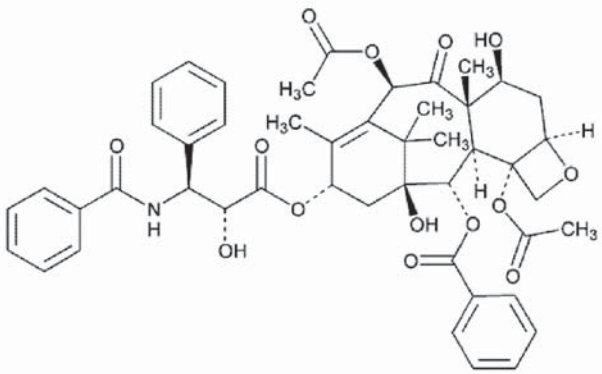
Paclitaxel



$C_{47}H_{51}NO_{14}$ 853.91

Benzenepropanoic acid, β-(benzoylamino)-α-hydroxy-, 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1*H*-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2a*R*-[2aα,4β,4aβ,6β,9α(α*R**,β*S**),11α,12α,12aα,12bα]]-. (2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5*H*-cyclodeca[3,4]-benz[1,2-*b*]oxet-5-one 6,12b-diacetate, 12-benzoate, 9-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine [*33069-62-4*].

» Paclitaxel contains not less than 97.0 percent and not more than 102.0 percent of $C_{47}H_{51}NO_{14}$, calculated on the anhydrous, solvent-free basis.

Caution—Paclitaxel is cytotoxic. Great care should be taken to prevent inhaling particles of Paclitaxel and exposing the skin to it.

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

Labeling— The labeling indicates the type of process used to produce the material and the *Related compounds* test with which the material complies.

USP Reference standards ⟨ 11 ⟩ **—** *USP Endotoxin RS*. *USP Paclitaxel RS*. *USP Paclitaxel Related Compound A RS*. *USP Paclitaxel Related Compound B RS*.

Identification—

A: *Infrared Absorption* ⟨ 197K ⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Specific rotation ⟨ 781S ⟩ **:** between -49.0° and -55.0° at 20°, calculated on the anhydrous, solvent-free basis.

Test solution: 10 mg per mL, in methanol.

Microbial limits ⟨ 61 ⟩ **—** The total aerobic microbial count does not exceed 100 cfu per g. It meets the requirements of the tests for the absence of *Staphylococcus aureus, Pseudomonas aeruginosa, Salmonella* species, and *Escherichia coli.*

Bacterial endotoxins ⟨ 85 ⟩ **—** It contains not more than 0.4 USP Endotoxin Unit per mg of paclitaxel.

Water, *Method Ic* ⟨ 921 ⟩ **:** not more than 4.0%.

Residue on ignition ⟨ 281 ⟩ **:** not more than 0.2%.

Heavy metals, *Method II* ⟨ 231 ⟩ **:** 0.002%.

Related compounds—

TEST 1 *(for material labeled as isolated from natural sources)*— If the material complies with this test, the labeling indicates that it meets *USP Related compounds Test 1.*

Diluent— Prepare as directed in the *Assay.*

Solution A— Prepare filtered and degassed acetonitrile.

Solution B— Prepare filtered and degassed water.

Mobile phase— Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨ 621 ⟩).

System suitability solution— Dissolve accurately weighed quantities of *USP Paclitaxel Related Compound A RS* and *USP Paclitaxel Related Compound B RS* in methanol to obtain a solution having known concentrations of about 10 µg of each per mL. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Standard solution— Dissolve, with the aid of sonication, an accurately weighed quantity of *USP Paclitaxel RS* in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 5 µg per mL.

Test solution— Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨ 621 ⟩)— The liquid chromatograph is equipped with a 227-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L43. The flow rate is about 2.6 mL per minute. The column temperature is maintained at 30°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–35	35	65	isocratic
35–60	35→80	65→20	linear gradient
60–70	80→35	20→65	linear gradient
70–80	35	65	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.78 for paclitaxel related compound A and 0.86 for paclitaxel related compound B (relative to the retention time for paclitaxel obtained from the *Test solution*); and the resolution, *R,* between paclitaxel related compound A and paclitaxel related compound B is not less than 1.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure— Inject a volume (about 15 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the areas for the major peaks. Calculate the percentage of each impurity in the portion of Paclitaxel taken by the formula:

$$100(Fr_i / r_U),$$

in which F is the relative response factor for each impurity peak (see *Table 1* for values); r_i is the peak area for each individual impurity; and r_U is the peak area for paclitaxel.

Table 1

Relative Retention Time	Relative Response Factor *(F)*	Name	Limit (%)
0.24	1.29	Baccatin III	0.2
0.53	1.00	10-Deacetylpaclitaxel	0.5
0.57	1.00	7-Xylosylpaclitaxel	0.2
0.78	1.26	Cephalomannine (paclitaxel related compound A)	a_1[1]

Relative Retention Time	Relative Response Factor *(F)*	Name	Limit (%)
0.78	1.26	2″,3″-Dihydrocephalomannine	a_2[1]
0.86	1.00	10-Deacetyl-7-epipaclitaxel (paclitaxel related compound B)	0.5
1.10	1.00	Benzyl analog[3]	b_1[2]
1.10	1.00	3′,4″-Dehydropaclitaxel C	b_2[2]
1.40	1.00	7-Epicephalomannine	0.3
1.85	1.00	7-Epipaclitaxel	0.5

[1] Resolution may be incomplete for these peaks, depending upon the relative amounts present; the sum of a_1 and a_2 is not more than 0.5%.

[2] Resolution may be incomplete for these peaks depending upon the relative amounts present; the sum of b_1 and b_2 is not more than 0.5%.

[3] The following chemical name is assigned to the related compound, benzyl analog: Baccatin III 13-ester with (2*R*,3*S*)-2-hydroxy-3-phenyl-3-(2-phenylacetylamino)propanoic acid.

In addition to not exceeding the limits for paclitaxel related impurities in *Table 1*, not more than 0.1% of any other single impurity is found; and not more than 2.0% of total impurities is found.

TEST 2 *(for material labeled as produced by a semisynthetic process)*— If the material complies with this test, the labeling indicates that it meets *USP Related compounds Test 2*.

Diluent— Use acetonitrile.

Solution A— Use a filtered and degassed mixture of water and acetonitrile (3:2).

Solution B— Use filtered and degassed acetonitrile.

Mobile phase— Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨ 621 ⟩).

System suitability solution— Dissolve accurately weighed quantities of *USP Paclitaxel RS* and *USP Paclitaxel Related Compound B RS* in *Diluent*, using shaking and sonication if necessary, to obtain a solution having known concentrations of about 0.96 mg and 0.008 mg per mL, respectively.

Test solution— Transfer about 10 mg of Paclitaxel, accurately weighed, to a 10-mL volumetric flask; dissolve in and dilute with *Diluent* to volume, using shaking and sonication if necessary; and mix.

Chromatographic system (see Chromatography ⟨ 621 ⟩)— The liquid chromatograph is equipped with a 227-nm detector and a 4.6-mm × 15-cm column that contains 3-µm packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–20	100	0	isocratic
20–60	100→10	0→90	linear gradient
60–62	10→100	90→0	linear gradient
62–70	100	0	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.94 for paclitaxel related compound B and 1.0 for paclitaxel; the resolution, *R,* between paclitaxel related compound B and paclitaxel is not less than 1.2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure— Separately inject equal volumes (about 15 µL) of the *Diluent* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Disregard any peaks due to the *Diluent.* Calculate the percentage of each impurity in the portion of Paclitaxel taken by the formula:

$$100(Fr_i / r_s),$$

in which F is the relative response factor for each impurity (see Table 2 for values); r_i is the peak area for each impurity obtained from the *Test solution;* and r_s is the sum of the areas of all the peaks obtained from the *Test solution.*

Table 2

Relative Retention Time	Relative Response factor *(F)*	Name	Limit (%)
0.11	1.24	10-Deacetylbaccatin III	0.1
0.20	1.29	Baccatin III	0.2
0.42	1.39	Photodegradant[2]	0.1
0.47	1.00	10-Deacetylpaclitaxel	0.5
0.80	1.00	2-Debenzoylpaclitaxel-2-pentenoate	0.7
0.92[1]	1.00	Oxetane ring opened, acetyl and benzoyl[2]	x_1
0.92[1]	1.00	10-Acetoacetylpaclitaxel	x_2
0.94[1]	1.00	10-Deacetyl-7-epipaclitaxel (paclitaxel related compound B)	x_3
1.37	1.00	7-Epipaclitaxel	0.4
1.45	1.00	10,13-Bissidechainpaclitaxel[2]	0.5
1.54	1.00	7-Acetylpaclitaxel	0.6

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