DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: March 8, 2004

From: Florian Zielinski, Environmental Reviewer, CDER, HFD-357

To: Dockets Management Branch, HFA-305

Subject: Docket # 92N-0489

Environmental Assessments and Finding of No Significant Impact for PMA P030025

Please place the attached Environmental Assessment and Finding of No Significant Impact for PMA P030025 in Docket #92N-0489.

92N-0489

EA 5

FINDING OF NO SIGNIFICANT IMPACT

AND

ENVIRONMENTAL ASSESSMENT FOR

PMA 030025

TAXUS Express^2 Paclitaxel-Eluting Coronary Stent System

CENTER FOR DRUG EVALUATION AND RESEARCH

September 2003

FINDING OF NO SIGNIFICANT IMPACT

PMA 030025

TAXUS Express^2 Paclitaxel-Eluting Coronary Stent System

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

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not, individually or cumulatively, have a significant effect on the quality of the human environment and therefore an environmental impact statement is not required.

In support of its Pre Market Approval (PMA) Application for TAXUS Express^2 Paclitaxel-Eluting Coronary Stent System, Boston Scientific Corporation has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the harvesting of a wild plant species from which paclitaxel is derived.

TAXUS Express^2 Paclitaxel-Eluting Coronary Stent System is a permanent implant into coronary arteries. It is indicated for improving luminal diameter, reducing restenosis and for the treatment of *de novo* lesions $\leq$28 mm in length in native coronary arteries $\geq$2.5 to $\leq$3.75 mm in diameter.

During the development phase for its product, the applicant used paclitaxel derived from the bark of Pacific Yew (*Taxus brevifolia*) trees from a reserve inventory of bark that was collected prior to December 1996. The bark was collected from both public and private land. No further Pacific Yew harvesting will occur for this product.

The harvesting from all private, state, and federal land was conducted in accordance with all applicable federal, state and local laws, regulations and guidances. Required permits were obtained prior to all harvests. The bark was collected in accordance with the recommendations in the Pacific Yew Final Environmental Impact Statement (August 1993, U.S. Forest Service).

The applicant has discussed, in the environmental assessment, the controls used during harvesting, oversight by the harvesting company and government agencies, compliance with applicable laws, regulations, and guidances, and mitigation measures. The information provided supports the conclusion that a finding of no significant impact is appropriate for the previous harvesting of Pacific Yew trees.

For the commercial product, the applicant intends to use paclitaxel derived from a man-made hybrid (*Taxus x media Rehder*) cultivated, grown, and harvested on private plantations.

American hospitals will dispose waste containing paclitaxel according to their standard procedures. No adverse effects are anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

The Center for Drug Evaluation and Research, in consultation with the Center for Devices and Radiological Health, has concluded that no adverse environmental effects are expected from the use and disposal of TAXUS Express^2 Paclitaxel-Eluting Coronary Stent System.

August 29, 2003 Florian W. Zielinski

DATE

PREPARED BY
Florian W Zielinski
Chemist, Center for Drug Evaluation and Research

9/2/03 Nancy B. Sager

DATE

CONCURRED BY
Nancy B Sager
Environmental Officer, Center for Drug Evaluation and Research

9/3/03

DATE

CONCURRED BY
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Acting Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

Distribution:

Original to PMA 030025, through Jennifer L Goode, HFZ-450, (301) 443-8517 x 173
HFD-357 / EA File / PMA 030025
HFD-110 / K. Srinivasachar
HFD-110 / N Chidambaram

Environmental Assessment

TAXUS Express² Paclitaxel-Eluting Coronary Stent System

1.	**Date**
	June 19, 2003
2.	**Name of Applicant or Petitioner**
	Boston Scientific Corporation
3.	**Address**
	One Boston Scientific Place Natick, MA 01760
4.	**Description of Proposed Action**
a. Requested Approval	Boston Scientific Corporation has filed a Premarket Approval Application for the TAXUS™ Express²™ Paclitaxel-Eluting Coronary Stent System (Monorail and Over-the-Wire), a device/drug combination product. This system consists of a paclitaxel-eluting balloon expandable stent, pre-mounted on a high-pressure delivery catheter and is used in the treatment of coronary artery disease. The stent portion of this product comes in lengths ranging from 8 mm to 32 mm and has a conformal drug-eluting coating containing between 50 and 209 μg of paclitaxel for the shortest and longest stents, respectively. An environmental assessment has been submitted pursuant to 21 CFR part 25 and has been formatted in accordance with FDA's July 1998 Guidance for Industry, "Environmental Assessment of Human Drug and Biologics Applications."
b. Need for Action	The TAXUS Express2 Paclitaxel-Eluting Coronary Stent System is indicated for improving luminal diameter and reducing restenosis for the treatment of de novo lesions $\leq$ 28mm in length in native coronary arteries $\geq$ 2.5 to $\leq$ 3.75 mm in diameter.
c. Location of Use	As a prescribed therapy for coronary artery disease, this product will be distributed and used throughout the United States. Locations of use include hospitals and catheter labs.
d. Disposal Sites	The stent is a permanent implant. All used catheters will be secured and disposed of in accordance with established procedures at the hospitals.

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

a. Nomenclature

i. Established Name
Paclitaxel

ii. Brand/Proprietary Name/Tradename
TAXUS™ Express²™ Paclitaxel-Eluting Coronary Stent System

iii. Chemical Name
Benzenepropanoic acid, β-(benzoylamino)-α-hydroxy-,6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1 *H*-cyclodeca[3,4]benz[1,2-b]oxet-9yl ester,[2a*R*-[2aα,4β,4aβ,6β,9α(α*R**,β*S**),11α,12α,12aα,12bα]]-.

(2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-1,2a,3,4,4a,6,9,10,11,12,12a,12b-Dodecahydro-4,6,9,11,12,12b-hexahydroxy-4a,8,13,13-tetramethyl-7,11-methano-5 *H*-cyclodeca[3,4]-benz[1,2-b]oxet-5-one 6,12b-diacetate, 12-benzoate, 9-ester with (2*R*,3*S*)-N-benzoyl-3-phenylisoserine

b. CAS registration number

33069-62-4

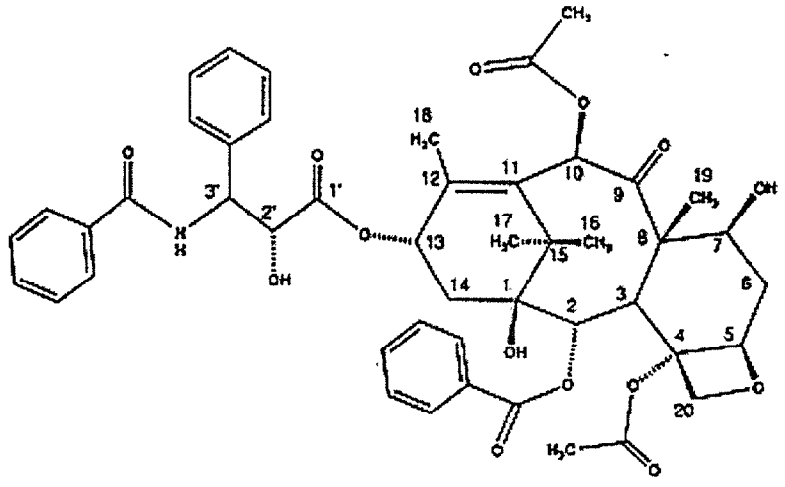
c. Molecular Formula

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

d. Molecular Weight

853.91 a.m.u.

e. Structural Formula



6. Environmental Issues

This Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25 and has been formatted in accordance with FDA's July 1998 Guidance for Industry, "Environmental Assessment of Human Drug and Biologics Applications." This EA is required because the product subject of this PMA incorporates paclitaxel derived from yew trees. (Note: Authorization letters for access to Drug Master Files have been included as **Confidential Attachment 1**.)

Developmental (including Clinical) testing of the TAXUS Express² Paclitaxel-Eluting Coronary Stent System was conducted using *Taxus brevifolia* as the source of paclitaxel. The source of paclitaxel planned for commercially available stent systems is *Taxus x media Rehder*, a human-produced hybrid which does not exist in the wild. The environmental issues associated with this application are therefore primarily related to "Use of Flora or Fauna," specifically related to the *Taxus brevifolia* source used in development. Information is presented in **Section 6.2** below. The paclitaxel was harvested under strict guidelines. No harvesting took place in sensitive areas such as protected habitats or primitive and scenic areas (Refer to Drug Master File #9765).

In no case will the source for commercially available product be obtained from biomass harvested from wild trees.

6.1 Assessing Toxicity to Environmental Organisms

Assessing toxicity to environmental organisms is not relevant to this PMA application because the estimated concentration of the substance at the point of entry into the aquatic environment will not be more than 1 part per billion, FDA's approval of the PMA will not alter significantly the concentration or distribution of paclitaxel, its metabolites, or degradation products in the environment, and at the expected level of exposure, there is no potential for serious harm to the environment. See **Confidential Attachment 2** for Expected Introduction Concentration Calculation (EIC).

6.2 Use of Flora or Fauna

This section of the Environmental Assessment will focus on information regarding the source of the biomass for the developmental testing, the mitigation measures associated with the harvesting of the biomass for the developmental testing, and a discussion of the reasonable alternatives.

6.2 Use of Flora or Fauna, Continued

a. Use of Resources

Overview

Paclitaxel used in developmental testing of TAXUS Express² is a natural product that was extracted, isolated and purified from biomass (bark) obtained from the wild Pacific Yew tree (*Taxus brevifolia*) and was supplied by Hauser Chemical. The bark obtained from the Pacific Yew is not a renewable resource. However, as noted above, the biomass obtained from the wild Pacific Yew tree was only used for developmental testing, and, in total, less than 4 kg was purchased. In no case will additional paclitaxel be obtained from this source in the future.

From 1992-1994, the primary company harvesting Pacific Yew for Hauser Chemical was Hauser Northwest, based in Cottage Grove, Oregon. This company dissolved at the end of 1994, and in 1995-96 was replaced by a company called Adverse, Inc., also based in Cottage Grove. The raw materials from which paclitaxel was extracted were contained in a reserve inventory of Pacific Yew bark that was collected prior to November 18, 1996, by or on behalf of Hauser, in accordance with the requirements of the Pacific Yew Act, 16 U.S.C. § 4801-4807, the Pacific Yew Final Environmental Impact Statement (FEIS) published in August 1993 by the U.S. Department of Agriculture (USDA) Forest service and under permits validly issued by the U.S. Forest Service or Bureau of Land Management (BLM), as applicable. In the course of such bark collection activities, all of the mitigation measures specified in the FEIS and in "An Interim Guide to the Conservation and Management of Pacific Yew" (USDA, March, 1992) were employed. Where bark was sourced from private lands, all required state permits applicable to bark collection were also obtained. This reserve inventory has been exhausted, to the best of my knowledge, and, in any case, will not be used to supply bulk drug substance in the future for Boston Scientific Corporation. A new source will be used for incorporating into commercial product from an alternative cultivated biomass source (see **Section 8**).

last harvest of bark

Geographic Region of Harvest

Harvest of Pacific Yew for paclitaxel production on public and private land was conducted under permit during the period 1992-1996. The last date of harvest on federal land occurred at the end of the harvest season (late fall), 1993. The last date of harvest on private land was in November of 1996. All harvesting activities on state lands were completed prior to September 1996. Harvest of yew took place on public and private lands in the states of Oregon, Washington, Idaho, and Montana, and on private lands in the state of California. See **Attachment A** for a list of yew harvest permitters to Hauser Northwest and Adverse Inc.

6.2 Use of Flora or Fauna, Continued

a. Use of Resources, **Continued**

Government Oversight and Method of Harvest

During the five years that yew was harvested, the harvesting companies obtained all required permits from federal, state, and private landowners. Permits were obtained prior to all harvest that was conducted. Permits stipulated the conditions of the harvest and provided a legal contract vehicle between the landowner and either Hauser Northwest or Adverse, Inc. The flowchart in Figure 1, **Attachment B** provides an overview of the entire process of paclitaxel production from yew tree harvesting to manufacturing.

The harvesting from all private, state and federal land was conducted in accordance with all applicable federal, state and local laws, regulations and guidances. Of the states mentioned, harvesting from state lands only occurred in Washington and Montana.

Given the large number of permitters (**Attachment A**), required information, including the permitting process, harvesting guidelines, and harvest methods, is provided by permitting authority: state agencies or federal agencies.

1. State and Private Owned Lands:

Government Oversight

Harvest of Pacific Yew on private and state lands is regulated under state legislation. An outline of governmental oversight agencies and the regulatory permitting authority/Act are provided in Table 1, below.

Table 1
Government Oversight Agencies and Permitting Authorities/Acts

State	Government Oversight Agency	Regulatory Permitting Authority	Act
Oregon	Oregon Department of Forestry	Sate Forest Practices Acts and Rules of Oregon	(ORS 527.610 and OAR Chapter 629)
Washington	Washington Department of Natural Resources	State Forest Practices Acts and Rules of Washington	(RCW 76.09 and WAC 222)
Idaho	Idaho State Department of Lands	State Forest Practices Acts and Rules of Idaho	(Title 38 Chapter 13 of Idaho Code and IDAPA 20.02.01)
California	California Department of Forestry and Fire Protection	State Forest Practices Acts and Rules of California	California (Title 14 CCR, Chapters 4 and 4.5 and PRC 4511-4628)
Montana	Montana State Department of Lands	Montana Environmental Policy Act	Act (MEPA – MCA 75-1-101-75-1-324 and ARM 26.2.628-26.2.663)
		Streamside Management Zone Act	(SMZ Law – MCA 77-5-301 – 77-5-3076, ARM 26.6.610).

6.2 Use of Flora or Fauna, Continued

***a. Use of Resources,* Continued**

Permitting Process and Harvesting Guidelines

In Washington State, yew harvest occurred on both privately owned lands and state trust lands. Harvest on privately owned land was exempt from requiring a Forest Practices Act permit due to the non-commercial nature of the harvest. Private landowners, such as Champion International Corp., required Hauser Northwest to obtain a special forest products permit from Washington State Department of Natural Resources (DNR). DNR had authority to inspect the harvest, but probably did so infrequently. Hauser Northwest conducted inspections on each harvest and filed reports internally. For harvest on state trust lands, DNR completed a State Environmental Policy Act (SEPA) checklist and issued a determination of non-significance. DNR issued permits to Hauser Northwest to harvest yew according to a specific set of operating requirements outlined in the contract (**Attachment C**). Hauser Northwest carried the primary responsibility for inspection of these harvests.

Similar processes were used in the states of Oregon, California, Idaho, and Montana. The harvest on private lands was authorized by landowners and subject to conditions of permits between landowners and Hauser Northwest (see example permit in **Attachment D**). In Oregon, the State Department of Forestry required landowners to file a Notification of Intent to Harvest Timber. Upon submitting this notice, a landowner implied consent to the State Forester to inspect the harvest operation for Forest Practices Act compliance. Landowners in California were required to notify the Department of Forestry and Fire Protection of the intent to harvest yew, and were issued exemption notices by the Department. These notices exempted the landowner from filing a timber harvesting plan but specified that compliance with all provisions of the Forest Practices Act would be required and inspections would be performed. Harvest on state lands in Montana was subject to environmental analysis under the Montana Environmental Policy Act. The Montana Department of Natural Resources conducted an analysis for each of two areas where yew harvest was later permitted. Harvest on private lands in Montana was not regulated by DNR, but was required to comply with the state's Streamside Management Zone Act. Harvest on private lands in Idaho was regulated similarly to that in Washington state. Permits issued by private landowners required compliance with the state Forest Practices Act, under the authority of Idaho State Department of Lands.

6.2 Use of Flora or Fauna, Continued

a. Use of Resources, **Continued**

Harvest Methods

Harvest of yew bark was conducted in a similar manner under most of the permits that were issued. Typically, yew harvest took place prior to a commercial timber harvest. Hauser Northwest initially received permission from landowners to conduct inventories for Pacific Yew on their land. Based on these inventories, Hauser proposed areas suitable for harvest to the landowner. Permits were issued and subcontractors were hired to conduct the harvest. A collector packet was issued to each subcontractor detailing the method of harvest to use (see Collector Packet in **Attachment E**). The standard method of harvest involved cutting of yew trees that were greater than three inches in diameter at stump height (approximately 12 inch above the ground). Trees having a diameter of less than three inches were left for regeneration. Cutting was done with chain saws. The typical operation involved a single cutter followed by four or five peelers who came through and peeled bark from the cut portion of the tree using hand peeling tools. Peeled bark was loaded by hand into 50 lb. bags, tied with twine, and carried to an established loading site for transportation to the dryer. All bags were ticketed with identification numbers that could be used to trace the bark to the permit under which it was harvested. This enabled verification of legal harvest.

2. Federal Lands:

Government Oversight

Harvest of Pacific Yew on Federal lands occurred under governmental oversight as outlined in Table 2, below.

Table 2
Government Oversight Agencies/Permitting Authorities and Act

Agencies Permitting Authority	Act
National Forest and Bureau of Land Management (BLM) in Oregon, Washington, Idaho, and Montana	The Pacific Yew Act, 16 U.S.C. □˜□˜ 4801-4807

6.2	**Use of Flora or Fauna, Continued**

***a. Use of Resources,* Continued**

Permitting Process and Harvesting Guidelines

Permits to harvest Pacific Yew were issued on National Forest and Bureau of Land Management (BLM) lands in Oregon, Washington, Idaho, and Montana. These agencies developed yew programs that were carried out at the local level and were closely monitored. An Interim Guide to the Conservation and Management of the Pacific Yew (USDA Forest Service 1992) was the guiding document used to establish Forest Service harvest programs. The BLM issued Pacific Yew Administrative Policies in 1992 as a guide to administering the yew harvest for that agency. These agencies were responsible for ensuring that harvest would be conducted according to agency guidelines as mandated by The Pacific Yew Act, 16 U.S.C. § 4801-4807. This often involved extensive on-the-ground inventory and assessment before any harvest was planned.

Once internal planning had taken place, District offices issued Administrative Use Permits for Yew Harvest to Hauser Northwest (see example in **Attachment F**). These permits specified the exact location harvest was to take place, the quantity of yew bark to be harvested, and specific instructions for conducting the harvest. These instructions included a detailed description of the ticketing process used for accounting of all yew that was transported, and provisions for the protection of other resources such as streams, cultural resources, fire, and wildlife.

Provisions of the contracts were passed on to the individual collectors under contract with Hauser Northwest. A collector packet was issued to all collectors, with detailed specifications for conducting the harvest. Inspection of harvest was made by both Hauser Northwest and the government inspectors. Work that did not meet specifications was required to be redone or, in some cases, the contract was terminated. Examples of Forest Service inspection reports are in **Attachment F**.

Harvest Methods

Harvest of Pacific Yew on federal land was conducted in association with the commercial timber sale program. Generally, areas that were to be harvested for Pacific Yew were either previously harvested for timber (such as through clearcutting or selective cutting), or were planned to be harvested for timber immediately following the yew harvest. In 1992, approximately half of the harvest sites were in clearcuts or otherwise harvested units. By 1993, nearly 90 percent of the harvest was conducted in units prior to commercial harvest of timber.

6.2 Use of Flora or Fauna, Continued

a. Use of Resources, **Continued**

The standard method of harvest involved cutting of yew trees that were greater than three inches in diameter at stump height (approximately 12 inch above the ground). Trees having a diameter of less than three inches were left for regeneration. Other restrictions were sometimes imposed on the harvest. For example, some contracts specified cutting only half of the harvestable trees. Many entailed leaving yew in green tree retention clumps within the harvest unit. Cutting was done with chain saws. The typical operation involved a single cutter followed by four or five peelers who came through and peeled bark from the cut portion of the tree using hand peeling tools. Peeled bark was loaded by hand into 50 lb. bags, tied with twine, and carried to an established loading site for transportation to the dryer. All bags were ticketed with identification numbers that could be traced to a permit for verification of legal harvest.

In most cases, felled and stripped yew trees were left on site; however, in at least one case where bark was not stripped immediately, trees were yarded and loaded onto trucks for transport to debarking facilities. There, the difficult to detach bark was stripped from the tree by machine. This method proved more costly than hand-peeling and was not done frequently. Another method that was also not used frequently (possibly only done in one case), was to leave yew trees standing and harvest the bark by stripping only a portion of it from living trees, leaving the rest of the bark intact. This occurred in one incident on federal land in southern Oregon.

Endangered Species and Yew

The Pacific Yew is not listed under the Federal Endangered Species Act (ESA), or under the Convention on International Trade in Endangered Species (CITES) as endangered or threatened. The Pacific Yew does comprise a component of habitat for several federally listed threatened or endangered animal species. This list appears in Appendix J of the Pacific Yew DEIS (USDA Forest Service et al. 1993) and has been reproduced in **Attachment G** of this document. As previously described in this section, Pacific Yew trees were harvested from lands in Oregon, Washington, Idaho, Montana and California. Within each of these states it was necessary for the harvesters to abide by all federal, state and local regulations and guidances that were intended to provide protection to endangered or threatened species under circumstances that would have included harvesting Pacific Yew.

6.2 Use of Flora or Fauna, Continued

a. Use of Resources, Continued

Idaho had no specific state or local laws pertaining to protection of endangered or threatened species. Montana had an endangered species act that was superseded by the federal law. Within these states, the Federal Endangered Species Act formed the basis of the restrictions on harvesting to protect endangered or threatened species. California (California Endangered Species Act), Oregon (ORS 564 and ORS 496.171-192) and Washington (Washington Endangered, Threatened, Sensitive Wildlife Species Classification) have specific state laws pertaining to identification and protection of endangered or threatened species. These state laws, in combination with the Federal Endangered Species Act, formed the basis of the restrictions on harvesting to protect the endangered or threatened species.

Within these states, permits were obtained for specific harvesting plans. State inspectors verified that the harvesting was being conducted in areas absent of endangered species. Some permits or harvest contracts granted by the states also listed applicable restrictions to the land use where endangered species lived.

For example, the Harvest Contract granted by the State of Washington Department of Natural Resources was included in Appendix C of the April 2, 1999 Major Amendment beginning on page 700022. On page 700027, under Section 7 Operating Requirements, numbers 7 and 8 both place restrictions on how close harvesting is allowed to any forest stand known to be occupied by marbled murrelets (no closer than 0.25 miles) and any known spotted owl site centers (no closer than 0.7 miles).

Hauser has certified that the harvesting of paclitaxel used in developmental testing of the TAXUS Express² Paclitaxel-Eluting Coronary Stent System complied with all state, local and federal regulations and guidances that were intended to provide protection to endangered or threatened species under circumstances that would have included harvesting Pacific Yew (refer to **Confidential Attachment 4**).

b. Mitigation Measures

Standard Mitigation

Standard mitigation measures on all land ownerships were included in the Hauser Northwest Collector Packet (**Attachment E**). These included leaving 12 inch stumps with bark intact (to increase the chances of regeneration through sprouting), leaving all suckers below the cut to increase the stump's chances of survival, and peeling only trees three inches in diameter and greater, leaving smaller trees to revegetate the area. Hauser Northwest personnel were responsible for inspecting for compliance with these guidelines. Inspection reports were completed and filed with Hauser Northwest. Inspection reports available in the files demonstrate a high rate of compliance. *See **Section 7** for more information.*

6.2	Use of Flora or Fauna, Continued
c. Alternatives to the Proposed Action	No further Pacific Yew will be collected for this product and any future supplies of paclitaxel will either come from non-endangered wild species or cultivated yew. At this time we have not selected a future alternate source. *See* ***Section 8*** *for more information.*

7. Mitigation Measures

State and Private Lands

As explained previously, no future harvest will occur. Most permits required some form of resource protection through mitigation or conservation measures. For example, the state of Washington issued operating requirements that included: no harvest of yew where the density of yew is less than five trees/acre, no harvest of yew within 0.25 miles of any forest known to be occupied by marbled murrelets, no yew harvest within 0.7 miles of any known spotted owl site center, and no yew harvest within 75 feet of perennial streams (**Attachment C**). Hauser Northwest was responsible for compliance with these operating requirements and final oversight authority rested with the Washington State Department of Natural Resources.

Federal Lands

Mitigation measures for yew harvest on federal lands were addressed in Appendix C of the Pacific Yew Draft Environmental Impact Statement (USDA Forest Service et al. 1993). Many of these measures were pre-emptive; rather than "repairing, rehabilitating, or restoring the resource," they conserved the resource through actions such as green-tree retention and leaving of stumps and saplings.

Measures required by the Forest Service Interim Guidelines are listed below:

- Establish genetic reserves.
- Include vigorous, undamaged, yew trees in the green-tree reserve whenever possible.
- No harvesting of yew trees less than three inches in stump diameter.
- All yew stumps should have intact bark and should be shaded with slash or adjacent vegetation. All stumps should be at least 12 inches high. Avoid damaging stumps.
- Where possible, position green trees to provide shade for yew stumps and advance yew regeneration.
- Favor logging systems and slash disposal methods that protect residual yew trees.
- No harvest within 75 feet of the average high water level of perennial streams.
- Incorporate spotted owl management guidelines within ¼ mile of active spotted owl nests.
- If harvesting outside of a timber sale unit, leave 50% of yew trees, or 5 trees per acre minimum.
- Apply special local restrictions if harvest is within ungulate winter range.
- Regenerate with sprouts, layers, cuttings, or seedlings to achieve at least the yew density estimated to have been present in the preharvest stand.

7. Mitigation Measures, Continued

Other Measures

Other measures were sometimes required by local Forest Service offices. For example, on the Butte Falls Ranger District, Rogue River National Forest, a special prescription for yew retention based on wildlife value was written (**Attachment H**). This required patches of 10-15 trees to be retained approximately every acre within harvest units.

The federal agencies were ultimately responsible for ensuring mitigation measures were implemented. Some measures were performed by the government and others by Hauser Northwest. The Mt. Hood National Forest in Oregon had a large Pacific Yew harvest program and can be used to illustrate the implementation of the Interim Guide with respect to mitigation measures.

One of the first actions taken prior to permitting yew harvest on the Mt. Hood National Forest was the establishment of genetic reserves where yews would be protected. This occurred as outlined in the Interim Guidelines. Timber sale units with abundant yew that occurred outside of genetic reserves were then planned for permitting yew harvest. The amount and quality of yew, as well as the likelihood of regeneration, were assessed prior to permitting. Within the units, green-tree reserves were established by the Forest Service to protect a portion of the yew trees from harvest. During harvest, Hauser Northwest and its contractors were responsible for implementing other mitigation measures such as leaving bark on stumps, providing shade for resprouting, and prohibiting harvest within riparian reserves. These measures were monitored by the Forest Service for compliance and documented on inspection report forms. The final measure to regenerate yew with sprouts, cutting, layers, or seedlings was the responsibility of the Forest Service. This was done as nursery stock supplies allowed. Most sites were regenerated naturally, due to lack of nursery stock for planting.

7. Mitigation Measures, Continued

Conclusion

In the course of such bark collection activities, all of the mitigation measures specified in the FEIS and in "An Interim Guide to the Conservation and Management of Pacific Yew" (USDA, March, 1992) were employed. Standard mitigation measures on all land ownerships were included in the Hauser Northwest Collector Packet (**Attachment E**). These included leaving 12 inch stumps with bark intact (to increase the chances of regeneration through sprouting), leaving all suckers below the cut to increase the stump's chances of survival, and peeling only trees three inches in diameter and greater, leaving smaller trees to revegetate the area. Hauser Northwest personnel were responsible for inspecting for compliance with these guidelines. Inspection reports were completed and filed with Hauser Northwest. Inspection reports available in the files demonstrate a high rate of compliance. Therefore, all mitigation measures required of Hauser, by federal, state and local governmental authorities, were accomplished.

8. Alternatives to the Proposed Action

Data supporting the proposed action in this application included the use of a supply of Pacific Yew bark (less than 4 kg) that was collected prior to November 1996 which was utilized in product used for developmental testing. No further Pacific Yew will be collected for this product and none of the Pacific Yew supply will be used on commercial product. In choosing a source for commercial product the following alternatives could be considered:

Alternative 1: It is possible to synthetically produce paclitaxel. This option would prevent the harvesting of any flora and would be expected to be of lesser environmental impact than harvesting options. However, no viable synthetic supply meeting Quality requirements has been identified at this time for evaluation. This option is therefore not viable at this time from a business standpoint.

Alternative 2: It is possible to extract paclitaxel from non-endangered wild species such as *Taxus yunnanensis*, *Taxus baccata* and *Taxus cuspidata*. As above, no viable supply meeting Quality requirements has been identified at this time for evaluation. In addition to business factors, several environmental factors would also require consideration before proposing this route as a commercial alternative. Environmental factors include confirmation that harvesting will be done within local, state and federal forestry and endangered species laws and that any other effects from the harvesting of these trees on the local ground and water habitats will be limited.

8. Alternatives to the Proposed Action, Continued

Alternative 3: It is possible to extract paclitaxel from cultivated yew species such as *Taxus Hicksii*, *Taxus media* and *Taxus x media Rehder*. A new supply of paclitaxel from cultivated yew (*Taxus x media Rehder*) has been identified and tested for use and will be used exclusively in the product for commercial release. An Environmental Assessment conducted by the manufacturer is included in **Confidential Attachment 3** for your information. Environmentally, this alternative is attractive, as the cultivated species are harvested from privately controlled plantations, thus assuring that no local, state and federal endangered species laws will be violated. The environmental impact on the local ground and water habitats is also easier to monitor and control. From an environmental standpoint, the use of cultivated yew species is preferable to harvesting on non-endangered wild yew species.

Alternative 4: Non-approval of this application for environmental reasons is not warranted because:

- No paclitaxel derived from Pacific Yew will be used in commercial product.
- The paclitaxel gathered from Pacific Yew used in developmental testing had already been harvested (ie. trees already harvested and paclitaxel extracted) and no further Pacific Yew will be harvested.
- Non-approval would deny the patient population another viable alternative to standard non-drug-eluting stents.

Therefore, non-approval of this application would not provide any benefit to the environment beyond that of approval of the application.

9. List of Preparers

Name:
Douglas E. Ferguson

Job Title:
Manager, Corporate Regulatory Affairs,
Boston Scientific Corporation

Qualifications:
12 years Regulatory experience

10. References

1. Pharmaceutical Manufacturers Association, *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA.* July, 1991.

2. U.S. Food and Drug Administration, *Environmental Technical Assistance Handbook*, PB87-175345, U.S. Department of Commerce National Technical Information Service, Springfield, VA. 1987

3. Center for Drug Evaluation and Research, *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July 1998).

4. *Notice for Paclitaxel Drug Products; Environmental Information Needed in New Drug Applications, Abbreviated New Drug Applications, and Investigational New Drug Applications* (Federal Register, November 18, 1996).

5. Pacific Yew, Draft Environmental Impact Statement (EIS), USDA Forest Service in Cooperation with USDI Bureau of Land Management and USDHHS Food and Drug Administration, 1992.

6. USDA Forest Service. 1992. An Interim Guide to the Conservation and Management of Pacific Yew. 72 pp.

7. USDA Forest Service, USDI Bureau of Land Management, and DHHS Food and Drug Administration. 1993. Pacific Yew Draft Environmental Impact Statement.

8. Non-Confidential Environmental Assessment for paclitaxel injection, Paxene® (Abbreviated New Drug Application 75-184), Baker Norton Pharmaceuticals, Inc. 2000.

11.	Attachments

Non-Confidential Attachments

Attachment A Partial List of Yew Harvest Permitters to Hauser Northwest and Adverse, Inc.

Attachment B Flow Chart of Yew Bark from Raw Material to Manufacturing

Attachment C Washington State Department of Natural Resources Pacific Yew Harvest Contract

Attachment D Example Yew Harvest Permit – Private Landowner.

Attachment E Hauser Northwest Collector Packet

Attachment F USDA Forest Service Example Yew Harvest Permit and Inspection Report

Attachment G Threatened & Endangered Species Possibly Affected by Pacific Yew Harvest

Attachment H Pacific Yew Harvest Wildlife Mitigation on Rogue River National Forest

Confidential Attachments

Attachment 1 Authorization Letters to Access Paclitaxel Source Drug Master Files

Attachment 2 Expected Introduction Concentration Calculation.

Attachment 3 *Taxus x media Rehder* Source Information

Attachment 4 Hauser Certification Information