CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-262/S-026, 027, 028

CHEMISTRY REVIEW(S)

APR - 2 1998

CHEMISTRY REVIEW

Division of Oncology Drug Products

Labeling Review

TYPE AND NUMBER OF APPLICATION : NDA 20-262/S-026 & S-028
LABELING SUB. : 2/19/98 (S-026) & 11/18/97 & 1/9/98 (S-028) ASSIGNED DATE: 3/27/98

STATUS OF APPLICATION: Active
NAME OF SPONSOR: **Bristol-Myers Squibb**
PRODUCT NAME: Taxol (paclitaxel) Injection
Proprietary: TAXOL®
Nonproprietary: paclitaxel
CHEMICAL STRUCTURE:

DOSAGE FORM, STRENGTH, AND ROUTE OF ADMINISTRATION:
Intravenous Injection, 6 mg/mL, 30 mg (5 mL) , 100 mg (16.7 mL),

PROPOSED MARKETING STATUS: Rx

PHARMACOL. CATEGORY/ INDICATION:
antimicrotubule agent, antitumor.

Package Insert:

Comments: NDA 20-262/S-013 requested the change in storage temperature to controlled temperature This change was supported by stability data. The range °C is within the temperature range provided in Supplement No. 13. From a CMC view point, this new range is acceptable.

The statement in the original package insert is replaced by

Comments: The following statement

... ... remain unchanged. This statement is of importance, since it further explains the state of the components in the vial as it relates to stability. From a CMC point of view, this change is acceptable.

Storage:
The temperature range is changed compared to the approved package insert, from to

Comments: Please see comments in the **Stability** section.

HOW SUPPLIED

/S/ , 4/2/98
Review Chemist, DNDC I, (HFD-150)

cc:
ORIG. NDA 20-262/S-026 & S-028
HFD-150/Div. File
HFD-150/JJee/ 4-02-98
HFD-150/RWood
HFD-150/DSpillman
R/D Init. by: /S/ 4-2-98
Doc. #: 20262s28.lab

SPILLMA

FEB - 3 1998

Chemistry Manufacturing Controls Review

Labeling Review

NDA:	20-262 / SE1-024 & 20-262/SE1-026
Product:	Taxol (paclitaxel)
Applicant:	Bristol-Myers Squibb
Date of Submission:	June 30, 1997 & October 7, 1997
Stamp Data:	August 19, 1997
Date of Review:	February 2, 1998
Material Reviewed:	TAXOL® (paclitaxel) for the Treatment of Advanced Non-Small Cell Lung Cancer (S-024, Vol. 1.2 and 2.2) & Ovarian Cancer (S-026, Vol. 1.2 and 2.2))
Other Documents:	NDA 20-262 and its supplements

Drug Substance

Drug substance by the same manufacturer was approved more recently on March 5,1997.

Manufacturer and Site

BMS-Swords and BMS Syracuse.

Method of Synthesis

More recently submitted in DMF

Specifications and Methods

More recently submitted in Supplement 17.

Stability Data.

Submitted in Supplement 17.

Drug Product

Refer to NDA 20-262 and its supplements.

Environmental Assessment (EA)

Found satisfactory by N. Sager on 11/6/97.

Labeling:

Submitted on Vol. 1 under section of Labeling. Description, Dosage and Administration, Preparation and Administration, Preparation for Intravenous Administration, Stability, How Supplied, and Storage sections were not revised.

Conclusions and Recommendations.

No new CMC information is submitted in these supplements. Reference for CMC would have to be from previous approved application/ supplements. These reviews mainly concentrate in the EA and Labeling revisions.

/S/

2/2/98

Josephine M. Jee, Review Chemist, HFD-150, DNDC I

/S/ 2-3-98

Rebecca H. Wood, Ph.D., Chemistry Team Leader, HFD-150, DNDC I

cc:
NDA 20-262/SE1-024 & SE1-26
HFD-150/Division File
HFD-150/JJee/ 2-2-98
HFD-150/RWood
HFD-150/DSpillman
F/T by JJee/ 2-2-98
R/D by:
File: 20262s24.lab

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-262/S-026, 027, 028

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

Spillman

ENVIRONMENTAL ASSESSMENT

NOV - 6 1997

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

TAXOL®

(paclitaxel)

INJECTION

NDA 20-262/S-026

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ONCOLOGY DRUG PRODUCTS
(HFD-150)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-262/S-026

TAXOL® (paclitaxel) INJECTION

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 that an environmental impact statement therefore will not be prepared.

In support of their supplemental new drug application for **TAXOL® (paclitaxel) INJECTION, Bristol-Myers Squibb Company** has prepared an environmental assessment in accordance with 21 CFR Part 25 (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

The supplemental application provides for a new use of TAXOL® as a first line treatment of ovarian cancer. The product is currently approved for use in the treatment of metastatic ovarian cancer after failure of first-line or subsequent chemotherapy and in the treatment of several other forms of cancer. The drug substance will be manufactured by the applicant in Swords, Ireland and Syracuse, New York. Extraction of the starting material from the biomass is performed in Italy. The drug product will be manufactured by the applicant in Mayaguez, Puerto Rico or Latina, Italy. The finished drug product will be used in hospitals and clinics.

The drug substance, paclitaxel, is produced by a semi-synthetic process. The starting material, 10-deacetyl baccatin III, is obtained from either *Taxus baccata* (European yews) or *Taxus wallichiana* (Himalayan yews). Biomass from *Taxus baccata* is collected from plants cultivated in public and private parks and gardens as well as from plantations in Europe. Biomass from *Taxus wallichiana* has been collected in India from wild plants or those cultivated on plantations. Future collection of biomass from *Taxus wallichiana* is not planned unless there is a supply problem with *Taxus baccata* and if performed, collection will only occur from plantation sources. In either case (*Taxus baccata* or *Taxus wallichiana*), renewable resources are used in that only twigs and needles are harvested by supervised, controlled pruning of the plants.

Taxus wallichiana is listed in Appendix II of the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES). Collection of *Taxus wallichiana* biomass used by the applicant occurred prior to the species being listed in CITES. The applicant has stated that the appropriate CITES documentation is obtained from the regional authorities in order to export the material collected from *Taxus wallichiana*. Example CITES documentation was provided to support this statement.

Paclitaxel and/or its metabolites may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. Ecotoxicity data previously submitted by the applicant indicates that, at the expected environmental concentration from use based on all treatement indications, no adverse effects on environmental organisms should be observed.

Disposal in the United States may result from returned, recalled or expired goods and user disposal of empty or partly used product and packaging. Disposal of pharmaceutical waste in the U.S. by the manufacturer will be handled consistent with EPA regulations and permitted disposal facilities will be used. Returned, recalled or expired goods will be sent by the manufacturer to a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

/S/

11/1/97
DATE

PREPARED BY
Nancy B. Sager
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

/S/

11-6-97
DATE

CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachments: Environmental Assessment

c.c. original to NDA 20-262/S-026 through DSpillman/HFD-150 /DNFiles
HFD-357/EA File NDA #20-262/S-026 /DSpillman
HFD-357/Docket File /J.Lee
HFD-205/FOI COPY
OCC (to N. Sager for distribution)

SPILLMAN

REVIEW

NOV - 6 1997

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-262/S-024/S-026

TAXOL®

(paclitaxel)

INJECTION

DIVISION OF ONCOLOGY DRUG PRODUCTS (HFD-150)

CENTER FOR DRUG EVALUATION AND RESEARCH

DATE COMPLETED: November 1, 1997

SUMMARY:

A FONSI is recommended.

EAs have been submitted for efficacy supplements S-024 (non-small cell lung cancer) and S-026 (first line ovarian cancer). A Federal Register notice, Paclitaxel Drug Products; Environmental Information Needed in New Drug Applications, Abbreviated New Drug Applications, and Investigational New Drug Applications, was published in the November 18, 1996 Federal Register [61 FR 58694]. This notice was issued to clarify the environmental information that must be submitted to CDER for drug products containing paclitaxel derived from Pacific Yew trees. The supplemental applications to approved NDA 20-262 cannot be categorically excluded under 21 CFR § 25.31(b) because paclitaxel derived from the bark of Pacific Yew trees (*Taxus brevifolia*) was used in a clinical trial that provides underlying data to support the application.

The EAs submitted are essentially identical to the environmental assessment information submitted in support of NDA 20-262/S-022 for which a FONSI was issued on August 4, 1997. Neither the total use estimate (120 kg) nor biomass source information has changed.

Toxicity of this compound to environmental organisms is not a concern. The expected introduction concentration into the environment for all approved and proposed uses (no consideration of metabolism or depletion mechanisms) is more than 4 orders of magnitude lower than the concentration of paclitaxel observed to cause effects in environmental organisms (acute toxicity testing/ laboratory studies).

The relevant environmental issue relating to this application is whether any increase in harvesting that may occur as a result of the approval for this new indication will have a significant environmental impact. The starting material, 10-deacetyl baccatin III, is obtained from either *Taxus baccata* (European yews) or *Taxus wallichiana* (Himalayan yews). Biomass from *Taxus baccata* is collected from plants cultivated in public and private parks and gardens as well as from plantations in Europe. Biomass from *Taxus wallichiana* has been collected in India from both wild plants or those cultivated on plantations. Future collection of biomass from *Taxus wallichiana* is not planned unless there is a supply problem with *Taxus baccata* and if performed, collection will only occur from plantation sources. In either case (*Taxus baccata* or *Taxus wallichiana*), renewable resources are used in that only twigs and needles are harvested by supervised, controlled pruning of the plants.

Taxus wallichiana is listed in Appendix II of the Convention on International Trade in Endangered Species of Wild Flora and Fauna (CITES). Listing in CITES does not prohibit harvesting but provides for heightened oversight of harvesting and export/import of material. Local officials, the Ministry of Forests and the Department of Forests, oversee the harvesting of the needles and twigs by issuance of a "Harvesting" permit. It is stated that IDENA obtains relevant documentation, as required by CITES, to export the biomass to Italy for further processing. CITES documentation was provided to support this statement. Collection of *Taxus wallichiana* biomass occurred prior to the species being listed in CITES and if any more biomass is collected it will be from plantations.

No significant environmental impact is anticipated based on (1) the supervised, controlled harvesting of the biomass, (2) the use of a renewable source of biomass (pruned twigs and leaves), (3) future biomass collection is planned only from cultivated sources, and (4) the information indicating that there is/has been appropriate government oversight, when necessary, of the harvesting.

ENVIRONMENTAL ASSESSMENT

1. Date:

EA dated: 9/4/97 (S-024)
EA dated: 9/5/97 (S-026)

CSO: Diane Spillman

2. Name of applicant/petitioner:

Bristol Myers Squibb Company

3. Address:

P.O. Box 4000
Princeton, NJ 08543-4000

Note:
The environmental information provided in support of NDA 20-262/S-024 (non-small cell lung cancer) and S-026 (first line ovarian cancer) is essentially identical to the information provided and reviewed for NDA 20-262/S-022. A FONSI was issued for NDA 20-262/S-022 on August 4, 1997. BMS, on October 27, 1997, provided an outline of the differences among the EA information provided in the supplements. The changes are mostly administrative. Neither the total use estimate (120 kg) nor biomass source information has changed. Only the differences between the new supplements and S-022 are documented in this review. Refer to the reviews for S-022 for the detailed environmental review.

1. The EAs have been revised to indicate the new indications that are proposed.

Adequate.

2. Information has been added for an alternate manufacturing site for the drug product (Latina, Italy). A certification of environmental compliance has been provided in a confidential appendix. In the past the applicant would have been asked to move this type of information to a non-confidential appendix. However, since under the new EA regulations manufacturing site information is not needed unless there is an extraordinary circumstance (and there is no evidence of an extraordinary circumstance), inclusion of

this information in a confidential appendix will not be cited as a deficiency.

Adequate.

3. Information that BMS submitted as an addendum to the EA for S-022 has been incorporated into the text.

Adequate.

Endorsements:

HFD-357/NBSager 11/1/97

HFD-800/EBSheinin 11-6-97

CC: Original to NDA 20-262/through PM: D. Spillman/HFD-150
HFD-150 / Div File / D. Spillman / J. Lee
EA File 20262

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-262/S-026, 027, 028

PHARMACOLOGY REVIEW(S)

See the 2-3-98 Pharm/Tox & the 2-3-98 & 4-2-98 Chemistry Labeling Reviews under the Pharmacology and Chemistry Review tabs.

Spillman

FEB - 3 1998

DIVISION OF ONCOLOGY DRUG PRODUCTS, HFD-150
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
NDA Supplemental Indication

SNDA Nos. 20,262/SE1-024
20,262/SE1-026

Date(s) of Submission: June 30, 1997
October 7, 1997

Information to be Conveyed to Sponsor: YES

Reviewer: Margaret E. Brower, Ph.D.

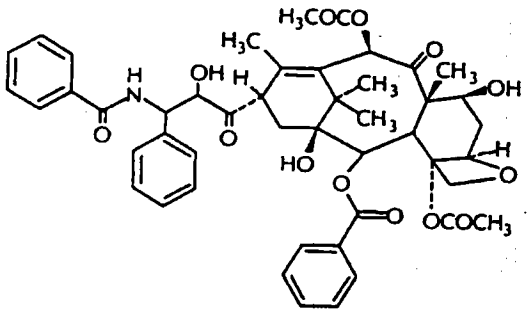
Date Review Completed: February 3, 1998

Sponsor: Bristol-Meyers Squibb
Wallingford, CT

Drug Name: Primary: Paclitaxel
Other names: Taxol

Chemical Name: 5β, 20-Epoxy-1, 2α, 4, 7β, 10β, 13α-hexahydroxytax-11-en-9-one 4, 10-diacetate 2-benzoate 13 ester with (2R,3S)-N-benzoyl-3-phenylisoserine

Structure:



CAS Number: 33069-62-4

Molecular Weight and formula: 853.9, $C_{47}H_{51}NO_{14}$

Related INDs/NDAs:NDA 20-261

Pharmacologic Class: cytotoxic antineoplastic agent

Indication: Non-small cell lung cancer, 1st line treatment of ovarian cancer

Comments:
1. The proposed label for the NSCLC indication for Taxol

These changes should be incorporated.

2. Since specific clinical data on paclitaxel overdosing are available, these data should be incorporated into the overdosage section of the label. If these data are not available, preclinical data should be added.

3. The drug label has been reviewed. All other pharmacology/toxicology data have been previously reviewed.

/S/

Margaret F. Brower, Ph.D.

2/3/98
Date

cc:
NDAORIG. and Div.File
HFD-150
/PAndrews
/MBrower
/DSpillman

2/3/98