CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200582Orig1s000

ENVIRONMENTAL ASSESSMENT

Environmental Assessment-
Finding of No Significant Impact

NDA 200-582
Topotecan Hydrochloride

Food and Drug Administration
Center for Drug Evaluation and Research

June 18, 2010

FINDING OF NO SIGNIFICANT IMPACT

NDA 200-582

Topotecan Hydrochloride

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 200-582 requests approval for Topotecan Hydrochloride as an anti-neoplastic/oncolytic agent for use in the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy, treatment of metastatic ovary carcinoma and stage IV-B cervical cancer. In support of its application for Topotecan Hydrochloride, Hospira, Inc. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25, which evaluates the potential environmental impacts of the use of *Mappia foetida* and *Camptotheca acuminate* 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
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CONCURRED BY
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Attachment: February 11th, 2010 Environmental Assessment

1.12.14 Environmental Consideration: Environmental Assessment or Claim of Categorical Exclusion

An Environmental Assessment is provided herein because a wild flora source (*Camptotheca acuminate* and/or *Mappia Foetida*) is used to source camptotheca, a starting material for Topotecan Hydrochloride.

Topotecan Injection will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect.

A signed environmental impact certification letter issued by Zydus Hospira Oncology Pvt. Ltd., India facility is provided herein.

1. Date

11 February 2010

2. Name of Applicant or Petitioner

Hospira, Inc.

3. Address for correspondence

Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg H2
Lake Forest, IL 60045-5046

4. Description of Proposed Action

4a. Requested Approval

Application Type	NDA
Application Number	200-582
Drug Name	Topotecan Injection
Sponsor	Hospira, Inc
Application Status	Pending
Active Ingredient	Topotecan Hydrochloride
Dosage Form	Injectable
Strengths	4 mg/4mL (1 mg/mL)
Brief Description of Product Packaging	Single-dose clear-glass vial
Proposed Action	Environmental Assessment is submitted pursuant to 21 CFR part 25

4b. Need for Action

Topotecan injection is indicated for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy, treatment of metastatic ovary carcinoma and stage IV-B cervical cancer.

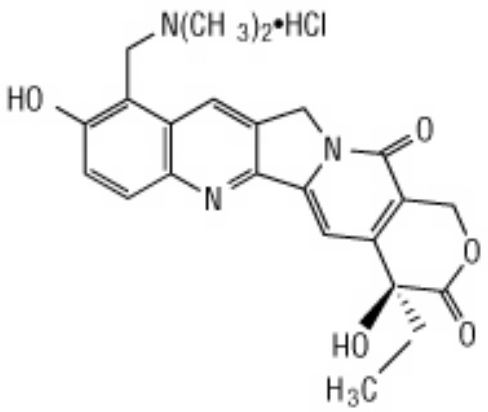
4c. Locations of Use

Topotecan injection is typically administered within hospitals and clinics under the supervision of a physician.

4d. Disposal Sites

Empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinical procedures.

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

Established Name (USAN)	Topotecan hydrochloride
Brand/Proprietary Name/Tradename	Topotecan Hydrochloride
Chemical Abstracts (CA) Index Name	Topotecan hydrochloride
Systematic (IUPAC) Name	(*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 monohydrochloride
Chemical Name	(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
Chemical Abstracts Service (CAS)	[119413-54-6]
Molecular formula	$C_{23}H_{23}N_3O_5$•HCl
Molecular Weight	457.9 g/mol
Structural (graphic) Formula	

6. Environmental Issues

Topotecan HCl is synt hesized fro m the starting material, 10-hydroxycamptothecin. 10 -Hydroxycamptothecin is in turn prepared from nat ure occurring camptothecin. Camptothecin is obtain ed from the fruits of *Camptotheca acuminate* or the ste m o f *Mappia foetida*. The inf ormation and source of plant materials harvested to obtain camptothecin is provided in the following.

6a. Biological Identification

Genus:	*Camptotheca*	*Mappia*
Species:	*Camptotheca acuminate*	*Mappia foetida*
Common Name:	Happy Tree, Xi Shu	Ghanera, tetu lakda, kalgur, amruta, narakya

2. Source:

Species:	*Camptotheca acuminate*	*Mappia foetida*

Origin:	Cultivated	Wild
3. Geographic Region:		
Species:	*Camptotheca acuminate*	*Mappia foetida*
Region of Growth:	Private lands in Sichun Provine, China	Government owned land in West Ghats area, India

6b. Species Conservation Status:

Camptotheca acuminate and *Mappia foetida* are 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 our knowledge, *Camptotheca acuminate* and *Mappia foetida* are 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.

*** The following information applies only to *Mappia foetida* only since *Camptotheca acuminate* is obtained by cultivate source in China.**

6c. Geographic Region

The raw material, stems of the *Mappia foetida*, is collected from wild specimens controlled by the Regional Forest Department (Government of India).

6d. Government Oversight of Harvesting

The tenders are issued by the Chief Regional Controller (Forest Department-Government of India) to collectors when the plant growth situation is adequate for harvesting in a particular forest area. The tenders are normally issued before the monsoon season, i.e. May / June or twice a year. These tenders allow removal of specific quantity and monitor growth in the forest area. The stems are cut manually, dried under the sun and cut into small pieces before supplying to the buyer. Dealers oversee the commercial activity, procure the proper Transit Permit for the *Mappia* movement and check the quality/quantity/packing and transportation from the collector to the buyer.

6e. Applicant's Oversight of Harvesting

The applicant, Hospira, Inc, procures the raw material, topotecan hydrochloride, from ScinoPharm. The documentation of the harvesting is maintained by the starting material extractor, S. M. Herbals Pvt. Ltd., who supplies camptothecin to ScinoPharm.

6f. Statements Pertaining to ESA and CITES

Mappia foetida is not listed in the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened and is abundantly cultivated and grown in the forest of the Western Ghats area of India. It is not entitled to special protection under some other Federal law or international treaty to which the United States is a party.

The only habitat of *Mappia foetida* in India is in the Western Ghats area, stretching from Maharashtra (Alibagh) to north part of Karnatka and Goa. Western Ghats area is entitled to special protection by the Indian Government and harvesting can be done only after getting proper approvals from the Regional Forest Authority. The area habitat where *Mappia* is found is not at all populated and there are no industrial activities.

To the best of our knowledge, *Mappia foetida* species is not 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). It is not entitled to special protection under some other Federal law or international treaty to which the United States is a party.

6g. Rate of Regeneration

Mappia is a fast growing tree. Only stems are allowed to be harvested. The tree is not uprooted. Fresh shoots start growing from the trunk and can be again harvested after 5 years. A *Mappia* tree naturally re-generates from the trunk since the tree grows in the wild. Proper harvesting rate is not available. The *Mappia foetida* stem is a renewable source of camptothecin.

6h. Methods of Harvest

The branch stems are cut manually, dried under the sun and cut into small pieces before supplying to the buyer. Only stems and not leaves are sold to the buyer and only stems are used for extraction of camptothecin. The frequency of harvesting is determined by the Chief Regional Controller (Forest Department- Government of India) to keep a check on overgrown areas. The harvesting technique does not affect the ecosystem as the main stem is intact and the branch stems will grow within a few years. The harvesting is conducted in accordance with government regulations of the Regional Forest Department- Government of India).

A picture of the dried stem of *Mappia foetida* and its chopped state before extraction immediately follows.

6i. Bulk Weight of Biomass Needed to Yield One Kilogram of Active Moiety

This information is provided in the **Confidential Appendix**.

6j. Amount of Biomass Needed to Produce Sufficient Amount of the Active Moiety to Treat the Average Patient

This information is provided in the **Confidential Appendix**.

6k. Estimate of the total Biomass in the Geographic Region Where the Biomass is Obtained

The Western Ghats measures 160, 000 sq. km. *Mappia foetida* is found in Karnataka, Satara, Pune, Kolhapur, Raigad, Ratnagiri and Jalagon in Maharashtra.

There is no official data regarding total number of the *Mappia foetida* trees grown in the Western Ghats area, about 160,000 sq. km. An estimate of the number of Mappia trees is based on the following assumptions:

(1) 1 tree needs 10 sq.m.,
(2) *mappia foetida* trees occupy about 0.3 % of Western Ghats area (i. e. 480 sq. km.),

It is estimated that Western Ghats has about 48 million *Mappia foetida* trees.

6l. Uses of the plant Biomass Other than the Proposed Use

The leaves of *Mappia foetida* are used to make plates and cups for use in the temples in India.

6m. Plant Growth Rate and/or Life Span and Rate of Regeneration

The *Mappia foetida* tree can grow to about 10 – 15 ft. with a diameter 8 – 12 inches. The main stem is intact and the rate of regeneration of the branch stems harvested is within 5 years. The life span can be more than 10 years.

6n. A Discussion of Whether the Harvesting Provides for Sustained Yield

The harvesting of the Mappia foetida is well controlled by the Regional Forest Department in India to ensure a sustainable supply of *Mappia foetida*. Under this 505(b)(2) NDA, Hospira, Inc. anticipates using the stems harvested from approximately 1 tree per year for manufacturing topotecan hydrochloride injection. This amount is minimal in comparison to the estimated 48 million trees in Western Ghats. The stems regenerate in the trees within 5 years. Based on the information provided, there is a sustainable supply of *Mappia foetida* to supply the annual needs based on the proposed use and any prior approved uses.

7. Mitigation Measures

As described in the above sections, the Regional Forest authorities in India issue permits when *Mappia foetida* in certain areas can be harvested. During the harvesting, only the branches can be cut and the main stem is left intact. The tree is not cut from the roots, and hence grows afresh within 5 years. Since only the branches are removed during the harvesting, the trees remain alive for the next harvesting. Currently, there is no reforestation plan.

8. Alternatives to the Proposed Action

No potential adverse environmental effects have been identified for the proposed action. As described in the above sections, the consumption of the *Mappia foetida* is estimated only about 1~2 trees per year. Further, cultivated *Camptotheca acuminate* has been used as the alternate source to produce camptothecin.

Alternatives such as extraction of camptothecin from cell culture is not available. However, 10-hydroxy camptothecin from total synthesis is now commercially available, which can be used to synthesize camptothecin. AVRA Laboratories Pvt. Ltd. in India has provided commercially available 10-hydroxy camptothecin produced via a total synthesis process since 2008. ScinoPharm Taiwan has included AVRA Laboratories Pvt. Ltd. as a qualified vendor of 10-hydroxy camptothecin in 2009.

We note that Curran et al. at University of Pittsburgh is granted the patent for full synthesis of camptothecin (US 6982333 B2) which can be used as an alternate source of camptothecin.

9. List of Preparers

Name	Sy-Ray Wen
Title	Senior Specialist, Regulatory Technical Services
Company	ScinoPharm Taiwan, Ltd. No. 1, Nan;Ke 8th Road Tainan Science-Based Industrial Park Shan-Hua, Tainan County 74144 Taiwan, R.O.C.
Contact Information	Tel: +886-6-505-2888 ext, 2321 Fax: +886-6-505-2855 email: syray.wen@scinopharm.com.tw
Qualifications	B.S. in Botany National Taiwan University, Taiwan M.S. in Molecular Medicine National Taiwan University, Taiwan

10. References

N/A

11. Appendices

- Confidential Appendix: Environmental Information, Use of Fauna or Flora

12. Certification

Hospira confirms that it and the other parties with which Hospira contracts for the harvest of biomass for camptothecin production will comply with all requirements in the region(s) in which the biomass is sourced relating to the harvest of *Mappia foetida* and *Camptotheca acuminate* for Hospira. Hospira commits that it will continue to comply with all applicable requirements in the region(s) in which the biomass is sourced 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.

Lisa Zboril

February 11, 2010

Lisa Zboril
Director, Global Regulatory Affairs
Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2
Lake Forest, IL 60045-5046

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200582	ORIG-1	HOSPIRA INC	TOPOTECAN INJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EMILY A MCVEY
06/18/2010

NAKISSA SADRIEH
06/21/2010

MOHEB M NASR
06/22/2010

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

Memorandum

Date: June 18, 2010

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

To: Deborah Mesmer
OPS/ONDQA

Through: Nakissa Sadrieh, Ph.D.
OPS/IO/SRS

Subject: **NDA 200-582:** Topotecan Hydrochloride Injection
Sponsor: Hospira, Inc.
Review of Environmental Assessment

A. Background

Hospira, Inc. requests approval of Topotecan Hydrochloride for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy, [redacted] (b) (4) An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

B. Discussion

Executive Summary

This Environmental Assessment, dated February 11, 2010, supports the NDA 200-582 for Topotecan Hydrochloride for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy, [redacted] (b) (4)
The EA was prepared in accordance with 21 CFR Part 25 by Hospira, Inc. [redacted] (b) (4)

The sponsor states that Topotecan Hydrochloride is derived from Camptothecin from *Mappia foetida* trees, which grow wildly on government owned land in Western Ghats area, India, as well as from *Camptotheca acuminate*, which is grown on cultivated lands in China. Since drug substance from *Mappia foetida* is obtained from the wild, the environmental assessment

was submitted and reviewed. The submitted information was as recommended in the CDER/CBER Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (July 1998).

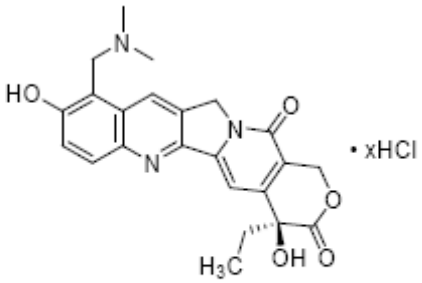
A FONSI is recommended.

C. Environmental Assessment Review

1. **Date:** February 11, 2010
2. **Applicant:** Hospira, Inc.
3. **Address:** 275 North Field Drive, Dept. 0389, Bldg H2, Lake Forest, IL 60045-5046
4. **Proposed Action:** Hospira, Inc. is filing an NDA pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Topotecan Hydrochloride for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy, (b) (4)

5. **Identification of Chemicals**

(i) Established Name: Topotecan Hydrochloride
(ii) Chemical Names: (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 monohydrochloride
(iii) Chemical Structure:



Note: x=1.0-1.5

6. **Environmental Characterization**

The starting material for Topotecan Hydrochloride synthesis is produced from Camptothecin, which Hospira, Inc. states that they purchase sourced from wild *Mappia foetida* harvested in the Western Ghats region of India under government supervision to ensure sustainable harvest, as well as from *Camptotheca acuminate* cultivated in China. The EA provides documentation of the harvesting of wild *Mappia foetida* stems in compliance with Indian law.

The sponsor estimates approximately (b) (4) of camptothecin is needed to produce (b) (4) of topotecan base. The harvest of *Mappia foetida* is regulated on government lands such that

particular areas may be harvested at different times. Only the stems may be harvested, so as to preserve the tree. Fresh shoots will begin go grow from the remaining trunk and may be harvested again after 5 years. *Mappia foetida* is a fast growing tree and may grow up to 15 feet in that time. The supplier states that a tree may grow for more than 100 years.

The average patient needs 1.5 mg/m^2 X 1.81 m^2 x 5 doses x 4 cycles 54.3 mg of topotecan or (b) (4) of camptothecin. This may be acquired from approximately (b) (4) of *Mappia* stems, with one tree producing about 250 kg of stems every 5 years. The sponsor thus estimates that (b) (4) and since the estimated number of patiences to be treated through this NDA (b) (4) should be needed to supply the appropriate amount of Topotecan HCL. There are estimated to be about 48 million *Mappia foetida* trees in the Western Ghats.

Since the Camptothecin is harvested from a carefully regulated wild source, as well as from a cultivated source, this harvesting is considered sustainable and no adverse environmental impact is expected.

7. Mitigation Measures and Alternatives

Since no adverse environmental impact is expected, no mitigation methods are addressed. It is possible to create camptothecin using biotechnology, but this method is not currently feasible for mass production. Since the harvesting from wild *Mappia foetida* is carefully regulated for sustainability, and the *Camptotheca acuminate* is a cultivated source, this is the best alternative available to date.

8. Certification

Hospira confirms that it and other parties with which Hospira contracts for the harvest of biomass for Camptothecin production will comply with all requirements within the region(s) in which the biomass is sourced, relating to the harvest of *Camptotheca acuminate* and *Mappia foetida* for Hospira. Hospira commits that it will continue to comply with all applicable requirements in the region(s) in which the biomass is sourced 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.

9. Literature Reviewed

1. 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>.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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 .

7. 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.

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

9. 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.

10. 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.

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

Findings: No outstanding issues were ascertained from the literature review.

10. Cumulative Impact

Since this NDA is only expected to use 1 tree, and other applications have used similarly few trees (1 to 5), and since the harvest of this resource is carefully regulated in India (and cultivated in China), no major cumulative impact is expected from the harvest of *Camptotheca acuminate* and *Mappia foetida* for this application and other existing applications for Topotecan HCl (b) (4)

11. 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 harvest of wild *Mappia foetida* or cultivated *Camptotheca acuminate* to produce Topotecan HCl for this NDA.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200582	ORIG-1	HOSPIRA INC	TOPOTECAN INJ

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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06/18/2010

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NAKISSA SADRIEH
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