{r2}\) = molecular weight of liothyronine, 650.98

Acceptance criteria: NMT 2.0% of liothyronine sodium

Additional requirements

- Packaging and Storage: Preserve in tight, light-resistant containers.
- 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)