

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
0200199Orig1s000

ENVIRONMENTAL ASSESSMENT

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

NDA 200-199
Topotecan Hydrochloride

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

September 17, 2010

FINDING OF NO SIGNIFICANT IMPACT

NDA 200-199

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 200-199 requests approval for Topotecan Hydrochloride as an anti-neoplastic/oncolytic agent for use in the treatment of [REDACTED] (b) (4) and small cell lung cancer sensitive disease after failure of first-line chemotherapy. In support of its application for Topotecan Hydrochloride, Sandoz, Inc. submitted an environmental assessment (attached) in accordance with 21 CFR Part 25, which evaluates the potential environmental impacts of the use of *Nothapodytes nimmoniana* (*Mappia foetida*) and *Camptotheca acuminata* 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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Attachment: October 4th, 2006 Environmental Assessment

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/s/

EMILY A MCVEY
09/17/2010

NAKISSA SADRIEH
09/20/2010

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09/22/2010



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

Memorandum

Date: September 17, 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 200-199:** Topotecan Hydrochloride Injection
Sponsor: Sandoz, Inc.
Review of Environmental Assessment

A. Background

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

B. Discussion

Executive Summary

This Environmental Assessment, dated October 4th, 2006, supports the NDA 200-199 for Topotecan Hydrochloride for the treatment of (b) (4) small cell lung cancer sensitive disease after failure of first-line chemotherapy. The EA was prepared in accordance with 21 CFR Part 25 by Sandoz, Inc. in conjunction with the suppliers of the natural product, (b) (4)

The sponsor states that Topotecan Hydrochloride is derived from Camptothecin from *Nothapodytes nimoniana* trees, which grow wildy on government owned land in (b) (4) India, as well as from *Camptotheca acuminata*, which is grown on

(b) (4) 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).

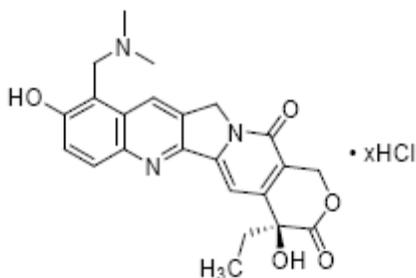
A FONSI is recommended.

C. Environmental Assessment Review

1. **Date:** October 4th, 2006
2. **Applicant:** Sandoz, Inc.
3. **Address:**
4. **Proposed Action:** Sandoz, 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 (b) (4) and small cell lung cancer sensitive disease after failure of first-line chemotherapy.

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

(b) (4) Topotecan Hydrochloride synthesis is produced from Camptothecin, which the applicant states that they purchase sourced from wild *Nothapodytes nimmoniana* and *Mappia foetida* harvested in the (b) (4) India under government supervision to ensure sustainable harvest, as well as from *Camptotheca acuminata* cultivated in China. The EA provides documentation of the harvesting of wild *Nothapodytes nimmoniana* (*Mappia foetida*) trunks and stems in compliance with Indian law.

The EA estimates approximately 650 kg of wood are yielded per *Nothapodytes nimoniana* tree, which results in (b) (4) of camptothecin, which in turn can produce about (b) (4) of topotecan base. The harvest of *Nothapodytes nimoniana* is regulated on government lands such that particular areas may be harvested at different times. Medium sized trees are carefully chosen for harvest and other trees are left to ensure sustainability of the harvest. In addition, reforestation measures are undertaken. *Nothapodytes nimmoniana* is also known as *Mappia foetida* and may also be sustainably harvested for camptothecin production through harvesting only the stems of a certain age. This harvest is regulated to ensure the health of the plant from which the stems are harvested. Both whole-tree and stem harvest are regulated by the government of India and permits and certifications are provided in the EA.

Camptotheca acuminata is cultivated in China and only the fruits are harvested. About (b) (4) (b) (4) of fruit are required for (b) (4) of camptothecin.

Since the camptothecin required to produce the Topotecan HCl for this application is harvested from carefully regulated wild sources, 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 *Nothapodytes nimoniana* (*Mappia foetida*) is carefully regulated for sustainability, and the *Camptotheca acuminata* is a cultivated source, this is the best alternative available to date.

8. Certification

The DMF holder (b) (4) confirms that it and other parties with which it 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 acuminata* and *Nothapodytes nimmoniana* (*Mappia foetida*) and in addition 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, Spittler 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 acuminata* seed and leaf extracts. *Phytomedicine* 14(1): 50-56.

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

10. Cumulative Impact

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 acuminata* and *Nothapodytes nimmoniana* (*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 *Nothapodytes nimmoniana* (*Mappia foetida*) or cultivated *Camptotheca acuminata* to produce Topotecan HCl for this NDA.

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

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/s/

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09/17/2010

NAKISSA SADRIEH
09/20/2010