Indomethacin Suppositories

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Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Indomethacin Suppositories monograph. The purpose of this revision is to delete the *Organic Impurities* test, in which the procedure is not suitable for the analysis of the only marketed product approved by the FDA and the *Acceptance criteria* are not consistent with the FDA-approved specifications. USP intends to publish an additional revision proposal in the *Pharmacopeial Forum* to add an *Organic Impurities* test to be consistent with the FDA-approved applications.

The Indomethacin Suppositories Revision Bulletin supersedes the currently official Indomethacin Suppositories monograph.

Should you have any questions, please contact Wei Yang, Scientific Liaison (301-816-8338 or wiy@usp.org).

Indomethacin Suppositories

DEFINITION

Indomethacin Suppositories contain NLT 90.0% and NMT 110.0% of the labeled amount of indomethacin ($C_{19}H_{16}ClNO_4$).

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*.
- **B.** The UV spectrum of the indomethacin peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Solution A: Prepare 0.1% of formic acid by diluting 1 mL of formic acid with water to 1 L.
Mobile phase: Acetonitrile and *Solution A* (45:55)
Diluent: *Mobile phase* adjusted with 0.2 M sodium hydroxide (NaOH) to a pH of 8.0
System suitability solution: 0.002 mg/mL of USP Indomethacin RS, 0.002 mg/mL of USP Indomethacin Related Compound A RS, and 0.01 mg/mL of USP Indomethacin Related Compound B RS in *Diluent*
Standard solution: 0.5 mg/mL of USP Indomethacin RS in *Diluent*. Sonicate if necessary.
Sample solution: Prepare a solution nominally equivalent to 0.5 mg/mL of indomethacin in *Diluent* as follows. Mash NLT 10 Suppositories in a beaker, and heat (at about 50°) on a water bath until melted. Mix well and cool. Transfer a portion of the mass equivalent to 10 mg of indomethacin into a 20-mL volumetric flask and add 10 mL of acetonitrile. Heat in a water bath at 50° to dissolve, and dilute with *Diluent* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: PDA (scan 200–600). Calculations should be based on the chromatograms collected at 240 nm. For *Identification* test *B*, use spectra at the scanned range.
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 4 between indomethacin related compound A and indomethacin related compound B, *System suitability solution*
Tailing factor: NMT 1.5, *Standard solution*
Relative standard deviation: NMT 1.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of indomethacin ($C_{19}H_{16}ClNO_4$) in the portion of Suppositories 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 Indomethacin RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of indomethacin in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

Medium: 0.1 M, pH 7.2 phosphate buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*); 900 mL
Apparatus 2: 50 rpm
Time: 60 min
Standard solution: USP Indomethacin RS at a known concentration in *Medium*
Sample solution: Proceed as directed for sample per *Dissolution* ⟨711⟩. Dilute with *Medium* as needed.
Instrumental conditions
Mode: UV
Analytical wavelength: 320 nm
Analysis
Samples: *Standard solution* and *Sample solution*
Tolerances: NLT 75% (*Q*) of the labeled amount of indomethacin ($C_{19}H_{16}ClNO_4$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩

Diluent: Methanol and glacial acetic acid (199:1)
Standard solution: 25 µg/mL of USP Indomethacin RS in *Diluent*
Sample solution: Place 1 Suppository into a 100-mL volumetric flask containing 80 mL of *Diluent*, shake by mechanical means until the Suppository is dissolved, and dilute with *Diluent* to volume. Filter a portion of the solution, discarding the first 15 mL of the filtrate, and dilute a volume of the clear filtrate with the *Diluent* to obtain a solution having a concentration of 25 µg/mL of indomethacin.
Instrumental conditions
Mode: UV
Detector: 320 nm
Blank: *Diluent*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of indomethacin ($C_{19}H_{16}ClNO_4$) in the Suppository taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Indomethacin RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of indomethacin in the *Sample solution* (µg/mL)

Acceptance criteria: Meet the requirements in *Uniformity of Dosage Units* ⟨905⟩

IMPURITIES

Delete the following:

▲- **ORGANIC IMPURITIES**

Mobile phase, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.
Standard solution: 0.002 mg/mL of USP Indomethacin RS, 0.002 mg/mL of USP Indomethacin Related Compound A RS, and 0.01 mg/mL of USP Indomethacin Related Compound B RS in *Diluent*
Sample solution: Prepare a solution nominally equivalent to 2.0 mg/mL of indomethacin in *Diluent* as follows. Mash NLT 10 Suppositories in a beaker, and heat (at about 50°) on a water bath until melted. Mix well and cool. Transfer a portion of the mass equivalent to 40 mg of indomethacin into a 20-mL volumetric flask and add 10 mL of acetonitrile.

Heat in a water bath at 50° to dissolve, and dilute with *Diluent* to volume.

System suitability

Sample: *Standard solution*

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 4 between indomethacin related compound A and indomethacin related compound B

Relative standard deviation: NMT 2.8%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of indomethacin related compound A and indomethacin related compound B in the portion of Suppositories taken:

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

r_U = peak response of indomethacin related compound A or indomethacin related compound B from the *Sample solution*

r_S = peak response of indomethacin related compound A or indomethacin related compound B from the *Standard solution*

C_S = concentration of the corresponding USP Indomethacin Related Compound A RS or USP Indomethacin Related Compound B RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of any unspecified impurity in the portion of Suppositories taken:

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

r_U = peak response of unspecified impurity from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 1*. Disregard any impurity peak less than 0.05%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Indomethacin related compound A	0.15	0.1
Indomethacin related compound B	0.25	0.5
Indomethacin	1	—
Any other individual, unidentified impurity	—	0.1
Total impurities	—	2.0▲ (RB 1-Dec-2019)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers at controlled room temperature.
- **USP REFERENCE STANDARDS** ⟨11⟩

  USP Indomethacin RS

  USP Indomethacin Related Compound A RS

  5-Methoxy-2-methyl-3-indoleacetic acid.

  $C_{12}H_{13}NO_3$ 219.24

  USP Indomethacin Related Compound B RS

  4-Chlorobenzoic acid.

  $C_7H_5ClO_2$ 156.57