

BRIEFING

**Irinotecan Hydrochloride.** This monograph has been posted on the USP Pending Standards Web page for review and public comment for more than 90 days. The Monograph Development—Ophthalmology, Oncology, and Dermatology Expert Committee reviewed the following comment, and approved the monograph as an Authorized USP Pending Standard.

**Comment:** It was proposed to revise the concentration of the *Test solution* in the test for *Specific rotation* to be suitable for all types of polymorphs.

**Response:** The comment was not incorporated, because no supporting data was provided. The Expert Committee is willing to consider further changes to this monograph upon receipt of supporting data.

This Authorized USP Pending Standard monograph uses the flexible monograph approach, and includes two *Related compounds* (impurity) tests suitable for the various synthetic routes. These tests are tentatively identified as *Test #* and *Test ##* and will be finalized after the FDA approves the drug product application(s), in which the drug master file(s) for the drug substance is (are) referenced. The *Labeling* statement will be added as needed.

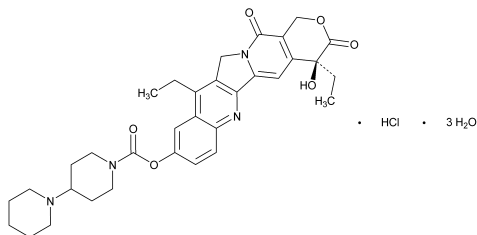
1. The liquid chromatographic procedure used in the test for *Limit of irinotecan hydrochloride enantiomer* is based on analyses performed with the Daicel Chiralcel OD 10- $\mu$ m brand of L40 column. The typical retention times for irinotecan enantiomer and irinotecan are about 10.7 and 15.1 minutes, respectively.
2. The liquid chromatographic procedure used in *Test #* under *Related compounds* is based on analyses performed with the Waters Symmetry Shield C18 5- $\mu$ m brand of L1 column. The typical retention times for irinotecan and irinotecan related compound A are about 15.8 and 18.2 minutes, respectively.
3. The liquid chromatographic procedure used in *Test ##* under *Related compounds* and in the *Assay* is based on analyses performed with the Waters Symmetry C18 5- $\mu$ m brand of L1 column. The typical retention times for irinotecan related compounds B and C and irinotecan are about 7.6, 8.2, and 13.7 minutes, respectively.

(MD-ODD: F. Mao)      RTS—C54822

**Add the following:**

► **Irinotecan Hydrochloride**

v. 1 Authorized September 1, 2008



$C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$

Anhydrous:      623.14

Trihydrate:      677.18

[1,4'-Bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3',4': 6,7]indolizino[1,2-*b*]quinolin-9-yl ester, monohydrochloride, trihydrate, (*S*)-.

(+)-7-Ethyl-10-hydroxycamptothecine 10-[1,4'-bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate  
[136572-09-3].

» Irinotecan Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of  $C_{33}H_{38}N_4O_6 \cdot HCl$ , calculated on the anhydrous basis.

**Packaging and storage**—Preserve in tight, light-resistant containers, and store at controlled room temperature.

**Labeling**—[To come].

**USP Reference standards** (11)—*USP Irinotecan Hydrochloride RS. USP Irinotecan Related Compound A RS. USP Irinotecan Related Compound B RS. USP Irinotecan Related Compound C RS. USP Irinotecan Related Compound D RS.*

**Identification**—

**A:** *Infrared Absorption* (197K).

**B:** The retention time of the major peak in the chromatogram of the *Test solution* corresponds to the irinotecan (*S*-enantiomer) peak in the *Identification solution*, as obtained in the test for *Limit of irinotecan hydrochloride enantiomer*.

**C:** *Chloride* (191)—A solution of about 2 mg per mL meets the requirements of the tests for *Chloride* (191).

**Specific rotation** (781S): between +61.0° and +69.0°, measured at 20°.

*Test solution:* 10 mg per mL, in water.

**Microbial limits** (61)—The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

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**Water, Method 1** (921): between 7.0% and 9.0%.

**Residue on ignition** (281): not more than 0.1%.

**Heavy metals, Method II** (231): not more than 10 ppm.

**Limit of irinotecan hydrochloride enantiomer—**

*Mobile phase*—Prepare a mixture of hexane, alcohol, and diethylamine (250 : 250 : 1).

*Diluent*—Prepare a mixture of alcohol and diethylamine (250 : 1).

*Resolution solution*—Dissolve an accurately weighed quantity of USP Irinotecan Hydrochloride RS and USP Related Compound D RS in *Diluent* to obtain a solution having known concentrations of about 0.1 mg each per mL.

*Identification solution*—Dissolve an accurately weighed quantity of USP Irinotecan Hydrochloride RS in *Diluent* to obtain a solution having a known concentration of about 1 mg per mL. [NOTE—This solution is used for *Identification* test B.]

*Standard solution*—Dissolve an accurately weighed quantity of USP Irinotecan Related Compound D RS in *Diluent*, quantitatively and stepwise if necessary, to obtain a solution having a known concentration of about 0.0015 mg per mL. [NOTE—USP Irinotecan Related Compound D RS is [1,4'-bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl ester, monohydrochloride, trihydrate, (*R*)-,  $R\text{-C}_{33}\text{H}_{38}\text{N}_4\text{O}_6 \cdot \text{HCl} \cdot 3 \text{H}_2\text{O}$ , 677.18.]

*Sensitivity solution*—Quantitatively dilute the *Standard solution* with *Diluent* to obtain a solution having a known concentration of about 0.0005 mg per mL.

*Test solution*—Dissolve an accurately weighed quantity of Irinotecan Hydrochloride in *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.

*Chromatographic system* (see *Chromatography* (621))—The liquid chromatograph is equipped with a 370-nm detector and a 4.6-mm × 25-cm column that contains 10- $\mu\text{m}$  packing L40. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution*, and record the peak areas as directed for *Procedure*: the relative retention times are about

0.71 for irinotecan related compound D (*R*-enantiomer) and 1.00 for irinotecan (*S*-enantiomer); and the resolution, *R*, between irinotecan related compound D and irinotecan is not less than 2.5. Chromatograph the *Standard solution*, and record the peak areas as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *Sensitivity solution*, and record the peak area as directed for *Procedure*: the irinotecan related compound D peak should be visible.

*Procedure*—Inject equal volumes (about 20  $\mu\text{L}$ ) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of irinotecan hydrochloride *R*-enantiomer in the portion of Irinotecan Hydrochloride taken by the formula:

$$100(C_s/C_U)(r_U/r_S)$$

in which  $C_s$  is the concentration, in mg per mL, of USP Irinotecan Related Compound D RS in the *Standard solution*;  $C_U$  is the concentration, in mg per mL, of Irinotecan Hydrochloride in the *Test solution*;  $r_U$  and  $r_S$  are the peak areas for irinotecan related compound D obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.15% of irinotecan hydrochloride enantiomer is found.

**Related compounds—**

[NOTE—On the basis of the synthetic route, perform either *Test #* or *Test ##*.]

TEST # (FOR MATERIAL LABELED AS PRODUCED BY A SEMISYNTHETIC PROCESS)—

*Solution A*—Dissolve 2.72 g of monobasic potassium phosphate in 1 L of water. Adjust with dilute phosphoric acid (1 in 20) to a pH of  $3.5 \pm 0.05$ .

*Solution B*—Prepare a mixture of acetonitrile and methanol (3 : 2).

*Diluent*—Prepare a mixture of *Solution A*, acetonitrile, and methanol (2 : 1 : 1).

*Resolution solution*—Dissolve suitable quantities of USP Irinotecan Hydrochloride RS and USP Irinotecan Related Compound A RS in *Diluent* to obtain a solution having known concentrations of about 0.1 mg each per mL.

*Standard solution*—Dissolve an accurately weighed quantity of USP Irinotecan Hydrochloride RS in *Diluent*, quantitatively and stepwise if necessary, to obtain a solution having a known concentration of about 0.001 mg per mL.

*Test solution*—Dissolve an accurately weighed quantity of Irinotecan Hydrochloride in *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.

*Chromatographic system* (see *Chromatography* (621))—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains 5-μm packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0–40	80→30	20→70	linear gradient
40–45	30	70	isocratic
45–50	30→80	70→20	linear gradient
50–55	80	20	equilibration

Chromatograph the *Resolution solution*, and record the peak areas as directed for *Procedure*: the resolution, *R*, between the peaks for irinotecan and irinotecan related compound A is not less than 3.0. Chromatograph the *Standard solution*, and record the peak areas as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 2.0%.

Table 1

Name	Relative Retention Time	Relative Response Factor ( <i>F</i> )	Limit (%)
7-Desethyl irinotecan <sup>a</sup>	0.82	0.77	0.15
Irinotecan	1.00	—	—
Irinotecan related compound A <sup>b</sup>	1.15	1.4	0.15
11-Ethyl irinotecan <sup>c</sup>	1.27	0.63	0.15
Camptothecin <sup>d</sup>	1.35	1.4	0.15
Irinotecan related compound B <sup>e</sup>	1.50	1.3	0.15
7-Ethylcamptothecin <sup>f</sup>	1.76	1.2	0.15
7,11-Diethyl-10-hydroxycamptothecin <sup>g</sup>	2.05	0.65	0.15
Any individual unspecified impurity	—	—	0.10
Total impurities	—	—	0.50

<sup>a</sup> (S)-4-Ethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione-9-yl (1,4'-bipiperidine)-1'-carboxylate [C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>, 558.62].

<sup>b</sup> (S)-4-Ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione [C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>, 364.35].

<sup>c</sup> (S)-4,8,11-Triethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione-9-yl (1,4'-bipiperidine)-1'-carboxylate [C<sub>35</sub>H<sub>42</sub>N<sub>4</sub>O<sub>6</sub>, 614.73].

<sup>d</sup> (S)-4-Ethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione [C<sub>20</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>, 348.35].

<sup>e</sup> (S)-4,11-Diethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione [C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>, 392.40].

<sup>f</sup> (S)-4,11-Diethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione [C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>, 376.41].

<sup>g</sup> (S)-4,8,11-Triethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione [C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>, 420.46].

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*Procedure*—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each related compound in the portion of Irinotecan Hydrochloride taken by the formula:

$$100(1/F)(C_s/C_v)(r_v/r_s)$$

in which  $F$  is the relative response factor for each impurity obtained from *Table 1*;  $C_s$  is the concentration, in mg per mL, of USP Irinotecan Hydrochloride RS in the *Standard solution*;  $C_v$  is the concentration of Irinotecan Hydrochloride in the *Test solution*; and  $r_v$  and  $r_s$  are the peak areas obtained from the *Test solution* and the *Standard solution*, respectively. The limits are given in *Table 1*.

TEST ## (FOR MATERIAL LABELED AS PRODUCED BY A SYNTHETIC PROCESS)—

*Mobile phase and Diluent*—Prepare as directed in the *Assay*.

*Standard solution*—Use the *Standard preparation*, prepared as directed in the *Assay*.

*Diluted standard solution*—Quantitatively dilute the *Standard solution* with *Diluent*, stepwise if necessary, to obtain a solution having a known concentration of about 0.002 mg per mL.

*Sensitivity solution*—Quantitatively dilute the *Standard solution* with *Diluent*, stepwise if necessary, to obtain a solution having a known concentration of about 0.0005 mg per mL. [NOTE—The Irinotecan Hydrochloride in this solution is 0.05% relative to the amount of Irinotecan Hydrochloride in the *Test solution*.]

*System suitability solution*—Dissolve suitable quantities of USP Irinotecan Related Compound B RS and USP Irinotecan Related Compound C RS in methanol, quantitatively and stepwise if necessary, to obtain a solution having known concentrations of about 0.001 mg each per mL. [NOTE—USP Irinotecan Related Compound C RS is [1,4'-bipiperidine]-1'-carboxylic acid, 4-methyl-11-ethyl-3,4,12,14-tetrahydro-4-

hydroxy-3,14-dioxo-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl ester, monohydrochloride, trihydrate, (*S*)-,  $C_{32}H_{36}N_4O_6 \cdot HCl \cdot 3H_2O$ , 663.16.]

*Test solution*—Use the *Assay preparation*.

*Chromatographic system* (see *Chromatography* (621))—Prepare as directed in the *Assay*. Chromatograph the *System suitability solution*, and record the peak areas as directed for *Procedure*: the resolution,  $R$ , between the peaks of irinotecan related compound B and irinotecan related compound C is not less than 1.1. Chromatograph the *Diluted standard solution*, and record the peak areas as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *Sensitivity solution*, and record the peak area as directed for *Procedure*: the irinotecan peak should be visible.

*Procedure*—Inject equal volumes (about 15 µL) of the *Standard solution* and the *Test solution* into a chromatograph, record the chromatograms, and measure the peak areas. Identify the peaks by their relative retention times: about 0.55 for irinotecan related compound B, 0.60 for irinotecan related compound C, and 1.00 for irinotecan. Calculate the percentage of related compound B, related compound C, and any unspecified impurities in the portion of Irinotecan Hydrochloride taken by the formula:

$$100(C_s/C_v)(r_v/r_s)$$

in which  $C_s$  is the concentration, in mg per mL, of USP Irinotecan Hydrochloride RS in the *Standard solution*;  $C_v$  is the concentration, in mg per mL, of Irinotecan Hydrochloride in the *Test solution*;  $r_v$  is the peak area for each impurity obtained from the *Test solution*; and  $r_s$  is the peak area for irinotecan obtained from the *Standard solution*: not more than 0.15% of irinotecan related compound B is found; not more than 0.10% of irinotecan related compound C is found; not more than 0.10% of any unspecified impurity is found; and not more than 0.5% of total impurities is found. Disregard any peak with an area less than the area of the irinotecan peak in the chromatogram obtained from the *Sensitivity solution*.

**Assay—**

*Phosphate buffer*—Dissolve 2.8 g of monobasic sodium phosphate monohydrate and 1.8 g of 1-octanesulfonic acid sodium salt monohydrate in 1 L of water, and filter the solution.

*Mobile phase*—Prepare a mixture of *Phosphate buffer*, methanol, and acetonitrile (59 : 24 : 17). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

*Diluent*—Use *Mobile phase* with the pH adjusted with diluted hydrochloric acid to  $3.65 \pm 0.15$ .

*Standard preparation*—Dissolve an accurately weighed quantity of USP Irinotecan Hydrochloride RS in *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.

*Assay preparation*—Dissolve an accurately weighed quantity of Irinotecan Hydrochloride in *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.

*Chromatographic system* (see *Chromatography* (621))—The liquid chromatograph is equipped with a 255-nm detector and a 4.6-mm × 25-cm column that contains 5- $\mu$ m packing

L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard preparation*, and record the peak areas as directed for *Procedure*: the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

*Procedure*—Inject equal volumes (about 15  $\mu$ L) of the *Standard preparation* and the *Assay preparation* into a chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of  $C_{33}H_{38}N_4O_6 \cdot HCl$  in the portion of Irinotecan Hydrochloride taken by the formula:

$$100 (C_s / C_u)(r_u / r_s)$$

in which  $C_s$  is the concentration, in mg per mL, of Irinotecan Hydrochloride in the *Standard preparation*;  $C_u$  is the concentration, in mg per mL, of Irinotecan Hydrochloride in the *Assay preparation*; and  $r_u$  and  $r_s$  are the peak areas obtained from the *Assay preparation* and the *Standard preparation*, respectively. ◀(1-Sep-2008)