Erythromycin Delayed-Release Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	22–Feb–2019
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Biologics Monographs 4–Antibiotics

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 Biologics Monographs 4–Antibiotics Expert Committee intends to revise the Erythromycin Delayed-Release Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 3* to the monograph.

- *Dissolution Test 3* was validated using Waters XBridge C18 brand L1 columns. The typical retention time for erythromycin is 7.8 and 3.8 min in the analysis of acid and buffer stages, respectively.

USP Reference Standards has been revised to include USP Erythromycin B RS and USP Erythromycin C RS to support the inclusion of *Dissolution Test 3*.

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 Julie Zhang, Scientific Liaison to the Biologics Monographs 4–Antibiotics Expert Committee (301-816-8350 or julie.zhang@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*.

Erythromycin Delayed-Release Tablets

DEFINITION

Erythromycin Delayed-Release Tablets contain NLT 90.0% and NMT 120.0% of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$).

IDENTIFICATION

• **A. Thin-Layer Chromatography**

Standard solution: 2.5 mg/mL of USP Erythromycin RS in methanol

Sample solution: Nominally 2.5 mg/mL of erythromycin from powdered Tablets in methanol

Chromatographic system

(See *Chromatography* ⟨621⟩, *General Procedures, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel

Application volume: 10 µL

Developing solvent system: Methanol and chloroform (85:15)

Spray reagent: Alcohol, *p*-methoxybenzaldehyde, and sulfuric acid (90:5:5)

Analysis

Samples: *Standard solution* and *Sample solution*

Place the plate in an unlined chromatographic chamber, and develop the chromatogram until the solvent front has moved about 7 cm. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Spray the plate with *Spray reagent*. Heat the plate at 100° for 10 min, and examine the chromatogram, in which erythromycin appears as a black-to-purple spot.

Acceptance criteria: The R_F value of the principal spot of the *Sample solution* corresponds to that of the *Standard solution*.

ASSAY

• **Antibiotics—Microbial Assays** ⟨81⟩

Sample solution: Place NLT 4 Tablets in a high-speed glass blender jar with 200 mL of methanol, and blend for 3 min. Add 300 mL of *Buffer B.3*, and blend for 3 min.

Analysis: Proceed as directed in the chapter. Dilute the *Sample solution* with *Buffer B.3* to obtain a *Test Dilution* having a concentration that is nominally equivalent to the median level of the standard.

Acceptance criteria: 90.0%–120.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩ ▲▲ (TBD)

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.

▲Proceed as directed in *Dissolution* ⟨711⟩, *Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure*.▲ (TBD)

Acid stage

Medium: Simulated gastric fluid TS, without pepsin; 900 mL

Apparatus 1: 100 rpm

Time: 60 min

Analysis: Do not analyze the sample at this stage.

Buffer stage

Medium: 0.05 M pH 6.8 phosphate buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*)

Apparatus 1: 100 rpm

Time: 60 min

Buffer: pH 1.2 buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*)

Solution A: 1 g/L of bromocresol purple in pH 4.5 phosphate buffer

Standard solution: Dissolve USP Erythromycin RS in *Medium* to obtain a concentration similar to that of the *Sample solution*.

Sample solution: If necessary, dilute a filtered portion of the solution under test with *Medium* to obtain a solution containing about 0.28 mg/mL of erythromycin.

Detector: UV 410 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Transfer 2.0 mL of the *Standard solution* and the *Sample solution* to individual separators of a suitable size. Add 6 mL of *Buffer* and 8 mL of *Solution A*, and mix. Extract with 40.0 mL of chloroform. Determine the amount of erythromycin ($C_{37}H_{67}NO_{13}$) dissolved from UV absorbances of the chloroform extracts.

Tolerances: NLT 75% (*Q*) of the labeled amount of erythromycin ($C_{37}H_{67}NO_{13}$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*. Proceed as directed under *Test 1*, except to use *Apparatus 2* at 75 rpm.

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

Acid stage

Acid stage medium: Simulated gastric fluid TS, without enzyme; 900 mL

Apparatus 1: 100 rpm

Time: 60 min

Solution A: 3.6 g/L of dibasic sodium phosphate in water. Adjust with diluted phosphoric acid to a pH of 9.0.

Mobile phase: *Solution A* and acetonitrile (1:1)

Solution B: 6.8 g/L of monobasic potassium phosphate and 1.2 g/L of sodium hydroxide in water

Peak identification solution: 0.05 mg/mL of USP Erythromycin B RS and USP Erythromycin C RS prepared as follows. Transfer 2.5 mg each of USP Erythromycin B RS and USP Erythromycin C RS to a 50-mL volumetric flask, add 12.5 mL of methanol, sonicate to dissolve, and dilute with *Solution B* to volume.

[NOTE—The typical retention times of erythromycin C and erythromycin B are 4.2 and 13.4 min, respectively.]

Standard solution: 2.5 mg/mL of USP Erythromycin RS prepared as follows. Transfer 125 mg of USP Erythromycin RS to a 50-mL volumetric flask, add 12.5 mL of methanol, sonicate to dissolve, and dilute with *Solution B* to volume.

[NOTE—The typical retention time of erythromycin A is 7.8 min.]

Sample solution 1: Determine the average Tablet weight by weighing NLT 20 Tablets. Carefully transfer the appropriate number of intact Tablets into a suitable volumetric flask (5 Tablets into a 500-mL flask for 250-mg Tablets, 8 Tablets into a 1000-mL flask for 333-mg Tablets, and 5 Tablets into a 1000-mL flask for 500-mg Tablets). Add methanol to about 25% of the final volume, and sonicate at room temperature for about 30 min with intermittent shaking. Further add about 25% of the final volume of *Solution B* and sonicate at room temperature for about 30 min with intermittent shaking. Dilute to volume with *Solution B* and mix well.

Centrifuge at 5000 rpm for 5 min and pass the supernatant through a polyvinylidene fluoride (PVDF) or other suitable filter of 0.45-µm pore size. Discard the first 5 mL of the filtrate.

Sample solution 2: At the end of *Acid stage* dissolution, discard *Acid stage medium* and carefully transfer 1 Tablet from the dissolution vessel into a suitable volumetric flask (use a 100-mL flask for 250-mg Tablets, 200-mL flask for 333-mg Tablets, and 200-mL flask for 500-mg Tablets). Add methanol to about 25% of the final volume, and sonicate at room temperature for about 30 min with intermittent shaking. Further add about 25% of the final volume of *Solution B* and sonicate at room temperature for about 30 min with intermittent shaking. Dilute to volume with *Solution B* and mix well. Centrifuge at 5000 rpm for 5 min and pass the supernatant through a PVDF or other suitable filter of 0.45-µm pore size. Discard the first 5 mL of the filtrate.

Blank: *Solution B* and methanol (75:25)

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

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

Temperature

Autosampler: 4°

Column: 50°

Flow rate: 1.5 mL/min

Injection volume: 25 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times of erythromycin C, erythromycin A, and erythromycin B are 0.53, 1.00, and 1.75, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for erythromycin A peak

Relative standard deviation: NMT 2.0% of the sum of erythromycin A, erythromycin B, and erythromycin C

Analysis

Samples: *Standard solution*, *Sample solution 1*, and *Sample solution 2*

Calculate the erythromycin content (*A*) as a percentage of the labeled amount of erythromycin:

$$\text{Result} = (r_U/r_S) \times W \times P \times (1/D_S) \times D_1 \times (1/L) \times 100$$

r_U = peak response of sum of erythromycin A, erythromycin B, and erythromycin C from *Sample solution 1*

r_S = peak response of sum of erythromycin A, erythromycin B, and erythromycin C from the *Standard solution*

W = standard weight of USP Erythromycin RS to prepare the *Standard solution*

P = potency of sum of erythromycin A, erythromycin B, and erythromycin C in USP Erythromycin RS

D_S = dilution factor used in preparing the *Standard solution* (mL)

D_1 = dilution factor used in preparing *Sample solution 1* (mL)

L = label claim (mg/Tablet)

Calculate the percentage (*T*) of the labeled amount of erythromycin retained:

$$\text{Result} = (r_U/r_S) \times W \times P \times (1/D_S) \times (1/L) \times D_2 \times 100$$

r_U = peak response of sum of erythromycin A, erythromycin B, and erythromycin C from *Sample solution 2*

r_S = peak response of sum of erythromycin A, erythromycin B, and erythromycin C from the *Standard solution*

W = standard weight of USP Erythromycin RS to prepare the *Standard solution* (mg)

P = potency of sum of erythromycin A, erythromycin B, and erythromycin C in USP Erythromycin RS

D_S = dilution factor used in preparing the *Standard solution* (mL)

L = label claim (mg/Tablet)

D_2 = dilution factor used in preparing *Sample solution 2* (mL)

Calculate the percentage of the labeled amount of erythromycin dissolved in *Acid stage*:

$$\text{Result} = A - T$$

A = erythromycin content as a percentage of the labeled amount

T = percentage of the labeled amount of erythromycin retained

[NOTE—If *T* is greater than *A*, consider the result to be zero.]

Tolerances: NMT 10% of the labeled amount of erythromycin is dissolved.

Buffer stage

Buffer stage medium: 6.8 g/L monobasic potassium phosphate in water with pH 6.8 adjusted by 5 N sodium hydroxide; 900 mL

Apparatus 1: 100 rpm

Time: 35 min

Solution A and **Mobile phase:** Prepare as directed in *Acid stage*.

Standard solution: Transfer a suitable amount of USP Erythromycin RS into an appropriate volumetric flask. See *Table 1*. Add methanol to about 5% of the final volume and sonicate to dissolve. Dilute with *Buffer stage medium* to volume with intermittent shaking and mix well. [NOTE—The typical retention time of erythromycin A is 3.8 min.]

Table 1

Tablet Label Claim (mg)	Weight of USP Erythromycin RS (mg)	Volumetric Flask (mL)
250	59	200
333	39	100
500	59	100

Sample solution: Prepare as directed in *Acid stage* with a new set of Tablets. After 60 min with *Acid stage medium*, immediately replace with *Buffer stage medium*. After 35 min, pass a portion of the solution through a PVDF or other 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 15-cm; 5-µm packing L1
Temperature
Autosampler: 5°
Column: 50°
Flow rate: 2.0 mL/min
Injection volume: 100 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for erythromycin A peak
Relative standard deviation: NMT 2.0% of erythromycin A

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of erythromycin dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times (1/L) \times V \times 100$$

r_U = peak response of erythromycin A from the *Sample solution*
r_S = peak response of erythromycin A from the *Standard solution*
C_S = concentration of erythromycin A in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of buffer medium

Tolerances: NLT 80% (Q) of the labeled amount of erythromycin is dissolved.▲ (TBD)

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

SPECIFIC TESTS

- **WATER DETERMINATION** ⟨921⟩**,** *Method I*

Analysis: Use 20 mL of methanol containing 10% of imidazole in place of methanol in the titration vessel.
Acceptance criteria: NMT 6.0%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **LABELING:** The labeling indicates the *Dissolution Test* with which the product complies.

Change to read:

- **USP REFERENCE STANDARDS** ⟨11⟩

USP Erythromycin RS
▲
USP Erythromycin B RS

USP Erythromycin C RS
▲ (TBD)