

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022453Orig1s000

ENVIRONMENTAL ASSESSMENT



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: May 5, 2009

From: Emily A. McVey, Ph.D.
OPS/IO/PARS

To: Susan Jenney
OND/DDQP

Through: Jon Clark, M.S.
OPS/IO/PARS

Subject: **NDA 22-453: Topotecan Hydrochloride Injection (1 mg base/mL)**
Review of Environmental Assessment

Sponsor: Teva Parenteral Medicines, Inc.

A. Background

Teva Parenteral Medicines, Inc. requests approval of Topotecan Hydrochloride 1 mg base/mL injection for use in the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy and Topotecan Hydrochloride injection in combination with cisplatin for the treatment of Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy (NDA 22-453). An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

B. Discussion

Executive Summary

This Environmental Assessment, dated December 11th, 2008 supports the new drug application for Topotecan Hydrochloride 1 mg base/mL injection for use in the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy and Topotecan Hydrochloride injection in combination with cisplatin for the treatment of Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy. The EA was prepared in accordance with 21 CFR Part 25 by Teva Parenteral Medicines, Inc.

Topotecan Hydrochloride is currently approved as an injectable drug product (Hycamtin, NDA 20-671) with the original holder, GlaxoSmithKline.

Topotecan HCl is derived from camptothecin, which is harvested from the “Happy Tree”, or *Camptotheca acuminata*. *Camptotheca acuminata* is native to China, where it grows both wild and cultivated. In the early 2000’s the Chinese government listed *Camptotheca* species as Class 2 protected on the National Protected Plants List of the State Forestry Administration. They submitted *Camptotheca* to be listed on the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), but later withdrew this application. The Chinese government placed regulations on the acquisition, trade, and use of *C. acuminata*. The extract used to produce Topotecan HCL, camptothecin, is not subject to export regulation.

Although the highest levels of camptothecin are found in the young leaves of the *Camptotheca acuminata*, Teva Parenteral Medicines, Inc. uses the fruits of the tree, which may be sustainably harvested from living trees, to obtain camptothecin, which is then exported. They certify that their supplier complies with all Chinese laws relating to the use of *C. acuminata*. In addition, Teva Parenteral Medicines, Inc. has a clause in their contract with the Chinese supplier of camptothecin stating that the “harvesting can not affect the normal growth of *camptotheca* trees”.

A FONSI is recommended.

C. Environmental Assessment Review

I. Date: 11 December, 2008

II. Applicant: TEVA Parenteral Medicines, Inc.

III. Address: 19 Hughes Irvine, CA 92618-1902 U.S.A.

IV. Proposed Action:

- a. Requested Approval: Teva Parenteral Medicines, Inc. is filing an Abbreviated New Drug Application, NDA No. 22-453, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Topotecan Hydrochloride injection, equivalent to 1 mg base/mL, packaged in single-dose glass mLs. An EA is submitted pursuant to 21 CFR Part 25.
- b. Need for Action: Topotecan Hydrochloride injection is indicated for the treatment of:
 - i. small cell lung cancer sensitive disease after failure of first-line chemotherapy.
 - ii. Topotecan Hydrochloride injection in combination with cisplatin is indicated for the treatment of stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.
- c. Location of Use: Topotecan Hydrochloride injection is used in hospitals and cancer treatment/oncology centers in the USA.

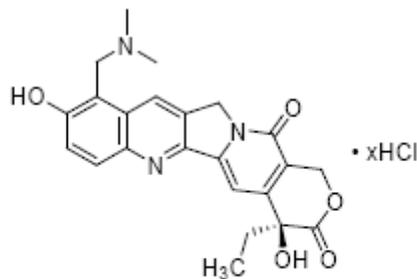
- d. Disposal Sites: The U.S. hospitals and cancer treatment centers will dispose Topotecan Hydrochloride injection according to their established procedures for oncolytic drugs.

ADEQUATE

V. Identification of Chemicals

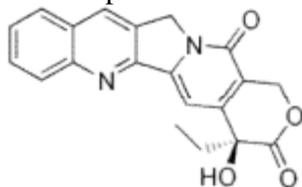
Nomenclature:

- (i) Established Name: Topotecan Hydrochloride injection (Generic Name)
- (ii) Brand/Proprietary Name/Tradename: Teva Parenteral Medicines, Inc. does not use a brand name for its product. It uses the generic name, Topotecan Hydrochloride injection. The innovator, GlaxoSmithKline, uses the brand name Hycamtin®.
- (iii) Chemical Names:
 - a. Topotecan Hydrochloride: (S)-10-[(Dimethylamino)methyl]-4-ethyl-4, 9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride
 - b. Camptothecin: 4-ethyl-4-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione
- (iv) Chemical Abstract Registration Number:
 - a. Topotecan Hydrochloride: 119413-54-6
 - b. Camptothecin: 7689-03-04
- (v) Molecular Formula:
 - a. Topotecan Hydrochloride: $C_{23}H_{23}N_3O_5 \cdot x \text{ HCl}$ (x= 1.0-1.5)
 - b. Camptothecin: $C_{20}H_{16}N_2O_4$
- (vi) Molecular Weight:
 - a. Topotecan Hydrochloride: 457.91 g/mol
 - b. Camptothecin: 348.352 g/mol
- (vii) Chemical Structure:
 - a. Topotecan Hydrochloride:



Note: x=1.0-1.5

- b. Camptothecin:



ADEQUATE

VI. Environmental Issues

Use of Fauna and Flora

- a. Use of Resources
 - a. Biological identification:
 - i. Kingdom Plantae
 - ii. Subkingdom Tracheobionta
 - iii. Division Magnoliophyta
 - iv. Class Magnoliopsida
 - v. Subclass Rosidae
 - vi. Order Cornales
 - vii. Family Nyssaceae
 - viii. Genus *Camptotheca decne*
 - ix. Species *Camptotheca acuminata*
 - x. Common Name Happy Tree, Xi Shu

ADEQUATE

- b. Statement of whether wild or cultivated specimens are used: The raw material, *camptotheca* fruits, is collected from *Camptotheca* trees grown in public and some private lands in China.

ADEQUATE

- c. Geographic region: *Camptotheca* is a native plant in China. Most of the land in South China has this plant. It grows in the wild in provinces such as Sichuan, Yunnan, Guizhou, Hunan, and Guangxi. Among which, almost 50% of this plant is in Sichuan Province. ScinoPharm uses the fruit of the *camptotheca* plant as the starting raw material for production of Topotecan Hydrochloride. The fruits are collected from the Sichuan Province in China. *Camptotheca* is widely cultivated in China as street trees on city roads and around the valleys and mountains to keep water and prevent soil erosion.

ADEQUATE

- d. Government oversight: There is no government oversight in China on the harvest of *camptotheca* fruit. *Camptotheca* is not covered under CITES or other international agreement or treaty against endangered species or protected species.

ADEQUATE

- e. Applicant's oversight of harvesting: The applicant, Teva Parenteral Medicines, Inc. procures the raw material, Topotecan Hydrochloride, from ScinoPharm. ScinoPharm signs contracts with raw material suppliers in China on the supply of *camptotheca*. One important clause in the contract is that the harvesting can not affect the normal growth of *camptotheca* trees. The suppliers in the yield area will arrange with the owner of *camptotheca* trees on the details of the *camptotheca* fruit collection or hire workers to collect the fruits (for trees in the valleys/mountains). After the contracted quantity of *camptotheca* fruits is obtained, the manufacturer will test the quality before its final

acceptance. The fruits of *camptotheca* will defoliate naturally, if not collected. During the harvesting season, the suppliers send their employees to collect the fruits in the area and provide supervision to the collection process.

ADEQUATE

- f. Statement indicating whether the species is (1) determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened, (2) entitled to special protection under some other Federal law or international treaty to which the United States is a party, or (3) the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to special protection under some other Federal law or international treaty to which the United States is a party:
 - a. *Camptotheca acuminata Decne* is not listed in the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened.
 - b. *Camptotheca* species is currently listed as a Class 2 protected plant on the National Protected Plants List of the State Forestry Administration in China. The Resolution of Conservation of Wild Plants of People's Republic of China requires the approval of the National Administration of Wild Plants to acquire, trade, and use *C. acuminata*. The tree can be exported but would require an export permit. Camptothecin, which is extracted from *C. acuminata*, currently does not require an export permit. To the best of Teva's knowledge, *Camptotheca acuminata* species is not determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). It is not entitled to special protection under some other Federal law or international treaty to which the United States is a party.
 - c. It is not a critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to special protection under some other Federal law or international treaty to which the United States is a party.

ADEQUATE

- g. Part of plant used/renewable: The fruit from the *camptotheca* trees is a renewable resource. The fruits will defoliate naturally, if not collected during harvesting season. The supplier states that the camptothecin is extracted from dried fruit from collected from wild grown *Camptotheca* and that it is a renewable resource.

ADEQUATE

- h. Method of harvest: *Camptotheca* fruit is collected during October to November every year. The usual method of harvest is to collect the mature fruits that are falling down naturally. It is an all-natural collecting method by manpower and does not utilize any tool or machine. There is no government regulation or guidance in China on the harvesting of the *camptotheca* fruit.

ADEQUATE

- i. Bulk weight of biomass needed per kg, amount harvested to date of application, amount expected to be harvested in the future: The production rate of topotecan hydrochloride from camptothecin is about 2.5 kg of camptothecin per kg of topotecan. To yield 1 kilogram of topotecan, about 3750 kg of *camptotheca* fruits is required.
 - a. One *camptotheca acuminata* tree can provide about 3 – 15 kg of *camptotheca*

(b) (4)

(b) (4)

ADEQUATE

- j. Amount of biomass needed to produce the active moiety or biological substance used to treat the average patient:
 - a. The quantity of the seeds from a single happy tree varies, depending on the age of the tree and the yield of the certain trees typically ranges from 3 kg to 15 kg per tree.
 - b. Based on the Maximum Daily Dose of 1.5 mg/m², the average patient size will need approximately the following amounts

(b) (4)

(b) (4)

(b) (4)

ADEQUATE

- k. Total number of plants or animals in the geographic region where the biomass is obtained: *Camptotheca* is a widely grown tree in China and there is no government record on the number of this tree in China or in any specific geographic region where the biomass is obtained (i.e., south China, central China and north China). The trees are grown in the wild and also in plantations. To the best of Sichuan Guangsong and ScinoPharm's knowledge, it is estimated that 14 % of China's total land area (9,640,821 km²) is forest area, which is equivalent to about 1.35 million km². Assuming that happy trees are grown in 0.05 % of this area and each tree needs approximately 10 m², the total population of happy trees in China is approximately over 60 million.

ADEQUATE

1. Uses of the plant or animal other than for the proposed use: *Camptotheca* is mostly used as firewood, since it is not strong enough to be suitable as a timber source for building or furniture. It grows fast. It is planted on the streets for virescence purpose and also planted around the valleys and mountains to prevent erosion.

ADEQUATE

- m. Plant or animal growth rate and/or life span and, if applicable, the rate of reproduction/regeneration: *Camptotheca* grows fast within a short time. It is estimated that a young tree can reach 1 m high within one year and the tree will reach its maximum height within 3-8 years. The street trees are on average, 3-5 year old trees. After 10 years, the growth of *camptotheca* tree slows down. It is estimated that the life span of the tree is about 20 years. The *camptotheca* tree is easily cultivated by planting new seedlings.

ADEQUATE

VII. Mitigation Measures

Generally speaking, the part of *camptotheca* used in ScinoPharm's production is the natural falling fruit. The total quantity of this species in China is abundant. The demand is not expected to be significant enough to affect the growth of the wild *camptotheca* tree. In addition, cultivated *camptotheca* can also be used as a source of supply for ScinoPharm's production. The supply and the production related with *camptotheca* is renewable and sustainable.

ADEQUATE

VIII. Alternatives to the Proposed Action

A Swiss company, ROOTec Gesellschaft für bioaktive Wirkstoffe mbH, claims that camptothecin can be produced using biotechnology which can be an alternate source of this critical material. ROOTec currently has no facility to produce multi-kilo quantities of camptothecin via their claimed biotechnology approach. The naturally isolated camptothecin from *mappia* tree is economical and poses no environmental adverse impact.

ADEQUATE

VI. Certification

Teva confirms that it and the other parties with which it contracts for this harvesting (e.g., any and all buyers and collectors) have complied with all requirements under the Chinese law to date relating to the harvesting for Teva. Teva commits that it will continue to comply with all requirements under the Chinese law relating to such harvesting, including any additional requirements that may be imposed in the future, and will take appropriate measures to ensure that all such other parties continue to comply as well.

ADEQUATE

V. Preparers

Job titles and qualifications for Younan Shih, Ph.D. and Mirabelle Pao B.S. were provided.

ADEQUATE

VI. References

Not applicable

ADEQUATE

VII. Appendices

Non-confidential appendices

Attachment I: Statement of Camptothecin Raw Material

Confidential appendices

Appendix A: Environmental Information, Use of Fauna or Flora

ADEQUATE

D. Literature reviewed & Models

CITES. 2000. Proposal inclusion of happytree (*Camptopheca acuminata* Decaisne) in CITES appendix II of convention in accordance with the provisions of Article II, paragraph 2(a). Viewed 5 May 2009. <<http://www.cites.org/eng/cop/11/prop/58.pdf>>.

Kusari S, Zuhlke S, Spiteller M. 2009. An Endophytic Fungus from *Camptotheca acuminata* That Produces Camptothecin and Analogues. *Journal of Natural Products* 72(1): 2-7.

Liu ZJ, Adams J. 1996. Camptothecin yield and distribution within *Camptotheca acuminata* trees cultivated in Louisiana. *Canadian Journal of Botany-Revue Canadienne De Botanique* 74(3): 360-365.

Liu ZJ, Adams JC, Viator HP, Constantin RJ, Carpenter SB. 1999. Influence of soil fertilization, plant spacing, and coppicing on growth, stomatal conductance, abscisic acid, and camptothecin levels in *Camptotheca acuminata* seedlings. *Physiologia Plantarum* 105(3): 402-408.

Liu ZJ, Carpenter SB, Bourgeois WJ, Yu Y, Constantin RJ, Falcon MJ, et al. 1998. Variations in the secondary metabolite camptothecin in relation to tissue age and season in *Camptotheca acuminata*. *Tree Physiology* 18(4): 265-270.

Maxwell, Douglas Wayne (May 2003). Propagation of *Camptotheca acuminata*. Master's thesis, Texas A&M University. Available electronically from <http://handle.tamu.edu/1969.1/454>.

Mukherjee AK, Basu S, Sarkar N, Ghosh AC. 2001. Advances in cancer therapy with plant based natural products. *Current Medicinal Chemistry* 8(12): 1467-1486.

Sirikantaramas S, Asano T, Sudo H, Yamazaki M, Saito K. 2007. Camptothecin: Therapeutic potential and biotechnology. *Current Pharmaceutical Biotechnology* 8(4): 196-202.

Vincent RM, LopezMeyer M, McKnight TD, Nessler CL. 1997. Sustained harvest of camptothecin from the leaves of *Camptotheca acuminata*. *Journal of Natural Products* 60(6): 618-619.

Wang HM, Zu YG, Wang WJ, Wu SX, Dong FL. 2006. Establishment of *Camptotheca acuminata* regeneration from leaf explants. *Biologia Plantarum* 50(4): 725-728.

Zhang H, Yu Y, Liu D, Liu ZJ. 2007. Extraction and composition of three naturally occurring anti-cancer alkaloids in *Camptotheca acuminata* seed and leaf extracts. *Phytomedicine* 14(1): 50-56.

DSSTox v2.0

Findings: No outstanding issues were ascertained from the literature review or DSSTox search. The extraction of camptothecin from fruits is one of several ways to sustainably obtain this base product without harming *Camptotheca acuminata*.

E. Comments and Conclusions

Based on an evaluation of the information provided in this EA and previous EAs, in FDA guidance, and on the scientific validity of the “no effects” conclusions of the EA, no significant adverse environmental impacts are expected from the use of *Camptotheca acuminata* fruits due to the approval of Topotecan Hydrochloride Injection.

A Finding of No Significant Impact (FONSI) is recommended.

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this page is the manifestation of the electronic signature.**

/s/

Emily Mcvey
5/8/2009 03:24:51 PM
MICROBIOLOGIST

Raanan Bloom
5/8/2009 03:32:25 PM
ENV ASSESSMENT

Jon E. Clark
5/18/2009 02:35:13 PM
CHEMIST

**Environmental Assessment-
Finding of No Significant Impact**

NDA 22-453
Topotecan Hydrochloride, 1 mg/mL

**Food and Drug Administration
Center for Drug Evaluation and Research**

May 5, 2009

FINDING OF NO SIGNIFICANT IMPACT

NDA 22-453

Topotecan Hydrochloride 1 mg base/mL injection

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of the regulatory process.

NDA 22-453 requests approval for Topotecan Hydrochloride 1 mg base/mL as an anti-neoplastic/oncolytic agent for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy, and (in combination with cisplatin) stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy. In support of its application for Topotecan Hydrochloride, Teva Parenteral Medicines, Inc. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25, which evaluates the potential environmental impacts of the use of *Camptotheca acuminata* fruits in the production of this drug product.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact due to approval of this application and has concluded that this action is not expected to have significant effect on the human environment. Therefore, an environmental impact statement will not be prepared.

PREPARED BY

Emily A. McVey, Ph.D.
Environmental Officer
Office of Pharmaceutical Science

CONCURRED BY

Jon Clark, M.S.
Associate Director for Policy
Office of Pharmaceutical Science

CONCURRED BY

Moheb Nasr, Ph.D.
Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science

Attachment: December 11, 2008 Environmental Assessment

Environmental Assessment

1. Date December 11, 2008
2. Name of Applicant Teva Parenteral Medicines, Inc.
3. Address 19 Hughes
Irvine, CA 92618-1902
U.S.A.
4. Description of Proposed Action

a. Requested Approval

Teva Parenteral Medicines, Inc. is filing a New Drug Application, NDA No. 22-453, pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Topotecan Hydrochloride Injection, equivalent to 1 mg base/mL, packaged in single-dose glass vials. An EA is submitted pursuant to 21 CFR Part 25.

b. Need for Action

Topotecan Hydrochloride Injection is indicated for the treatment of:

- small cell lung cancer sensitive disease after failure of first-line chemotherapy.

Topotecan Hydrochloride Injection in combination with cisplatin is indicated for the treatment of:

- stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.

c. Location of Use

Topotecan Hydrochloride Injection is used in hospitals and cancer treatment/oncology centers in the USA.

d. Disposal sites

The U.S. hospitals and cancer treatment centers will dispose Topotecan Hydrochloride Injection according to their established procedures for oncolytic drugs.

5. Identification of Substances that are the Subject of the Proposed Action

a. Nomenclature

(i) Established Name (U.S. Adopted Name- USAN)

Finished drug product – Topotecan Hydrochloride Injection (Generic Name)

Drug substance – Topotecan Hydrochloride

Source of drug substance starting material – Camptothecin

(ii) Brand/Proprietary Name/Tradename

Teva Parenteral Medicines, Inc. does not use a brand name for its product.

It uses the generic name, Topotecan Hydrochloride Injection

The innovator, GlaxoSmithKline, uses the brand name Hycamtin®.

(iii) Chemical Names or Genus/Species of Biologic Product (e.g., virus)

Topotecan Hydrochloride:

(S)-10-[(Dimethylamino)methyl]-4-ethyl-4, 9-dihydroxy-1*H*- pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4*H*,12*H*)-dione hydrochloride

Camptothecin:

4-ethyl-4-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4*H*,12*H*)-dione

b. Chemical Abstract Registration Number

Topotecan Hydrochloride: 119413-54-6

Camptothecin: 7689-03-04

c. Molecular Formula

Topotecan Hydrochloride: $C_{23}H_{23}N_3O_5 \cdot x HCl$ ($x= 1.0-1.5$)

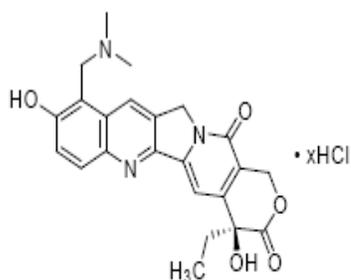
Camptothecin: $C_{20}H_{16}N_2O_4$

d. Molecular Weight

Topotecan Hydrochloride: 457.91 g/mol

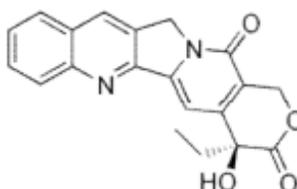
Camptothecin: 348.352 g/mol

e. Structural Formula
Topotecan Hydrochloride:



Note: $x=1.0-1.5$

Camptothecin:



6. Environmental Issues (Section IV.B. Specific Guidance- Environmental Issues)

2. Use of Fauna and Flora

a. Use of Resources

Information relating to the source of the plant or animal, such as biological identification, government oversight of harvesting, geographic region where biomass is obtained, and harvesting methods and techniques should be included in the EA. The EA should include, but not be limited to, the following types of information.

- Biological identification (i.e., common names, synonyms, variety, species, genus, and family)

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Cornales
Family	Nyssaceae
Genus	<i>Camptotheca decne</i>
Species	<i>Camptotheca acuminata</i>
Common Name	Happy Tree, Xi Shu

- A statement as to whether wild or cultivated specimens are used.

The raw material, *camptotheca* fruits, is collected from *Camptotheca* trees grown in public and some private lands in China.

- The geographic region (e.g., country, state, province) where biomass is obtained and whether harvesting occurred on public or private land.

Camptotheca is a native plant in China. Most of the land in South China has this plant. It grows in the wild in provinces such as Sichuan, Yunnan, Guizhou, Hunan, and Guangxi. Among which, almost 50% of this plant is in Sichuan Province.

ScinoPharm uses the fruit of the *camptotheca* plant as the starting raw material for production of Topotecan Hydrochloride. The fruits are collected from the Sichuan Province in China.

Camptotheca is widely cultivated in China as street trees on city roads and around the valleys and mountains to keep water and prevent soil erosion.





- A brief description of government oversight of the harvesting including, if applicable, the identity of the authority permitting harvesting and identity of authorities consulted regarding the harvesting. Submission of copies of permits or harvesting regulations relating to the specific species is helpful. For species covered under CITES, CDER or CBER could request copies of relevant permits.

There is no government oversight in China on the harvest of *camptotheca* fruit. *Camptotheca* is not covered under CITES or other international agreement or treaty against endangered species or protected species.

Teva confirms that it and the other parties with which it contracts for this harvesting (e.g., any and all buyers and collectors) have complied with all requirements under the Chinese law to date relating to the harvesting for Teva. Teva commits that it will continue to comply with all requirements under the Chinese law relating to such harvesting, including any additional requirements that may be imposed in the future, and will take appropriate measures to ensure that all such other parties continue to comply as well.

- A brief description of the applicant's oversight of the harvesting.

The applicant, Teva Parenteral Medicines, Inc. procures the raw material, Topotecan Hydrochloride, from ScinoPharm. ScinoPharm signs contracts with raw material suppliers in China on the supply of *camptotheca*. One important clause in the contract is that the harvesting can not affect the normal growth of *camptotheca* trees. Presented in [Attachment 1](#) is a statement from ScinoPharm's *camptotheca acuminata* fruit supplier, Sichuan Guangsong Pharmaceutical Co., Ltd. regarding the source of their camptothecin.

The suppliers in the yield area will arrange with the owner of *camptotheca* trees on the details of the *camptotheca* fruit collection or hire workers to collect the fruits (for trees in the valleys/mountains). After the contracted quantity of *camptotheca* fruits is obtained, the manufacturer will test the quality before its final acceptance.

The fruits of *camptotheca* will defoliate naturally, if not collected. During the harvesting season, the suppliers send their employees to collect the fruits in the area and provide supervision to the collection process.

- A statement indicating whether the species is (1) determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened, (2) entitled to special protection under some other Federal law or international treaty to which the United States is a party, or (3) the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to special protection under some other Federal law or international treaty to which the United States is a party.

Camptotheca acuminata Decne is not listed in the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened.

Camptotheca species is currently listed as a Class 2 protected plant on the National Protected Plants List of the State Forestry Administration in China. The Resolution of Conservation of Wild Plants of People's Republic of China requires the approval of the National Administration of Wild Plants to acquire, trade, and use *C. acuminata*. The tree can be exported but would require an export permit. Camptothecin, which is extracted from *C. acuminata*, currently does not require an export permit.

To the best of Teva's knowledge, *Camptotheca acuminata* species is not determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). It is not entitled to special protection under some other Federal law or international treaty to which the United States is a party. It is not a critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to special protection under some other Federal law or international treaty to which the United States is a party.

- A statement describing the part of plant or animal used and whether it is a renewable resource.

The fruit from the *camptotheca* trees is a renewable resource. The fruits will defoliate naturally, if not collected during harvesting season. Presented in [Attachment 1](#) is a statement from ScinoPharm's *camptotheca acuminata* fruit supplier, Sichuan Guangsong Pharmaceutical Co., Ltd. regarding the source of their camptothecin.

- A detailed description of the method of harvest including such information as the type of harvesting (e.g., clear cut, gleaning from timber stands destined for clear cutting, salvaging, pruning), frequency of harvest, whether the harvesting technique will affect the ecosystem (and if so, how), and whether the harvesting is conducted in accordance with government regulations or guidances (include citations to applicable regulations or guidances).

Camptotheca fruit is collected during October to November every year. The usual method of harvest is to collect the mature fruits that are falling down naturally. It is an all-natural collecting method by manpower and does not utilize any tool or machine.

There is no government regulation or guidance in China on the harvesting of the *camptotheca* fruit.

- Bulk weight or other appropriate measure of biomass needed to yield on kilogram of active moiety or biologic substance, the amount that has been harvested to date support the proposed Agency action for the product, and the amount expected to be harvested in the future.

The production rate of topotecan hydrochloride from camptothecin is about 2.5 kg of camptothecin per kg of topotecan. To yield 1 kilogram of topotecan, about 3750 kg of *camptotheca* fruits is required.

The amount that has been harvested to date to support the proposed Agency action for the product, and the amount expected to be harvested in the future are provided in the **Confidential Appendix A**.

- The amount of biomass needed to produce the active moiety or biological substance used to treat the average patient. This should be provided in terms easy to understand (e.g., 2-3 trees per patient). The expected patient population and number of kilograms of active moiety or biologic substance needed per year should be provided.

The quantity of the seeds from a single happy tree varies, depending on the age of the tree and the yield of the certain trees typically ranges from 3 kg to 15 kg per tree. The amount of biomass needed to produce the active moiety or biological substance used to treat the average patient, the expected patient population and the number of kilograms of active moiety or biologic substance needed per year are provided in the **Confidential Appendix A**.

- An estimate of the total number of plants or animals in the geographic region where the biomass is obtained.

Camptotheca is a widely grown tree in China and there is no government record on the number of this tree in China or in any specific geographic region where the biomass is obtained (i.e., south China, central China and north China). The trees are grown in the wild and also in plantations.

To the best of Sichuan Guangsong and ScinoPharm's knowledge, it is estimated that 14 % of China's total land area (9,640,821 km²) is forest area, which is equivalent to about 1.35 million km². Assuming that happy trees are grown in 0.05 % of this area and each tree needs approximately 10 m², the total population of happy trees in China is approximately over 60 million.

- Any uses of the plant or animal other than for the proposed use (humans, food source, and habitat for fauna).

Camptotheca is mostly used as firewood, since it is not strong enough to be suitable as a timber source for building or furniture. It grows fast. It is planted on the streets for virescence purpose and also planted around the valleys and mountains to prevent erosion.

- Plant or animal growth rate and/or life span and, if applicable, the rate of reproduction/regeneration.

Camptotheca grows fast within a short time. It is estimated that a young tree can reach 1 m high within one year and the tree will reach its maximum height within 3-8 years. The street trees are on average, 3-5 year old trees. After 10 years, the growth of *camptotheca* tree slows down. It is estimated that the life span of the tree is about 20 years. The *camptotheca* tree is easily cultivated by planting new seedlings.

- A discussion of whether the harvesting provides for sustained yield (e.g., percentage of sustainable harvest needed to supply annual needs based on the proposed use and any prior approved uses).

Camptotheca is wildy grown and available in large quantities in China. The harvesting provides for sustained yield based on the proposed use for producing camptothecin. The harvesting of fruit will not affect the natural growth of this plant.

7. Mitigation Measures

Mitigation measures taken before (e.g., developing a process that uses a renewable part of a plant), during (e.g., limiting/selecting specimens to be harvested), and after harvesting (e.g., reforestation) should be included in the discussion of mitigation measures (see 40 CFR 1508.20).

The anti-cancer function of *camptotheca* was found about 20 years ago, long before the active ingredient, Camptothecin, was developed. At present, the total demand of camptothecin is not very significant and the wildy grown *camptotheca* trees are abundant enough to sustain more than the present demand. It is expected that in the future years, there will adequate supplies of camptothecin. There is an increasing growth of cultivated *camptotheca* trees, and given the natural regeneration of the *camptotheca* trees, the supply is renewable and sustainable.

Generally speaking, the part of *camptotheca* used in ScinoPharm's production is the natural falling fruit. The total quantity of this species in China is abundant. The demand is not expected to be significant enough to affect the growth of the wild *camptotheca* tree. In addition, cultivated *camptotheca* can also be used as a source of supply for ScinoPharm's production. The supply and the production related with *camptotheca* is renewable and sustainable.

8. Alternatives to the Proposed Action

A discussion must be provided of the reasonable alternatives that were considered when deciding which biomass source would be used to produce the active moiety or biologic substance (21 CFR 25.40(a)). All alternatives that were considered (e.g., other species, wild or cultivated sources, chemical synthesis) should be discussed. A

brief discussion of the factors (e.g., environmental effects) that were considered in deciding whether or not the alternative would be used should be provided. The no-action (i.e., no approval) alternative should also be discussed. It should be indicated if any of the alternatives not currently used are planned for use in the future.

A Swiss company, ROOTec Gesellschaft für bioaktive Wirkstoffe mbH, claims that camptothecin can be produced using biotechnology which can be an alternate source of this critical material.

ROOTech currently has no facility to produced multi-kilo quantities of camptothecin via their claimed biotechnology approach. The naturally isolated camptothecin from *mappia* tree is economical and poses no environmental adverse impact.

A no-action alternative will prevent a generic alternative to the branded Hycamtin® drug for the treatment of patients with small cell lung cancer sensitive disease after failure of first-line chemotherapy and in combination with cisplatin, for the treatment of patients with stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy. This is inconsistent with the FDA initiative of improving access to generic drugs, as provided in the Drug Price Competition and Patent Term Restoration Act of 1984.

9. List of Preparers

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10. References

Not Applicable

11. Appendices

Attachment 1

Sichuan Guangsong Pharmaceutical Co., Ltd. May, 2007

Statement of Camptothecin Raw Material

May 10, 2007

To whom it may concern,

The Camptothecin produced by our company is extracted from wild grown Camptotheca Decne, and the part using for production is the dried fruit collected from Sichuan Province, China.

It is a renewable resource.

Liu Bo



General Manager
Sichuan Guangsong Pharmaceutical Co., Ltd.

**This is a representation of an electronic record that was signed electronically and
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/s/

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5/13/2009 09:46:00 AM

Jon E. Clark
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