

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203585Orig1s000

ENVIRONMENTAL ASSESSMENT



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

Memorandum

Date: July 30, 2012

From: Raanan A. Bloom, Ph.D.
OPS/IO/PARS

To: Jewell Martin
OPS/OGD

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

Subject: **NDA 203-585:** Omacetaxine mepesuccinate injection, 3.5 mg single use vials.

Sponsor: Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Review of Environmental Assessment

A. Background

Cephalon, Inc. requests approval of Omacetaxine mepesuccinate injection, 3.5 mg single use vials. The applicant states that the drug is “indicated for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to prior tyrosine kinase inhibitors (TKI) including imatinib, dasatinib or nilotinib” (NDA 203585, dated April 20th, 2012, section 4b, p. 2). An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

B. Discussion

Executive Summary

The submitted EA, dated April 20th, 2012, supports the NDA for omacetaxine mepesuccinate injection, 3.5 mg single use vials. The EA was prepared in accordance with 21 CFR Part 25 by Cephalon, Inc.

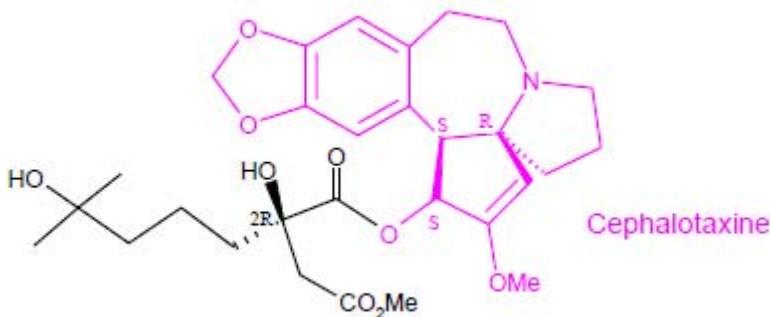
Omacetaxine mepesuccinate is a semi-synthetic derivative of Cephalotaxine from the *Cephalotaxus fortunei* (Plum Yew) species, which is native to Eastern and Central China. Omacetaxine mepesuccinate is partially cultivated and partially obtained from wildy grown sources, therefore an EA was submitted 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).

C. Environmental Assessment Review

1. **Date:** April 20th, 2012
2. **Applicant:** Cephalon, Inc.
3. **Address:** 41 Moores Road, Frazer, PA 19355
4. **Proposed Action:** Cephalon, Inc. is filing an NDA pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for omacetaxine mepesuccinate injection, 3.5 mg single use vials for the treatment of chronic or accelerated phase chronic myeloid leukemia (CML) in adults following unsuccessful treatment with prior tyrosine kinase inhibitors (TKI) including imatinib, dasatinib or nilotinib.

5. Identification of Chemicals

- (i) Established Name: Omacetaxine mepesuccinate
- (ii) Brand/Proprietary Name/Tradename: OMASONA
- (iii) Chemical Name: Cephalotaxine, 4-methyl (2R)-2-hydroxy-2-(4-hydroxy-4-methylpentyl) butanedioate (ester)
- (iv) Chemical Abstract Registration Number: 26833-87-4
- (v) Molecular Formula: C₂₉H₃₉NO₉
- (vi) Molecular Weight: 545.6 g/mol
- (vii) Chemical Structure:



6. Environmental Characterization

Omacetaxine mepesuccinate is isolated from young leaves, needles, and twigs of *Cephalotaxus fortunei* from the *Cephalotaxaceae* family. Wild and cultivated plants are sourced in the Henan, Shanxi, and Gansu provinces of China. *Cephalotaxus fortunei* is listed as an endangered species in the Henan Province, but the Chinese Chamber of International Commerce has granted the suppliers rights to harvest. *Cephalotaxus fortunei* is not currently listed on either the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or the US Wildlife Service for Endangered Species Act (ESA), but it is listed as an endangered species within the Henan Province. The suppliers have been authorized by the Chinese Chamber of International Commerce to harvest *Cephalotaxus fortunei* from the Henan Province and have submitted documentation with this EA (NDA 203-585, dated April 20th, 2012). A database query for the Latin name, *Cephalotaxus fortunei*, yielded no results from CITES and confirms the sponsor's claim. New branches and leaves are harvested from the current years growth. New branches and leaves are regenerated yearly making this method of harvesting a sustainable practice with no expected adverse environmental effects on the environment.

Approximately 250kg of *Cephalotaxus fortunei* biomass is harvested to yield approximately (b) (4) of cephalataxine which, in turn, is used to produce approximately (b) (4) of Omacetaxine mepesuccinate (active moiety). This equates to approximately (b) (4) vials at 3.5mg/vial. The U.S. patient population is expected to require approximately (b) (4) vials at 3.5mg/vial.

Cephalotaxus fortunei biomass is harvested from new leaves and branches that regenerate yearly. This method of harvest is a sustainable practice and no adverse environmental impact is expected.

7. Mitigation Measures and Alternatives

Since no adverse environmental impact is expected, no mitigation methods are addressed.

8. Certification

The following certification is provided:

"The DMF holder, Stragen Pharma SA, confirms that to date it and the other parties involved in the harvesting of *Cephalotaxus* species have complied with all requirements under Chinese law and commits to continue complying with all requirements under 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 (see Appendix 5). Cephalon will monitor on regular basis any potential change in harvesting or culture processes."

Appendix 5 provides a statement of compliance from Stragen Pharma.

9. Literature Reviewed

1. Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) database.
2. US Wildlife Service for Endangered Species Act (ESA) database.

10. Comments and Conclusions

Based on an evaluation of the information provided in this EA and in FDA guidance, no significant adverse environmental impacts are expected from the harvest of wild *Cephalotaxus fortunei* to produce omacetaxine mepesuccinate injection, 3.5 mg single use vials. The suppliers have been authorized by the Chinese Chamber of International Commerce to harvest *Cephalotaxus fortunei* from the Henan Province and have submitted documentation to that effect with this EA.

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

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/s/

RAANAN A BLOOM
07/30/2012

NAKISSA SADRIEH
07/30/2012

**Environmental Assessment
Finding of No Significant Impact**

**NDA 203-585
Omacetaxine Mepesuccinate Injection**

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

July 30, 2012

FINDING OF NO SIGNIFICANT IMPACT

NDA 203-585

Omacetaxine Mepesuccinate 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 203-585 requests approval of omacetaxine mepesuccinate injection, 3.5 mg single use vials indicated for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to prior tyrosine kinase inhibitors (TKI) including imatinib, dasatinib or nilotinib. In support of its application, Cephalon, Inc., submitted an Environmental Assessment in accordance with 21 CFR Part 25, which evaluates the potential environmental impacts of approval of this application for omacetaxine mepesuccinate injection.

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 a significant impact on the environment. Therefore, an environmental impact statement will not be prepared.

PREPARED BY:

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Office of Pharmaceutical Science

CONCURRED BY:

Nakissa Sadrieh, Ph.D.
Associate Director for Research Policy and Implementation
Office of Pharmaceutical Science

Attachment: April 20, 2012, Environmental Assessment

ENVIRONMENTAL ANALYSIS

1 DATE:

April 20, 2012

2 NAME OF THE APPLICANT /PETITIONER:

Cephalon, Inc.

Name of DMF 20542 Holder for Drug Substance : Stragen Pharma S.A.

3 ADDRESS:

41 Moores Road
Frazer, PA 19355
Tel : (610) 727 6152
Fax: (610) 738-6642

4 DESCRIPTION OF PROPOSED ACTION

a. Requested Approval

Cephalon, Inc, a wholly owned subsidiary of Teva Pharmaceuticals Ltd, has filed the NDA # 203-585 for omacetaxine mepesuccinate for injection 3.5 mg pursuant to 21 CFR part 25. The drug product is a lyophilized powder in a single-use vial containing 3.5 mg omacetaxine mepesuccinate.

The NDA references Stragen Pharma SA Type II DMF 20542 for the source of the drug substance. Information located in the Appendices 1 to 5 in this submission and the DMF is proprietary and confidential to and is not to be disclosed to public.

b. Need for Action

Omacetaxine mepesuccinate for injection, 3.5 mg is indicated for the treatment of adult patients with chronic or accelerated phase chronic myeloid leukemia (CML) with resistance and/or intolerance to prior tyrosine kinase inhibitors (TKI) including imatinib, dasatinib or nilotinib.

c. Locations of Use

Omacetaxine mepesuccinate for injection, 3.5 mg, will be primarily administered by patients or caregivers in the home. It may also be used in hospital/hospice settings by healthcare providers. Use of this product will not be concentrated in any specific geographic region within the US.

d. Disposal Sites

Patients and caregivers who administer the drug at home will be provided with appropriate containers for disposal of empty or partially empty containers. Instructions for the return of the containers will also be provided to ensure state and local regulations are followed.

5 IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

Nomenclature

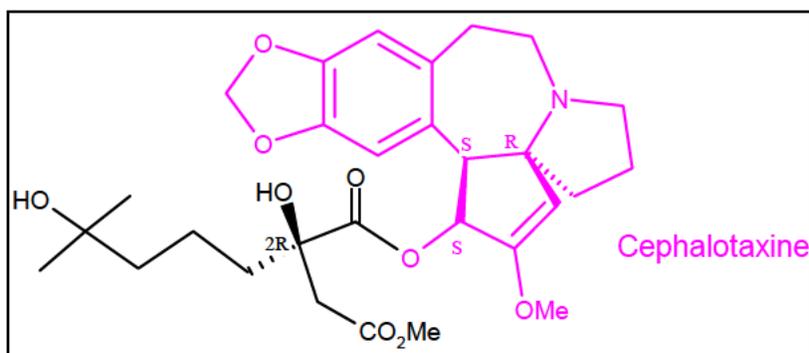
- i. Established Name (USAN) and INN: Omacetaxine mepesuccinate
- ii. Proposed Brand/Proprietary Name/Tradename of associated drug product: OMASONA (NDA 203-585)
- iii. Chemical Name: Cephalotaxine, 4-methyl (2R)-2-hydroxy-2-(4-hydroxy-4-methylpentyl) butanedioate (ester)

CAS: 26833-87-4

Molecular Formula: C₂₉H₃₉NO₉

Molecular Weight: 545.6 g/mol

Structural formula:



6 ENVIRONMENTAL ISSUES

An Orphan Drug Designation 05-2182 was granted for this product to Chemgenex, prior to its acquisition by Cephalon in 2011. Although the estimated aquatic concentration is well below the threshold of the Environmental Introduction Concentration of 1 ppb; this environmental assessment is required due to the fact that omacetaxine mepesuccinate is derived from plum yew trees, some of which are grown in the wild. Leaves and young twigs are used as source material for the drug substance. Because the trees remain intact and are not harmed by the harvesting process, this source therefore represents a renewable biomass.

Assessing Toxicity to Environmental Organisms

Assessing toxicity to environmental organisms is not applicable pursuant to 21CFR25.31(B), as the use of the active moiety is expected to result in an EIC (Environmental Introduction Concentration) well below the threshold of 1 ppb. To the best of the Company's knowledge no extraordinary circumstances exist in regard to the action. See [Appendix 1](#) for calculation.

Use of Resources

- Introduction

The drug substance omacetaxine mepesuccinate is a semi-synthetic compound manufactured using an extract [Cephalotaxine (CTXOH)] from *Cephalotaxus* species and subsequent chemical synthesis. The inactive alkaloid cephalotaxine is contained solely in the *Cephalotaxus* genus, an evergreen tree naturally found in Asia ([Tripp, 1995](#))¹. This inactive alkaloid, a pre-cursor of omacetaxine, is obtained from the renewable parts (leaves and young twigs) of the *Cephalotaxus* species. The overall renewable *Cephalotaxus* biomass to be used per year is approximately 250kg. See [Appendix 1](#) for calculation.

- Biological Identification

Cephalotaxus fortunei, commonly called the Chinese Plum Yew, or simply Plum Yew, Chinese Cowtail Pine or, in Chinese, as San Jian Shan, is a coniferous shrub or small tree in the plum yew family. It is a native of China ([Tripp, 1995](#))^{1,2} from genus *Cephalotaxus* and family of *Cephalotaxaceae*. The genus comprises several species and is **endemic** to eastern **Asia**. The species are evergreen shrubs and small trees reaching 1-10 m (rarely to 20 m) tall.

Species include:

- *Cephalotaxus fortunei* (Native of Eastern & Central China) - *Cephalotaxus* : The Plum Yews ([Tripp, 1995](#))¹, *Cephalotaxus fortunei* ([Hook](#)).³ *Cephalotaxus harringtonii* 'Fastigiata' (Upright Japanese Plum Yew)
- *Cephalotaxus harringtonii* 'Prostrata'
- *Cephalotaxus drupacea*

C. fortunei, *C. hainanensis* and *C. harringtonia* contain richer ester alkaloids than other species of the genus. *C. fortunei* has a wide distribution in many provinces of China and is not on the Convention on International Trade in Endangered Species (CITES) list of protected species.

(See http://www.cites.org/eng/prog/criteria/1st_meeting/trees.shtml). For these reasons, *C. fortunei* has been selected for manufacture of this drug substance, which is subsequently used in the manufacture of omacetaxine mepesuccinate for injection 3.5 mg ([Powell, 2009](#); [Powell et al, 1972](#)).^{4,5}

- Description of *Cephalotaxus fortunei* parts of the plants used

The leaves and young twigs are described below and a representative picture of the leaves is presented in [Figure 1](#).

Figure 1 Representative Picture of the Leaves and Twigs



- **Branches:** Shoots slightly pendant. Leafy branchlets obovate, obtriangular, or almost rectangular in outline, plane ([Tripp, 1995](#)).
 - **Leaves:** Leaves almost horizontally spreading, borne at 30-110° to branchlet axis; petiole 0.5-2 mm; blade deep green and glossy adaxially, linear-lanceolate, distally gradually attenuate (from proximal 1/3 of blade), falcate or ± straight, flat, (1.5-)3.5-12.5 cm × (1.5-)3.2-5 mm (longest in the genus), leathery but usually rather soft and flexible, midvein 0.2-0.5 mm wide abaxially, stomatal bands (0.8-)1.2-2.1 mm wide, usually of (13-)17-24 rows of stomata, 2-5 × as wide as midvein, marginal bands 0.1-0.4 mm wide, base cuneate or shortly attenuate, asymmetric, margin flat or very narrowly revolute when dry, apex cuspidate, cusp 0.5-2 mm, often breaking off ([Tripp, 1995](#)).
- Geographic Region, Sources of Material

Both natural (wild) and cultivated materials are collected in China, in the Henan, Shanxi and Gansu provinces. The list of sources collecting either from wild or cultivated trees is provided in [Appendix 2](#).

- Description of Government Oversight

C. fortunei is not listed in the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES); neither is it listed in Chinese National Endangered Species of Wild Fauna and Flora. Additionally, we have searched and confirmed that no *Cephalotaxus* species are listed on the US Wildlife Service for Endangered Species Act (ESA). *Cephalotaxus fortunei* is classified as “lower risk/least concern” by the IUCN (International Union for Conservation of Nature and Natural Resources).

However, *Cephalotaxus fortunei* is listed in Henan’s Provincial Endangered Species, and the supplier has been granted harvesting authorization by the Chinese Chamber of International Commerce (see [Appendix 3](#)). An attestation for the other regions that the leaves are not subject to special licensing by Chinese Authorities is included in [Appendix 4](#). A commitment from the DMF holder Stragen Pharma SA is also provided in [Appendix 5](#).

Oversight of Harvesting

The suppliers collect young leaves/needles and young twigs according to a specified process and time period to assure the protection of the *Cephalotaxus* genus as required by Stragen Pharma S.A. Thus, these parts (young leaves/needles and young twigs) of the *Cephalotaxus* plants are considered as renewable resources. Cephalon monitors on a regular basis any change in Stragen Pharma S.A. processes including their oversight of the suppliers. Additionally, the suppliers guarantee the cultivation and/or the collection of *Cephalotaxus* according to relevant laws and regulations of China and the respective provinces under supervision of trained technical personnel.

In order to promote the protection, development and utilization of *Cephalotaxus*, a specific cultivated area of the plant has been established by one supplier in the Henan province.

Harvesting of the biomass from the natural resources is from specific areas under relevant agreement with the Chinese government according to defined harvesting processes. The processes are in accordance with calculations by forestry protection personnel, and meet the collection, cultivation and distribution demand while not destroying the natural ecological balance in order to assure that the resources are renewable. The collection plan has the following objectives to assure a continued and sustained renewable resource of *Cephalotaxus*:

Collection principle: protection first, combined with collection and cultivation

Collection time: during the rest period of *Cephalotaxus*

Collection part (of the tree): leaves and new branches among the lateral *Cephalotaxus* branches developed during the current year, which is a renewable resource. Caution should be exercised not to damage the trunks.

The collection process, including material, training and supervision and the harvesting technique do not affect the ecosystem.

In addition to the use for medicinal purposes, the fruit and seeds are considered edible and plants may be used as hedges or for ground cover (Hook).³

Rationale for the Choice of *Cephalotaxus* species

In order to determine the peak harvest period, the contents and composition of alkaloids including homoharringtonine, harringtonine, and cephalotaxine were determined using the Korean native plum yew tree (*Cephalotaxus koreana*) collected from 17 different sites. The alkaloid content of *C. koreana* varied with locations and plant populations from 11.8 mg/g to 195.2 mg/g of dry weight while *C. koreana* in southern area had higher alkaloid content. The alkaloid compositions in *C. koreana* were highest for homoharringtonine (40%) and followed by harringtonine (32%) and cephalotaxine (28%).

Total alkaloids and homoharringtonine content in needles were two-fold higher than the stems. Alkaloid content of *C. koreana* was the highest in winter, and the lowest in summer.

Comparison of alkaloid content and composition with other species of *Cephalotaxus* revealed that *C. koreana* was different from *C. harringtonia*, and contents of homoharringtonine were higher than other species. Harvesting takes place in winter, during the dormant period of the *Cephalotaxus* species.

A study was also performed with the following goals:

Find reliable sources of alkaloids *Cephalotaxus* in conifer generally belonging to the families Cephalotaxaceae and Taxaceae, or in other relative coniferous families.

Determine if some markers such as taxanes and cephalotaxanes are specific to each family / genre.

Verify the lack of impact on the final active ingredient of the wild plant species harvested (for contamination or adulteration).

Identify the best species to propagate and cultivate for production.

The results showed that *Cephalotaxus* species was best for providing Cephalotaxine. Information on the content of the various species tested is provided in [Table 1](#).

Table 1 Content of Alkaloids in *Cephalotaxus* Species and in *Taxus* Species

Family	Species	Number of samples tested	CTX ¹ (g/L) Mean	HHT ² (g/L) Mean	HA ³ (g/L) Mean	10-DAB ⁴ (g/L) Mean	Paclitaxel (g/L) Mean
Cephalotaxaceae	<i>Cephalotaxus fortunei</i>	28	1.07	0.18	0.76	0	0
	<i>C. harringtonia harringtonia</i>	34	1.84	0.17	0.22	0	0
	<i>C. harringtonia fastigiata</i>	20	1.09	0.04	0.04	0	0
	<i>C. harringtonia prostata</i>	1	2.79	-	-	-	-
	<i>C. sinensis</i>	3	0.38	0.13	0.17	0	0
Taxaceae	<i>Taxus</i> species	8	0	0	0	0.14	0.02
	<i>Toreya</i> species	7	0	0	0	0	0

¹- CTX: cephalotaxine
²- HHT: homoharringtonine
³- HA: harringtonine
⁴- 10-DAB: 10-deacetylbaccatin

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Based on results, the *Cephalotaxus* genus was chosen.

As further support to the above, the following information is provided from Northern Regional Research Center (*Delfel, 1980*)⁶ a study that evaluated the distribution of alkaloids in the upper portions of laboratory plants to determine the location of the highest alkaloid concentration levels. The amount of total alkaloid was highest in the youngest tissues (upper tier of branches), see [Table 2](#).

Table 2 :Alkaloid Distribution in Laboratory-grown *Cephalotaxus Harringtonia* tree

Alkaloid	Plant part	Alkaloid concentration (µg/g) in branch tier			
		upper	2nd	3rd	lower
Homoerythrina alkaloids	Leaf	0	0	10	35
	Stem	26	16	10	16
	Whole branch	8	5	10	27
Cephalotaxine	Leaf	13	8	17	41
	Stem	33	25	9	20
	Whole branch	20	13	14	32
Deoxyharringtonine	Leaf	10	2	20	5
	Stem	65	49	36	9
	Whole branch	28	17	26	7
Harringtonine	Leaf	198	158	222	280
	Stem	82	65	35	33
	Whole branch	160	128	152	176
Isoharringtonine	Leaf	105	69	118	182
	Stem	71	71	48	43
	Whole branch	94	70	92	123
Homoharringtonine	Leaf	2030	1500	2430	3190
	Stem	958	575	687	797
	Whole branch	1690	1200	1780	2180
Total alkaloids	Leaf	2360	1740	2820	3730
	Stem	1240	800	825	920
	Whole branch	2000	1430	2080	2540

7 MITIGATION MEASURES

As described in section 6 above, harvesting from *Cephalotaxus* plants only involves the plum yew leaves (needles) and young twigs / branches. These are considered renewable resources and therefore do not involve destruction of the plumyew trees. Thus, there are no potential adverse environmental effects associated with the harvesting of *Cephalotaxus* biomass. Therefore, no additional mitigation measures are deemed necessary.

8 ALTERNATIVES TO THE PROPOSED ACTION PLAN

No potential adverse environmental effects have been identified for the proposed action. As described in section 6 under Sources of Material, in addition to natural sources, cultivation of the *Cephalotaxus* plant was also evaluated. Cultivation began in 2007,

with harvesting to begin once the trees are mature, i.e., older than 5 years. Therefore, the plan is in progress and further data needs to be gathered.

9 CERTIFICATION

The DMF holder, Stragen Pharma SA, confirms that to date it and the other parties involved in the harvesting of *Cephalotaxus* species have complied with all requirements under Chinese law and commits to continue complying with all requirements under 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 (see [Appendix 5](#)). Cephalon will monitor on regular basis any potential change in harvesting or culture processes.

10 LIST OF PREPARERS

Stephanie Pierre Stragen Pharma S.A. Chemical engineer, 5 years experience in development, Regulatory Affairs/Quality Assurance

Sylvie Peltier; Cephalon Inc; Pharm.D., Master Health Law, 22 years experience in Regulatory Affairs.

11 REFERENCES

1. Tripp Kim E, [Cephalotaxus: The Plum Yews](#); *Arnoldia*, Spring 1995, Vol. 55(1): pp. 25-39
2. Hook, 2009, *Cephalotaxus fortunei*
3. Powell, R.G., [Plant Seeds as Sources of Potential Industrial Chemicals, Pharmaceuticals, and Pest Control Agents](#); *J. Nat. Prod.*, 2009, Vol. 72, pp. 516-523
4. Powell, R.G., Mikolajczak, K.L., Weisleder D., et al; [Alkaloids of Cephalotaxus Wilsoniana](#), *Phytochemistry* 1972, Vol. 11, pp. 3317-3320
5. Delfel, Norman E., [Alkaloid Distribution and Catabolism in Cephalotaxus Harringtonia](#), *Phytochemistry*, 1980, Vol. 19, pp. 403-408

12 APPENDICES

All the appendices contain trade secret and/or confidential information. As provided by 21 CFR 20.61 do not disclose to the public.

Appendix 1: Expected Introduction Concentration and Biomass Requirement Calculations

Appendix 2: List of sources

Appendix 3: China Council for the Promotion of International Trade, China Chamber of International Commerce Certificate

Appendix 4: Statement from TIANJIN C Ltd

Appendix 5: Commitment from Stragen Pharma SA

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/s/

RAANAN A BLOOM
07/30/2012

NAKISSA SADRIEH
07/30/2012