CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-190

Generic Name: Paclitaxel Injection, 6mg/mL and 300mg/mL

Sponsor: Bedford Laboratories

Approval Date: January 28, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-190

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-190

APPROVAL LETTER

ANDA 75-190

JAN 28 2002

Bedford Laboratories
Attention: Molly Rapp
270 Northfield Road
Bedford, Ohio 44146

Sent by Facsimile and U.S. Mail

Dear Ms. Rapp:

This is in reference to your abbreviated new drug application dated August 21, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Paclitaxel Injection, 6 mg/mL (packaged in 30 mg/5 mL, 100mg/16.7 mL, and 300 mg/50 mL multiple-dose vials).

Reference is also made to your amendments dated October 20, 1999; June 16, 2000; and January 24, May 15, May 25, May 30, June 8, June 13, and July 25, 2001, your approval letter dated July 27, 2001, any intervening supplements that were approved, and the rescission of your approval and Tentative Approval dated January 25, 2002.

The listed drug product referenced in your application, Taxol® Injection of Bristol Myers Squibb Co. Pharmaceutical Research Institute, is subject to periods of patent protection which expire on August 3, 2012, [U.S. Patent No. 5,641,803 (the '803 patent), and U.S. Patent No. 5,670,537 (the '537 patent)]; May 08, 2001,[U.S. Patent No. 6150398 (the '398 patent); and March 9, 2013 [U.S. Patent No. 5,496,804 (the '804 patent)]. Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Paclitaxel Injection will not infringe on the '803, '804, or '537 patents. Your application also contains a statement under Section 505(j)(2)(A)(viii) of the Act indicating that the '398 patent is a methods of use patent, and that your labeling does not claim the indications or methods of use covered by this patent. You have informed the Agency that Bedford Laboratories has complied with the requirements of Section 505(j)(2)(B) of the Act and that

Bristol Myers Squibb Co. Pharmaceutical Research Institute initiated a patent infringement suit against you in the United States District Court for the District of New Jersey with respect to the '803 and '537 patents (Bristol Myers Squibb Company v. Boehringer Ingelheim Corp., Ben Venue Laboratories, Inc. and Bedford Laboratories, Civil Action No. 97CV-6050(WHW). The Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired.

Taxol® is also covered by periods of Waxman-Hatch exclusivity, D-57, I-270, I-226 and I-230; and Orphan Drug Exclusivity (ODE) that are listed in Approved Drug Products with Therapeutic Equivalence Evaluations, 21st Edition (Orange Book). You have made a statement that your labeling for paclitaxel injection does not claim the indications or methods of use covered by such exclusivity.

Please note that on January 17, 2002, Bristol Myers Squibb withdrew the listing of U.S. Patent No. 6,096,331. This patent is no longer listed in the Orange Book for Taxol®, the RLD identified in your ANDA. Therefore, you are not required to submit a certification under section 505(j)(2)(A)(vii) of the Act for this patent.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Paclitaxel Injection, 6 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Taxol® Injection, 6 mg/mL, of Bristol Myers Squibb Co. Pharmaceutical Research Institute).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the changes may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 1/25/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-190

TENTATIVE APPROVAL LETTER

41 7/25/01

ANDA 75-190

25 2002

Bedford Laboratories
Attention: Molly Rapp
270 Northfield Road
Bedford, Ohio 44146

Sent by Facsimile and U.S. Mail

Dear Ms. Rapp:

This is in reference to your abbreviated new drug application (ANDA) for Paclitaxel Injection, 6 mg/mL, packaged in 30 mg/5 mL, 100 mg/16.7 mL, and 300 mg/50 mL multiple-dose vials, dated August 21, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act (Act). This letter is to inform you that, in light of the January 24, 2002, Order entered by Judge Colleen Kollar-Kotelly in *ABI v. Thompson*, Civil Action No. 02247 (CKK), in the U.S. District Court for the District of Columbia (Order), the final approval given to Bedford Laboratories on July 27, 2001, for this application, including all amendments and supplements thereto, is hereby rescinded.

The January 24, 2002, Order is attached. It is based upon a finding that U.S. Patent No. 6,096,331 was timely filed under section 505(c)(2) of the Act at the time your ANDA was approved. Because, at that time, ANDA 75-190 did not contain a patent certification as required by section 505(j)(2)(A)(vii) of the Act, it did not meet the statutory standard for approval. Therefore, pursuant to the Order, the Agency finds that the final approval for this application, including all amendments and supplements thereto, is rescinded.

The Agency notes, that based upon the information you have presented to date, the drug described in your ANDA is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, i.e., information in your application and the status of current good

manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug products, and is subject to change on the basis of new information that may come to our attention.

The listed drug product referenced in your application (RLD), Taxol® Injection of Bristol Myers Squibb Co. Pharmaceutical Research Institute, is subject to periods of patent protection which expire on August 3, 2012, [U.S. Patent No. 5,641,803 (the '803 patent), and U.S. Patent No. 5,670,537 (the '537 patent)]; May 08, 2011[U.S. Patent No. 6150398 (the '398 patent)]; and March 9, 2013 [U.S. Patent No. 5,496,804 (the '804 patent)]. Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Paclitaxel Injection will not infringe on the '803 '804 or '537 patents. Your application also contains statements under Section 505(j)(2)(A)(viii) of the Act indicating that the '398 patent is a methods of use patent, and that your labeling for paclitaxel injection does not claim the indications or methods of use covered by this patent. You have informed the Agency that Bedford Laboratories has complied with the requirements of Section 505(j)(2)(B) of the Act and that Bristol Myers Squibb Co. Pharmaceutical Research Institute initiated a patent infringement suit against you in the United States District Court for the District of New Jersey with respect to the '803 and '537 patents (Bristol Myers Squibb Company v. Boehringer Ingelheim Corp., Ben Venue Laboratories, Inc. and Bedford Laboratories, Civil Action No. 97CV-6050(WHW). The Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired.

Taxol® is also covered by periods of Waxman-Hatch exclusivity, D-57, I-270, I-226 and I-230; and Orphan Drug Exclusivity (ODE) that are listed in Approved Drug Products with Therapeutic Equivalence Evaluations, 21st Edition (Orange Book). You have made a statement that your labeling for paclitaxel injection does not claim the indications or methods of use covered by such exclusivity.

Please note that on January 17, 2002, Bristol Myers Squibb withdrew the listing of U.S. Patent No. 6,096,331. This patent is no longer listed in the Orange Book for Taxol®, the RLD identified in your ANDA. Therefore, you are not required to submit a certification under section 505(j)(2)(A)(vii) of the Act for this patent.

Because the Agency is granting a **tentative approval** for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. To reactivate your application, please submit an amendment prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final printed labeling, chemistry, manufacturing, and controls data as appropriate. Please note that this amendment should be submitted even if none of these changes were made. The amendment should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above. Any changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

The drug products that are the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery or introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 301(d) of the Act. Also, until the Agency issues the final approval letter, these drug products will not be listed in the Orange Book.

Please contact Cecelia Parise, R.Ph., Regulatory Policy Advisor to the Director, Office of Generic Drugs, at (301) 827-5845, for further information regarding this issue.

Sincerely yours,

/S/ 1/25/02

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-190

Final Printed Labeling

PACLITAXEL INJECTION
Patient Information

BEDFORD LABORATORIES™

JUL 27 2001

APPROVED

What is PACLITAXEL?

PACLITAXEL Is a prescription cancer medicine, it is injected into a vein and it is used to treat different types of tumors. The tumors include advanced ovary and breast cancer.

What is cancer?

Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood.

A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

How does PACLITAXEL work?

PACLITAXEL is a type of medical treatment called chemotherapy. The purpose of chemotherapy is to kill cancer cells or prevent their growth.

All cells, whether they are healthy cells or cancer cells, go through several stages of growth. During one of the stages, the cell starts to divide. PACLITAXEL may stop the cells from dividing and growing, so they eventually die. In addition, normal cells may also be affected by PACLITAXEL causing some of the side effects. (See **What are the possible side effects of PACLITAXEL?** below.)

Who should not take PACLITAXEL?

Patients who have a history of hypersensitivity (allergic reactions) to PACLITAXEL or other drugs containing Cremophor® EL-P (polyoxyethylated castor oil), like cyclosporine or teniposide, should not be given PACLITAXEL. In addition, PACLITAXEL should not be given to patients with dangerously low white blood cell counts.

How is PACLITAXEL given?

PACLITAXEL is injected into a vein (intravenous (IV) infusion). Before you are given PACLITAXEL, you will have to take certain medicines (premedications) to prevent or reduce the chance you will have a serious allergic reaction. Such reactions have occurred in a small number of patients while receiving PACLITAXEL and have been rarely fatal. (See **What are the possible side effects of PACLITAXEL?** below.)

What are the possible side effects of PACLITAXEL?

Most patients taking PACLITAXEL will experience side effects, although it is not always possible to tell whether such effects are caused by PACLITAXEL, another medicine they may be taking, or the cancer itself. Important side effects are described below; however some patients may experience other side effects that are less common. Report any unusual symptoms to your doctor.

Important side effects observed in studies of patients taking PACLITAXEL were as follows:

-*allergic reactions.* Allergic reactions can vary in degrees of severity. They may cause death in rare cases. When a severe allergic reaction develops, it usually occurs at the time the medicine is entering the body (during PACLITAXEL infusion). Allergic reactions may cause trouble breathing, very low blood pressure, sudden swelling, and/or hives or rash. The likelihood of a serious allergic reaction is lowered by the use of several kinds of medicines that are given to you before the PACLITAXEL infusion.

-*heart and blood vessel (cardiovascular) effects.* PACLITAXEL may cause a drop in heart rate (bradycardia) and low blood pressure (hypotension). The patient usually does not notice these changes. These changes usually do not require treatment. Your heart function, including blood pressure and pulse, will be monitored while you are receiving the medicine. You should notify your doctor if you have a history of heart disease.

-*infections due to low white blood cell count.* Among the body's defenses against bacterial infections are white blood cells. Between your PACLITAXEL treatment cycles, you will often have blood tests to check your white blood cell counts.

PACLITAXEL usually causes a brief drop in white blood cells. *If you have a fever (temperature above 100.4°F) or other sign of infection, tell your doctor right away. Sometimes serious infections develop that require treatment in the hospital with antibiotics. Serious illness or death could result if such infections are not treated when white blood cell counts are low.*

-*hair loss.* Complete hair loss, or alopecia, almost always occurs with PACLITAXEL. This usually involves the loss of eye-brows, eyelashes, and pubic hair, as well as scalp hair. It can occur suddenly after treatment has begun, but usually happens 14 to 21 days after treatment. *Hair generally grows back after you've finished your* PACLITAXEL *treatment.*

-*joint and muscle pain.* You may get joint and muscle pain a few days after your PACLITAXEL treatment. These symptoms usually disappear in a few days. Although pain medicine may not be necessary, tell your doctor if you are uncomfortable.

-*irritation at the injection site.* PACLITAXEL sometimes causes irritation at the site where it enters the vein. Reactions may include discomfort, redness, swelling, inflammation (of the surrounding skin or of the vein itself), and ulceration (open sores). These reactions are usually caused by the IV (intravenous) fluid leaking into the surrounding area. *If you notice anything unusual at the site of the injection (needle), either during or after treatment, tell your doctor right away.*

-*low red blood cell count.* Red blood cells deliver oxygen to tissues throughout all parts of the body and take carbon dioxide from the tissues by using a protein called hemoglobin. A lowering of the volume of red blood cells may occur following PACLITAXEL treatment causing anemia. Some patients may need a blood transfusion to treat the anemia.

Patients can feel tired, tire easily, appear pale, and become short of breath. Contact your doctor if you experience any of these symptoms following PACLITAXEL treatment.

-*mouth or lip sores (mucositis).* Some patients develop redness and/or sores in the mouth or on the lips. These symptoms might occur a few days after the PACLITAXEL treatment and usually decrease or disappear within one week. Talk with your doctor about proper mouth care and other ways to prevent or reduce your chances of developing mucositis.

-*numbness, tingling, or burning in the hands and/or feet (neuropathy).* These symptoms occur often with PACLITAXEL and usually get better or go away without medication within several months of completing treatment. However, if you are uncomfortable, tell your doctor so that he/she can decide the best approach for relief of your symptoms.

-*stomach upset and diarrhea.* Some patients experience nausea, vomiting, and/or diarrhea following PACLITAXEL use. If you experience nausea or stomach upset, tell your doctor. Diarrhea will usually disappear without treatment; however, *if you experience severe abdominal or stomach area pain and/or severe diarrhea, tell your doctor right away.*

Talk with your doctor or other healthcare professional to discuss ways to prevent or reduce some of these side effects.

Because this leaflet does not include all possible side effects that can occur with PACLITAXEL, it is important to talk with your doctor about other possible side effects.

Can I take PACLITAXEL if I am pregnant or nursing a baby?

PACLITAXEL could harm the fetus when given to a pregnant woman. Women should avoid becoming pregnant while they are undergoing treatment with PACLITAXEL. Tell your doctor if you become pregnant or plan to become pregnant while taking PACLITAXEL.

Because studies have shown PACLITAXEL to be present in the breast milk of animals receiving the drug, it may be present in human breast milk as well. Therefore, nursing a baby while taking PACLITAXEL is NOT recommended.

This medicine was prescribed for your particular condition. This summary does not include everything there is to know about PACLITAXEL. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about PACLITAXEL, your doctor or pharmacist have the complete prescribing information upon which this guide is based. You may want to read it and discuss it with your doctor. Remember, no written summary can replace careful discussion with your doctor.

This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.

BEDFORD LABORATORIES

PTXP00C

PACLITAXEL INJECTION

Rx ONLY.

WARNING

Paclitaxel Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteriods, diphenhydramine, and H_2 antagonists. (See **DOSAGE AND ADMINISTRATION** section.) Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

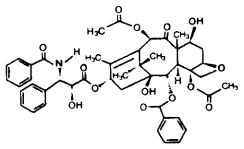
Paclitaxel therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1,500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil counts of less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel.

DESCRIPTION

Paclitaxel Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL-P (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol.

Paclitaxel is a natural product with antitumor activity. Paclitaxel is obtained via a semi-synthetic process from *Taxus baccata*. The chemical name for paclitaxel is (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.

Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the molecular formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.93. It is highly lipophilic, insoluble in water, and melts at around 216° to 217°C.

CLINICAL PHARMACOLOGY

Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Following intravenous administration of paclitaxel injection, paclitaxel plasma concentrations declined in a biphasic manner. The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Pharmacokinetic parameters of paclitaxel following 3 and 24 hour infusions of paclitaxel at dose levels of 135 and 175 mg/m^2 were determined in a Phase 3 randomized study in ovarian cancer patients and are summarized in the following table:

Summary of Pharmacokinetic Parameters - Mean Values

Dose (mg/m^2)	Infusion Duration (h)	N (patients)	C_{max} (ng/mL)	AUC(0–∞) (ng•h/mL)	T-HALF (h)	CL_T (L/h/m^2)
135	24	2	195	6300	52.7	21.7
175	24	4	365	7993	15.7	23.8
135	3	7	2170	7952	13.1	17.7
175	3	5	3650	15007	20.2	12.2

C_{max} = Maximum plasma concentration
AUC(0-∞) = Area under the plasma concentration-time curve from time 0 to infinity
CL_T = Total body clearance

It appeared that with the 24 hour infusion of paclitaxel injection, a 30% increase in dose (135 mg/m^2 versus 175 mg/m^2) increased the C_{MAX} by 87%, whereas the AUC(0-∞) remained proportional. However, with a 3 hour infusion, for a 30% increase in dose, the C_{MAX} and AUC(0-∞) were increased by 68% and 89%, respectively. The mean apparent volume of distribution at steady state, with the 24 hour infusion of paclitaxel, ranged from 227 to 688 L/m^2, indicating extensive extravascular distribution and/or tissue binding of paclitaxel.

The pharmacokinetics of paclitaxel were also evaluated in adult cancer patients who received single doses of 15 to 135 mg/m^2 given by 1 hour infusions (n=15), 30 to 275 mg/m^2 given by 6 hour infusions (n=36), and 200 to 275 mg/m^2 given by 24 hour infusions (n=54) in Phase 1 and 2 studies. Values for CL_T and volume of distribution were consistent with the findings in the Phase 3 study.

JUL 27 2000

APPROVED

In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 mcg/mL, indicate that between 89% to 98% of drug is bound; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

After intravenous administration of 15 to 275 mg/m^2 doses of paclitaxel as 1, 6, or 24 hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In five patients administered a 225 or 250 mg/m^2 dose of radiolabeled paclitaxel as a 3 hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6α-hydroxypaclitaxel, accounted for the balance. *In vitro* studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to two minor metabolites, 3′-*p*-hydroxypaclitaxel and 6α, 3′-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. (See **PRECAUTIONS: Drug Interactions** section.) The effect of renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated.

Possible interactions of paclitaxel with concomitantly administered medications have not been formally investigated.

Clinical Studies

Ovarian Carcinoma

Second-Line Data - Data from five Phase 1 and 2 clinical studies (189 patients), a multicenter randomized Phase 3 study (407 patients), as well as an interim analysis of data from more than 300 patients enrolled in a treatment referral center program were used in support of the use of paclitaxel injection in patients who have failed initial or subsequent chemotherapy for metastatic carcinoma of the ovary. Two of the Phase 2 studies (92 patients) utilized an initial dose of 135 to 170 mg/m^2 in most patients (>90%) administered over 24 hours by continuous infusion. Response rates in these two studies were 22% (95% CI=11% to 37%) and 30% (95% CI=18% to 46%) with a total of 6 complete and 18 partial responses in 92 patients. The median duration of overall response in these two studies measured from the first day of treatment was 7.2 months (range: 3.5 to 15.8 months) and 7.5 months (range: 5.3 to 17.4 months), respectively. The median survival was 8.1 months (range: 0.2 to 36.7 months) and 15.9 months (range: 1.8 to 34.5 + months).

The Phase 3 study had a bifactorial design and compared the efficacy and safety of paclitaxel, administered at two different doses (135 or 175 mg/m^2) and schedules (3 or 24 hour infusion). The overall response rate for the 407 patients was 16.2% (95% CI=12.8% to 20.2%), with 6 complete and 60 partial responses. Duration of response, measured from the first day of treatment was 8.3 months (range: 3.2 to 21.6 months). Median time to progression was 3.7 months (range: 0.1+ to 25.1+ months). Median survival was 11.5 months (range: 0.2 to 26.3+ months).

Response rates, median survival and median time to progression for the 4 arms are given in the following table:

Efficacy in the Phase 3 Second-Line Ovarian Carcinoma Study

	175/3 (n=96)	175/24 (n=106)	135/3 (n=99)	135/24 (n=106)
• **Response**				
– rate (percent)	14.6	21.7	15.2	13.2
– 95% Confidence Interval	(8.5 - 23.6)	(14.5 - 31.0)	(9.0 - 24.1)	(7.7 - 21.5)
• **Time to Progression**				
– median (months)	4.4	4.2	3.4	2.8
– 95% Confidence Interval	(3.0 - 5.6)	(3.5 - 5.1)	(2.8 - 4.2)	(1.9 - 4.0)
• **Survival**				
– median (months)	11.5	11.8	13.1	10.7
– 95% Confidence Interval	(8.4 - 14.4)	(8.9 - 14.6)	(9.1 - 14.6)	(8.1 - 13.6)

Analyses were performed as planned by the bifactorial study design described in the protocol, by comparing the two doses (135 or 175 mg/m2) irrespective of the schedule (3 or 24 hours) and the two schedules irrespective of dose. Patients 175 mg/m^2 dose had a response rate similar to that for those 135 mg/m^2 dose: 18% vs. 14% (p=0.28). No difference in response ra ed when comparing the 3 hour with the 24 hour infusion: 15% vs. Patients receiving the 175 mg/m^2 dose of paclitaxel had a longer time than those receiving the 135 mg/m^2 dose: median 4.2 vs. 3.1 months median time to progression for patients patients receiving the 3 hour infusion: 4.0 months vs. 3.7 months, respectively. Median survival wa in patients receiving the 175 mg/m^2 dose of paclitaxel and 11.0 mor receiving the 135 mg/m^2 dose (p=0.92). Median survival was 11 patients receiving the 3 hour infusion of paclitaxel and 11.2 mont receiving the 24 hour infusion (p=0.91). These statistical analyses sh with caution because of the multiple comparisons made.

Paclitaxel remained active in patients who had developed resistance tc taining therapy (defined as tumor progression while on, or tumor 6 months from completion of, a platinum-containing regimen) with re 14% in the Phase 3 study and 31% in the Phase 1 and 2 clinical stuc

The adverse event profile in this Phase 3 study was consistent with pooled analysis performed on 812 patients treated in 10 clinical adverse events from the Phase 3 second-line ovarian carcinoma stuc in the **ADVERSE REACTIONS** section in tabular and narrative form.

The results of this randomized study support the use of paclitaxel in of 135 to 175 mg/m^2, administered by a 3 hour intravenous infu doses administered by 24 hour infusion were more toxic. How had insufficient power to determine whether a particular dose and sch superior efficacy.

Breast Carcinoma

After Failure of Initial Chemotherapy - Data from 83 patients a Phase 2 open label studies and from 471 patients enrolled in a Phas study were available to support the use of paclitaxel injection metastatic breast carcinoma.

Phase 2 Open Label Studies: Two studies were conducted in 53 pa treated with a maximum of one prior chemotherapeutic regimen administered in these 2 trials as a 24 hour infusion at 250 mg/m^2 (with G-CSF support) or 200 mg/m^2. The response (95% CI: 37% to 75%) and 52% (95% CI: 32% to 72%), respectively 2 study was conducted in extensively pretreated patients who had cline therapy and who had received a minimum of 2 chemotherapy treatment of metastatic disease. The dose of paclitaxel was 200 mg infusion with G-CSF support. Nine of 30 patients achieved a pa response rate of 30% (95% CI: 15% to 50%).

Phase 3 Randomized Study: This multicenter trial was conducte viously treated with one or two regimens of chemotherapy. Patients to receive paclitaxel injection at a dose of either 175 mg/m^2 or 135 a 3 hour infusion. In the 471 patients enrolled, 60% had symptom impaired performance status at study entry, and 73% had visceral m patients had failed prior chemotherapy either in the adjuvant s metastatic setting (39%), or both (31%). Sixty-seven percent of the previously exposed to anthracyclines and 23% of them had disease tant to this class of agents.

The overall response rate for the 454 evaluable patients was 26 to 30%), with 17 complete and 99 partial responses. The me response, measured from the first day of treatment, was 8.1 mon 18.1+ months). Overall for the 471 patients, the median time to 3.5 months (range: 0.03 to 17.1 months). Median survival was 11 0 to 18.9 months).

Response rates, median survival and median time to progression given in the following table:

Efficacy in Breast Cancer after Failure of Initial Chemo or Within 6 Months of Adjuvant Chemotherapy

	175/3 (n=235)	
• **Response**		
– rate (percent)	28	
– p-value		0.135
• **Time to Progression**		
– median (months)	4.2	
– p-value		0.027
• **Survival**		
– median (months)	11.7	
– p-value		0.321

The adverse event profile of the patients who received single-age Phase 3 study was consistent with that seen for the pooled ana 812 patients treated in 10 clinical studies. These adverse events breast carcinoma study are described in the **ADVERSE REACTIO** lar and narrative form.

INDICATIONS AND USAGE

Paclitaxel injection is indicated, after failure of first-line or subseq for the treatment of metastatic carcinoma of the ovary.

Paclitaxel injection is indicated for the treatment of breast car

ule (3 or 24 hours) and the two schedules irrespective of dose. Patients receiving the 175 mg/m^2 dose had a response rate similar to that for those receiving the 135 mg/m^2 dose: 18% vs. 14% (p=0.28). No difference in response rate was detected when comparing the 3 hour with the 24 hour infusion: 15% vs. 17% (p=0.50). Patients receiving the 175 mg/m^2 dose of paclitaxel had a longer time to progression than those receiving the 135 mg/m^2 dose: median 4.2 vs. 3.1 months (p=0.03). The median time to progression for patients patients receiving the 3 hour vs. the 24 hour infusion: 4.0 months vs. 3.7 months, respectively. Median survival was 11.6 months in patients receiving the 175 mg/m^2 dose of paclitaxel and 11.0 months in patients receiving the 135 mg/m^2 dose (p=0.92). Median survival was 14.7 months for patients receiving the 3 hour infusion of paclitaxel and 11.2 months for patients receiving the 24 hour infusion (p=0.91). These statistical analyses should be viewed with caution because of the multiple comparisons made.

Paclitaxel remained active in patients who had developed resistance to platinum-containing therapy (defined as tumor progression while on, or tumor relapse within 6 months from completion of, a platinum-containing regimen) with response rates of 14% in the Phase 3 study and 31% in the Phase 1 and 2 clinical studies.

The adverse event profile in this Phase 3 study was consistent with that seen for a pooled analysis performed on 812 patients treated in 10 clinical studies. These adverse events from the Phase 3 second-line ovarian carcinoma study are described in the **ADVERSE REACTIONS** section in tabular and narrative form.

The results of this randomized study support the use of paclitaxel injection at doses of 135 to 175 mg/m^2, administered by a 3 hour intravenous infusion. The same doses administered by 24 hour infusion were more toxic. However, the study had insufficient power to determine whether a particular dose and schedule produced superior efficacy.

Breast Carcinoma

After Failure of Initial Chemotherapy - Data from 83 patients accrued in three Phase 2 open label studies and from 471 patients enrolled in a Phase 3 randomized study were available to support the use of paclitaxel injection in patients with metastatic breast carcinoma.

Phase 2 Open Label Studies: Two studies were conducted in 53 patients previously treated with a maximum of one prior chemotherapeutic regimen. Paclitaxel was administered in these 2 trials as a 24 hour infusion at initial doses of 250 mg/m^2 (with G-CSF support) or 200 mg/m^2. The response rates were 57% (95% CI: 37% to 75%) and 52% (95% CI: 32% to 72%), respectively. The third phase 2 study was conducted in extensively pretreated patients who had failed anthracycline therapy and who had received a minimum of 2 chemotherapy regimens for the treatment of metastatic disease. The dose of paclitaxel was 200 mg/m^2 as a 24 hour infusion with G-CSF support. Nine of 30 patients achieved a partial response, a response rate of 30% (95% CI: 15% to 50%).

Phase 3 Randomized Study: This multicenter trial was conducted in patients previously treated with one or two regimens of chemotherapy. Patients were randomized to receive paclitaxel injection at a dose of either 175 mg/m^2 or 135 mg/m^2 given as a 3 hour infusion. In the 471 patients enrolled, 60% had symptomatic disease with impaired performance status at study entry, and 73% had visceral metastases. These patients had failed prior chemotherapy either in the adjuvant setting (30%), the metastatic setting (39%), or both (31%). Sixty-seven percent of the patients had been previously exposed to anthracyclines and 23% of them had disease considered resistant to this class of agents.

The overall response rate for the 454 evaluable patients was 26% (95% CI: 22% to 30%), with 17 complete and 99 partial responses. The median duration of response, measured from the first day of treatment, was 8.1 months (range: 3.4 to 18.1+ months). Overall for the 471 patients, the median time to progression was 3.5 months (range: 0.03 to 17.1 months). Median survival was 11.7 months (range: 0 to 18.9 months).

Response rates, median survival and median time to progression for the 2 arms are given in the following table:

Efficacy in Breast Cancer after Failure of Initial Chemotherapy or Within 6 Months of Adjuvant Chemotherapy

	175/3 (n=235)		135/3 (n=236)
• **Response**			
– rate (percent)	28		22
– p-value		0.135	
• **Time to Progression**			
– median (months)	4.2		3.0
– p-value		0.027	
• **Survival**			
– median (months)	11.7		10.5
– p-value		0.321	

The adverse event profile of the patients who received single-agent paclitaxel in the Phase 3 study was consistent with that seen for the pooled analysis of data from 812 patients treated in 10 clinical studies. These adverse events from the Phase 3 breast carcinoma study are described in the **ADVERSE REACTIONS** section in tabular and narrative form.

INDICATIONS AND USAGE

Paclitaxel injection is indicated, after failure of first-line or subsequent chemotherapy for the treatment of metastatic carcinoma of the ovary.

Paclitaxel injection is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

CONTRAINDICATIONS

Paclitaxel injection is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor® EL-P (polyoxyethylated castor oil).

Paclitaxel injection should not be used in patients with solid tumors who have baseline neutrophil counts of <1,500 cells/mm3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm^3.

WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine and H_2 antagonists. (See **DOSAGE AND ADMINISTRATION** section.) Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. Frequent monitoring of blood counts should be instituted during paclitaxel treatment. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3.

Severe conduction abnormalities have been documented in <1% of patients during paclitaxel therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Pregnancy: Paclitaxel can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Drug Interactions: In a Phase 1 trial using escalating doses of paclitaxel (110 to 200 mg/m^2) and cisplatin (50 or 75 mg/m^2) given as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (i.e. paclitaxel before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin.

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. (See **CLINICAL PHARMACOLOGY** section.)

Potential interactions between paclitaxel, a substrate of CYP3A4 and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4 have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

Hematology: Paclitaxel therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for seven days or more) during a course of paclitaxel therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

Hypersensitivity Reactions: Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL- P (e.g. cyclosporin for injection concentrate and teniposide for injection concentrate) should not be trea
injection. In order to avoid the occurrence of severe hypersensi
patients treated with paclitaxel should be premedicated with corti
dexamethasone), diphenhydramine and H_2 antagonists (such as c
dine). Minor symptoms such as flushing, skin reactions, dyspn
tachycardia do not require interruption of therapy. However, severe
hypotension requiring treatment, dyspnea requiring bronchodilat
generalized urticaria require immediate discontinuation of paclita
symptomatic therapy. Patients who have developed severe hypers
should not be rechallenged with paclitaxel.

Cardiovascular: Hypotension, bradycardia and hypertension ha
during administration of paclitaxel, but generally do not require tr
ally paclitaxel infusions must be interrupted or discontinued becaus
rent hypertension. Frequent vital sign monitoring, particularly dur
paclitaxel infusion, is recommended. Continuous cardiac monitor
except for patients with serious conduction abnormalities. (See **W**

Nervous System: Although, the occurrence of peripheral neurope
development of severe symptomatology is unusual and requires
20% for all subsequent courses of paclitaxel.

Paclitaxel contains dehydrated alcohol, 396 mg/mL; considerati
to possible CNS and other effects of alcohol. (See **PRECAU
Use** section).

Hepatic: There is evidence that the toxicity of paclitaxel is enhan
elevated liver enzymes. Caution should be exercised when admini
patients with moderate to severe hepatic impairment and dose
be considered.

Injection Site Reaction: Injection site reactions, including reac
extravasation, were usually mild and consisted of erythema, tend
oration, or swelling at the injection site. These reactions have b
frequently with the 24 hour infusion than with the 3 hour infusion
reactions at a site of previous extravasation following administrat
different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulit
exfoliation, necrosis and fibrosis have been received as part
surveillance of paclitaxel safety. In some cases the onset of the ir
either occurred during a prolonged infusion or was delayed by a

A specific treatment for extravasation reactions is unknown at
possibility of extravasation, it is advisable to closely monitor t
possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The ca
of paclitaxel has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromos
human lymphocytes) and *in vivo* (micronucleus test in mice).
mutagenic in the Ames test of CHO/HGPRT gene mutation assay

Administration of paclitaxel prior to and during mating produced
ity in male and female rats at doses equal to or greater than 1 mg
the daily maximum recommended human dose on a mg/m^2 basis
taxel caused reduced fertility and reproductive indices, and incr
fetotoxicity (see **WARNINGS** section).

Pregnancy: Teratogenic Effects, Pregnancy Category D. (See

Nursing Mothers: It is not known whether the drug is excre
Following intravenous administration of carbon-14 labeled paclit
9 to 10 postpartum, concentrations of radioactivity in milk v
plasma and declined in parallel with the plasma concentrations. E
are excreted in human milk and because of the potential for seriou
in nursing infants, it is recommended that nursing be discontin
paclitaxel therapy.

Pediatric Use: The safety and effectiveness of paclitaxel in pedia
been established.

There have been reports of central nervous system (CNS) toxici
with death) in a clinical trial in pediatric patients in which pa
intravenously over 3 hours at doses ranging from 350 mg/m^2
toxicity is most likely attributable to the high dose of the ethan
paclitaxel vehicle given over a short infusion time. The u
antihistamines may intensify this effect. Although a direct effect
cannot be discounted, the high doses used in this study (over two
adult dosage) must be considered in assessing the safety of pac
population.

ADVERSE REACTIONS

Pooled Analysis of Adverse Event Experiences from Single-
in the following table are based on the experience of 812 patien
carcinoma and 319 with breast carcinoma) enrolled in 10 studies
agent paclitaxel. Two hundred and seventy-five patients were tr
2 studies with paclitaxel doses ranging from 135 to 300 mg/m
24 hours (in four of these studies, G-CSF was administered as he
Three hundred and one patients were treated in the randomized
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received paclitaxel (135 or 175 mg/m^2) administered over 3 hours

) schedules irrespective of dose. Patients receiving the ponse rate similar to that for those receiving the % (p=0.28). No difference in response rate was detect- ır with the 24 hour infusion: 15% vs. 17% (p=0.50). m2 dose of paclitaxel had a longer time to progression ng/m2 dose: median 4.2 vs. 3.1 months (p=0.03). The patients patients receiving the 3 hour vs. the 24 hour onths, respectively. Median survival was 11.6 months ng/m2 dose of paclitaxel and 11.0 months in patients se (p=0.92). Median survival was 11.7 months for infusion of paclitaxel and 11.2 months for patients (p=0.91). These statistical analyses should be viewed ultiple comparisons made.

ıtients who had developed resistance to platinum-con- umor progression while on, or tumor relapse within ı platinum-containing regimen) with response rates of 31% in the Phase 1 and 2 clinical studies.

iis Phase 3 study was consistent with that seen for a ı 812 patients treated in 10 clinical studies. These 3 second-line ovarian carcinoma study are described section in tabular and narrative form.

study support the use of paclitaxel injection at doses istered by a 3 hour intravenous infusion. The same our infusion were more toxic. However, the study nine whether a particular dose and schedule produced

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the 454 evaluable patients was 26% (95% CI: 22% and 99 partial responses. The median duration of first day of treatment, was 8.1 months (range: 3.4 to ə 471 patients, the median time to progression was 1 months). Median survival was 11.7 months (range:

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	175/3 (n=235)	135/3 (n=236)
	28	22
	0.135	
	4.2	3.0
	0.027	
	11.7	10.5
	0.321	

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DICATIONS AND USAGE

after failure of first-line or subsequent chemotherapy carcinoma of the ovary.

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CONTRAINDICATIONS.

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Paclitaxel injection should not be used in patients with solid tumors who have baseline neutrophil counts of <1,500 cells/mm3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm3.

WARNINGS

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine and H_2 antagonists. (See **DOSAGE AND ADMINISTRATION** section.) Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm3. Frequent monitoring of blood counts should be instituted during paclitaxel treatment. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,500 cells/mm3 and platelets recover to a level >100,000 cells/mm3.

Severe conduction abnormalities have been documented in <1% of patients during paclitaxel therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Pregnancy: Paclitaxel can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If paclitaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Drug Interactions: In a Phase 1 trial using escalating doses of paclitaxel (110 to 200 mg/m2) and cisplatin (50 or 75 mg/m2) given as sequential infusions, myelosuppression was more profound when paclitaxel was given after cisplatin than with the alternate sequence (i.e. paclitaxel before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when paclitaxel was administered following cisplatin.

The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. (See **CLINICAL PHARMACOLOGY** section.)

Potential interactions between paclitaxel, a substrate of CYP3A4 and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4 have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

Hematology: Paclitaxel therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1,500 cells/mm3 and platelets recover to a level >100,000 cells/mm3. In the case of severe neutropenia (<500 cells/mm3 for seven days or more) during a course of paclitaxel therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

Hypersensitivity Reactions: Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL- P (e.g. cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with paclitaxel injection. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel should be premedicated with corticosteriods (such as dexamethasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel.

Cardiovascular: Hypotension, bradycardia and hypertension have been observed during administration of paclitaxel, but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. (See **WARNINGS** section).

Nervous System: Although, the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of paclitaxel.

Paclitaxel contains dehydrated alcohol, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol. (See **PRECAUTIONS: Pediatric Use** section).

Hepatic: There is evidence that the toxicity of paclitaxel is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering paclitaxel to patients with moderate to severe hepatic impairment and dose adjustments should be considered.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24 hour infusion than with the 3 hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of paclitaxel safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of paclitaxel has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosomal aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test of CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m2 basis). At this dose, paclitaxel caused reduced fertility and reproductive injices, and increased embryo- and fetotoxicity (see **WARNINGS** section).

Pregnancy: Teratogenic Effects, Pregnancy Category D. (See **WARNINGS** section.)

Nursing Mothers: It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon-14 labeled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving paclitaxel therapy.

Pediatric Use: The safety and effectiveness of paclitaxel in pediatric patients have not been established.

There have been reports of central nervous system (CNS) toxicity (rarely associated with death) in a clinical trial in pediatric patients in which paclitaxel was infused intravenously over 3 hours at doses ranging from 350 mg/m2 to 420 mg/m2. The toxicity is most likely attributable to the high dose of the ethanol component of the paclitaxel vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of paclitaxel for use in this population.

ADVERSE REACTIONS

Pooled Analysis of Adverse Event Experiences from Single-Agent Studies: Data in the following table are based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies who received single-agent paclitaxel. Two hundred and seventy-five patients were treated in eight Phase 2 studies with paclitaxel doses ranging from 135 to 300 mg/m2 administered over 24 hours (in four of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m2) and two schedules (3 or 24 hours) of paclitaxel. Two hundred and thirty-six patients with breast carcinoma received paclitaxel (135 or 175 mg/m2) administered over 3 hours in a controlled study.

Summary[a] of Adverse Events in Patients With Solid Tumors Receiving Single-Agent Paclitaxel		% of Patients (n=812)
• **Bone Marrow**		
– Neutropenia	<2,000/mm³	90
	<500/mm³	52
– Leukopenia	<4,000/mm³	90
	<1,000/mm³	17
– Thrombocytopenia	<100,000/mm³	20
	<50,000/mm³	7
– Anemia	<11 g/dL	78
	<8 g/dL	16
– Infections		30
– Bleeding		14
– Red Cell Transfusions		25
– Platelet Transfusions		2
• **Hypersensitivity Reaction[b]**		
– All		41
– Severe[c]		2
• **Cardiovascular**		
– Vital Sign Changes[c]		
– Bradycardia (N=537)		3
– Hypotension (N=532)		12
– Significant Cardiovascular Events		1
• **Abnormal ECG**		
– All Pts		23
– Pts with normal baseline (N=559)		14
• **Peripheral Neuropathy**		
– Any symptoms		60
– Severe symptoms[c]		3
• **Myalgia/Arthralgia**		
– Any symptoms		60
– Severe symptoms[c]		8
• **Gastrointestinal**		
– Nausea and vomiting		52
– Diarrhea		38
– Mucositis		31
• **Alopecia**		87
• **Hepatic** (Pts with normal baseline and on study data)		
– Bilirubin elevations (N=765)		7
– Alkaline phosphatase elevations (N=575)		22
– AST (SGOT) elevations (N=591)		19
• **Injection Site Reaction**		13

[a] Based on worst course analysis.
[b] All patients received premedication.
[c] During the first 3 hours of infusion.
* Severe events are defined as at least Grade III toxicity.

None of the observed toxicities were clearly influenced by age.

Disease Specific Adverse Event Experiences

Second-Line Ovary: For the 403 patients who received single-agent paclitaxel in the Phase 3 second-line ovarian carcinoma study, the following table shows the incidence of important adverse events.

Frequency[a] of Important Adverse Events in the Phase 3 Second-Line Ovarian Carcinoma Study		Percent of Patients			
		175/3[b] (n=95)	175/24[b] (n=105)	135/3[b] (n=98)	135/24[b] (n=105)
• **Bone Marrow**					
– Neutropenia	<2,000/mm³	78	98	78	98
	<500/mm³	27	75	14	67
– Thrombocytopenia	<100,000/mm³	4	18	8	6
	<50,000/mm³	1	7	2	1
– Anemia	<11 g/dL	84	90	68	88
	<8 g/dL	11	12	6	10
– Infections		26	29	20	18
• **Hypersensitivity Reaction[c]**					
– All		41	45	38	45
– Severe*		2	0	2	1
• **Peripheral Neuropathy**					
– Any symptoms		63	60	55	42
– Severe symptoms*		1	2	0	0
• **Mucositis**					
– Any symptoms		17	35	21	25
– Severe symptoms*		0	3	0	2

[a] Based on worst course analysis.
[b] Paclitaxel dose in mg/m2/infusion duration in hours.
[c] All patients received premedication.
* Severe events are defined as at least Grade III toxicity.

Myelosuppression was dose and schedule related, with the schedule effect being more prominent. The development of severe hypersensitivity reactions (HSRs) was rare; 1% of the patients and 0.2% of the courses overall. There was no apparent dose or schedule effect seen for the HSRs. Peripheral neuropathy was clearly dose-related, but schedule did not appear to affect the incidence.

Breast Cancer After Failure of Initial Chemotherapy: For the 458 patients who received single-agent paclitaxel in the Phase 3 breast carcinoma study, the following table shows the incidence of important adverse events by treatment arm (each arm was administered by a 3 hour infusion).

Frequency[a] of Important Adverse Events in the Phase 3 Study of Breast Cancer After Failure of Initial Chemotherapy or Within 6 Months of Adjuvant Chemotherapy		Percent of Patients	
		175/3[b] (n=229)	135/3[b] (n=229)
• **Bone Marrow**			
– Neutropenia	<2,000/mm³	90	81
	<500/mm³	28	19
– Thrombocytopenia	<100,000/mm³	11	7
	<50,000/mm³	3	2
– Anemia	<11 g/dL	55	47
	<8 g/dL	4	2
– Infections		23	15
– Febrile Neutropenia		2	2
• **Hypersensitivity Reaction[c]**			
– All		36	31
– Severe*		0	<1
• **Peripheral Neuropathy**			
– Any symptoms		70	46
– Severe symptoms*		7	3
• **Mucositis**			
– Any symptoms		23	17
– Severe symptoms*		3	<1

[a] Based on worst course analysis.
[b] Paclitaxel dose in mg/m²/infusion duration in hours.
[c] All patients received premedication.
* Severe events are defined as at least Grade III toxicity.

Myelosuppression and peripheral neuropathy were dose related. There was one severe hypersensitivity reaction (HSR) observed at the dose of 135 mg/m².

Adverse Event Experiences by Body System: Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent paclitaxel in clinical studies. The frequency and severity of important adverse events for the Phase 3 ovarian carcinoma and breast carcinoma are presented above in tabular form by treatment arm. In addition, rare events have been reported from postmarketing experience or from other clinical studies.

Hematologic: Bone marrow suppression was the major dose-limiting toxicity of paclitaxel. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in the Phase 3 second-line ovarian study with a 3 hour infusion, neutrophil counts declined below 500 cells/mm³ in 14% of the patients treated with a dose of 135 mg/m² compared to 27% at a dose of 175 mg/m² (p=0.05). In the same study, severe neutropenia (<500 cells/mm³) was more frequent with the 24 hour than with the 3 hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 second-line ovarian study, infectious episodes were reported in 20% and 26% of the patients treated with a dose of 135 mg/m² or 175 mg/m² given as 3 hour infusions, respectively. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications.

Thrombocytopenia was uncommon, and almost never severe (<50,000 cells/mm³). Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm³ at least once while on treatment; 7% had a platelet count <50,000 cells/mm³ at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the paclitaxel dose and schedule. In the Phase 3 second-line ovarian study, bleeding episodes were reported in 10% of the patients; no patients treated with the 3 hour infusion received platelet transfusions.

Anemia (Hb<11 g/dL) was observed in 78% of all patients and was severe (Hb<8 g/dL) in 16% of the cases. No consistent relationship between dose or schedule and the frequency of anemia was observed. Among all patients with normal baseline hemoglobin, 69% became anemic on study but only 7% had severe anemia. Red cell transfusions were required in 25% of all patients and in 12% of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSRs): All patients received premedication prior to paclitaxel injection (see **WARNINGS** and **PRECAUTIONS, Hypersensitivity Reactions** sections). The frequency and severity of HSRs were not affected by the dose or schedule of paclitaxel administration. In the Phase 3 second-line ovarian study the 3 hour infusion was not associated with a greater increase in HSRs when compared to the 24 hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients. These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within
quent symptoms observed during
chest pain and tachycardia.

The minor hypersensitivity reaction
hypotension (4%), dyspnea (2%),
frequency of hypersensitivity react
treatment period.

Rare reports of chills and reports
reactions have been received as par

Cardiovascular: Hypotension, durin
all patients and 3% of all courses ac
infusion, occurred in 3% of all patie
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sion and bradycardia. These vital si
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Significant cardiovascular events p
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The arrhythmias included asym
complete AV block requiring pacem

Electrocardiogram (ECG) abnormali
abnormalities on study did not usu
required no intervention. ECG abnc
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abnormal tracing while on study. Th
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anthracylines did not influence the

Cases of myocardial infarction hav
been reported typically in patient
anthracyclines. (See **PRECAUTION**

Rare reports of atrial fibrillation ar
as part of the continuing surveilla

Respiratory: Rare reports of in
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safety. Rare reports of radiation p
concurrent radiotherapy.

Neurologic: The frequency a
dose-dependent, but were not inf
was observed in 60% of all pat
patients without pre-existing neu

The frequency of peripheral neur
symptoms were observed in 27
and in 34 to 51% from course 2

Peripheral neuropathy was the
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Other than peripheral neuropat
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Rare reports of autonomic neuro
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who have received higher doses
have been reversible. However, r
potentials in patients have sugg

Arthralgia/Myalgia: There was
of paclitaxel and the frequency
patients treated experienced ar
The symptoms were usually tr
administration, and resolved w
culoskeletal symptoms remaine

Hepatic: No relationship was
either dose or schedule of pa
baseline liver function 7%, 2
phosphatase and AST (SGOT), r
associated with cumulative hep

Rare reports of hepatic necros
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Gastrointestinal (GI): Nausea
52%, 38% and 31% of all pat
mild to moderate. Mucositis w
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Rare reports of intestinal obs
colitis, and dehydration have b
paclitaxel safety. Rare report

458 patients who study, the following ment arm (each arm

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81	
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<1	
46	
3	
17	
<1	

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limiting toxicity of pacli- was dose and schedule nts treated in the Phase l counts declined below 35 mg/m^2 compared to dy, severe neutropenia with the 3 hour infusion; than dose. Neutropenia l not appear to be more radiation therapy.

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symptoms occurred generally within the first hour of paclitaxel infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia.

The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%) and hypertension (1%). The frequency of hypersensitivity reactions remained relativity stable during the entire treatment period.

Rare reports of chills and reports of back pain in association with hypersensitivity reactions have been received as part of the continuing surveillance of paclitaxel safety.

Cardiovascular: Hypotension, during the first 3 hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3% of all patients and 1% of all courses. In the Phase 3 second-line ovarian study, neither dose nor schedule had an effect on the frequency of hypotension and bradycardia. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. The frequency of hypotension and bradycardia were not influenced by prior anthracycline therapy.

Significant cardiovascular events possibly related to single-agent paclitaxel occurred in approximately 1% of all patients. These events included syncope, rhythm abnormalities, hypertension and venous thrombosis. One of the patients with syncope treated with paclitaxel at 175 mg/m^2 over 24 hours had progressive hypotension and died. The arrhythmias included asymptomatic ventricular tachycardia, bigeminy and complete AV block requiring pacemaker placement.

Electrocardiogram (ECG) abnormalities were common among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 23% of all patients. Among patients with a normal ECG prior to study entry, 14% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, sinus tachycardia and premature beats. Among patients with normal ECGs at baseline, prior therapy with anthracylines did not influence the frequency of ECG abnormalities.

Cases of myocardial infarction have been reported rarely. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines. (See **PRECAUTIONS, Drug Interactions** section.)

Rare reports of atrial fibrillation and supraventricular tachycardia have been received as part of the continuing surveillance of paclitaxel safety.

Respiratory: Rare reports of interstitial pneumonia, lung fibrosis and pulmonary embolism have been received as part of the continuing surveillance of paclitaxel safety. Rare reports of radiation pneumonitis have been received in patients receiving concurrent radiotherapy.

Neurologic: The frequency and severity of neurologic manifestations were dose-dependent, but were not influenced by infusion duration. Peripheral neuropathy was observed in 60% of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy.

The frequency of peripheral neuropathy increased with cumulative dose. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34 to 51% from course 2 to 10.

Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. The incidence of neurologic symptoms did not increase in the subset of patients previously treated with cisplatin. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

Other than peripheral neuropathy, serious neurologic events following paclitaxel administration have been rare (<1%) and have included grand mal seizures, syncope, ataxia and neuroencephalopathy.

Rare reports of autonomic neuropathy resulting in paralytic ileus have been received as part of the continuing surveillance of paclitaxel safety. Optic nerve and/or visual disturbances (scintillating scotomata) have also been reported, particularly in patients who have received higher doses than those recommended. These effects generally have been reversible. However, rare reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.

Arthralgia/Myalgia: There was no consistent relationship between dose or schedule of paclitaxel and the frequency or severity of arthralgia/myalgia. Sixty percent of all patients treated experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred two or three days after paclitaxel administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.

Hepatic: No relationship was observed between liver function abnormalities and either dose or schedule of paclitaxel administration. Among patients with normal baseline liver function 7%, 22% and 19% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. Prolonged exposure to paclitaxel was not associated with cumulative hepatic toxicity.

Rare reports of hepatic necrosis and hepatic encephalopathy leading to death have been received as part of the continuing surveillance of paclitaxel safety.

Gastrointestinal (GI): Nausea/vomiting, diarrhea and mucositis were reported by 52%, 38% and 31% of all patients, respectively. These manifestations were usually mild to moderate. Mucositis was schedule dependent and occurred more frequently with the 24 hour than with the 3 hour infusion.

Rare reports of intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, and dehydration have been received as part of the continuing surveillance of paclitaxel safety. Rare reports of neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, were observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic agents.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24 hour infusion than with the 3 hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of paclitaxel at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis and cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of paclitaxel safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Other Clinical Events: Alopecia was observed in almost all (87%) of the patients. Transient skin changes due to paclitaxel-related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with paclitaxel administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most commonly focal and disease-related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.

Rare reports of skin abnormalities related to radiation recall as well as reports of maculopapular rash and pruritus have been received as part of the continuing surveillance of paclitaxel safety.

Reports of asthenia and malaise have been received as part of the continuing surveillance of paclitaxel safety.

Accidental Exposure: Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported. Following topical exposure, events have included tingling, burning and redness.

OVERDOSAGE

There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity (see **PRECAUTIONS: Pediatric Use** section).

DOSAGE AND ADMINISTRATION

Note: Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel injection solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel.

In patients previously treated with chemotherapy for carcinoma of the ovary, paclitaxel has been used at several doses and schedules; however, the optimal regimen is not yet clear (see **CLINICAL STUDIES: Ovarian Carcinoma** section). The recommended regimen is paclitaxel 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

For patients with carcinoma of the breast, the following regimens are recommended (see **CLINICAL STUDIES: Breast Carcinoma** section). After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, paclitaxel at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective.

For therapy of patients with solid tumors (ovary and breast), courses of paclitaxel should not be repeated until the neutrophil count is at least 1,500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe peripheral neuropathy during paclitaxel therapy should have dosage reduced by 20% for subsequent courses of paclitaxel. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Preparation and Administration Precautions: Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling paclitaxel injection. The use of gloves is recommended. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning and redness. If paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration (see **PRECAUTIONS: Injection Site Reaction** section).

Preparation for Intravenous Administration: Paclitaxel Injection must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, or 5% Dextrose in Ringer's Injection to a final conc solutions are physically and chemically stable temperature (approximately 25°C) and room ligh

Upon preparation, solutions may show haziness tion vehicle. No significant losses in potency ha delivery of the solution through IV tubing contain

Data collected for the presence of the extrac hexyl)phthalate] show that levels increase with ti are prepared in PVC containers. Consequently, t and administration sets is not recommended. Pa and stored in glass, polypropylene, or polyol administration sets, such as those which arepot

Paclitaxel should be administered through an in brane not greater than 0.22 microns. Use of fi which incorporate short inlet and outlet PVC significant leaching of DEHP.

The Chemo Dispensing Pin™ device or simila used with vials of paclitaxel since they can caus loss of sterile integrity of the paclitaxel solution.

Stability: Unopened vials of Paclitaxel Injection the package when stored between 20° to 25°C Neither freezing nor refrigeration adversely affe refrigeration components in the paclitaxel vial upon reaching room temperature with little or product quality under these circumstances. If insoluble precipitate is noted, the vial should prepared as recommended are stable at ambie and lighting conditions for up to 27 hours.

Note: Parenteral drug products should be inspe discoloration prior to administration whenever

HOW SUPPL

Paclitaxel Injection, 6 mg/mL, is supplied as fo

30 mg multiple-dose vial individually boxed, N

100 mg multiple-dose vial individually boxed, I

300 mg multiple-dose vial individually boxed, I

Storage: Store the vials in original cartons bet in the original package to protect from light.

Handling and Disposal: Procedures for prop drugs should be considered. Several guidelines There is no general agreement that all of guidelines are necessary or appropriate.

REFEREN

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4. Clinical Oncological Society of Australi Safe Handling of Antineoplastic Agents
5. Jones RB, et al: Safe Handling of Cher Mount Sinai Medical Center, CA-A Canc 258-263.
6. American Society of Hospital Pharmac dling Cytotoxic and Hazardous Drugs.
7. Controlling Occupational Exposure to TICE GUIDELINES.) *Am J Health-Syst P*

Manufactured for: Bedford Laboratories™, E
Manufactured by: Ben Venue Laboratories, In

January 2001

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DOSAGE AND ADMINISTRATION

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All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel.

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Preparation and Administration Precautions: Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised in handling paclitaxel injection. The use of gloves is recommended. If paclitaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning and redness. If paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration (see **PRECAUTIONS: Injection Site Reaction** section).

Preparation for Intravenous Administration: Paclitaxel Injection must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C) and room lighting conditions.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 micron) filter.

Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl)phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVCcontaining administration sets, such as those which arepolyethylene-lined, should be used.

Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

The Chemo Dispensing Pin™ device or similar devices with spikes should not be used with vials of paclitaxel since they can cause the stopper to collapse resulting in loss of sterile integrity of the paclitaxel solution.

Stability: Unopened vials of Paclitaxel Injection are stable until the date indicated on the package when stored between 20° to 25°C (68° to 77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration components in the paclitaxel vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as recommended are stable at ambient temperature (approximately 25°C) and lighting conditions for up to 27 hours.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Paclitaxel Injection, 6 mg/mL, is supplied as follows:

30 mg multiple-dose vial individually boxed, **NDC 55390-114-05.**

100 mg multiple-dose vial individually boxed, **NDC 55390-114-20.**

300 mg multiple-dose vial individually boxed, **NDC 55390-114-50.**

Storage: Store the vials in original cartons between 20° to 25°C (68° to 77°F). Retain in the original package to protect from light.

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-7]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents; US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA 1985; 253 (11): 1590-1592.
3. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts, 02115.
4. Clinical Oncological Society of Australia. Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia 1983; 1:426-428.
5. Jones RB, et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians 1983; Sept/Oct. 258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA WORK-PRACTICE GUIDELINES.) *Am J Health-Syst Pharm* 1996; 53:1669-1685.

Manufactured for: Bedford Laboratories™, Bedford, OH 44146

Manufactured by: Ben Venue Laboratories, Inc., Bedford, OH 44146

January 2001 PTXP00C

JUL 27 2001

Note: Keyline does not print.

PACLITAXEL INJECTION

6 mg/mL

MUST BE DILUTED PRIOR TO IV USE.
Read enclosed package insert.
Rx ONLY.

NDC 55390-114-50 APPROVED 50 mL Multiple-Dose Vial

Usual Dosage: See package insert.

Each mL contains 6 mg paclitaxel, 527 mg Cremophor® EL - P (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

WARNING: Cytotoxic Agent

Store between 20° to 25°C (68° to 77°F). **Protect from light.** Retain in carton until time of use.

Mfg for:
Bedford Laboratories™
Bedford, OH 44146

BEDFORD LABORATORIES™

Mfg by:
Ben Venue Labs, Inc.
Bedford, OH 44146

PTXVB00A

LOT

EXP

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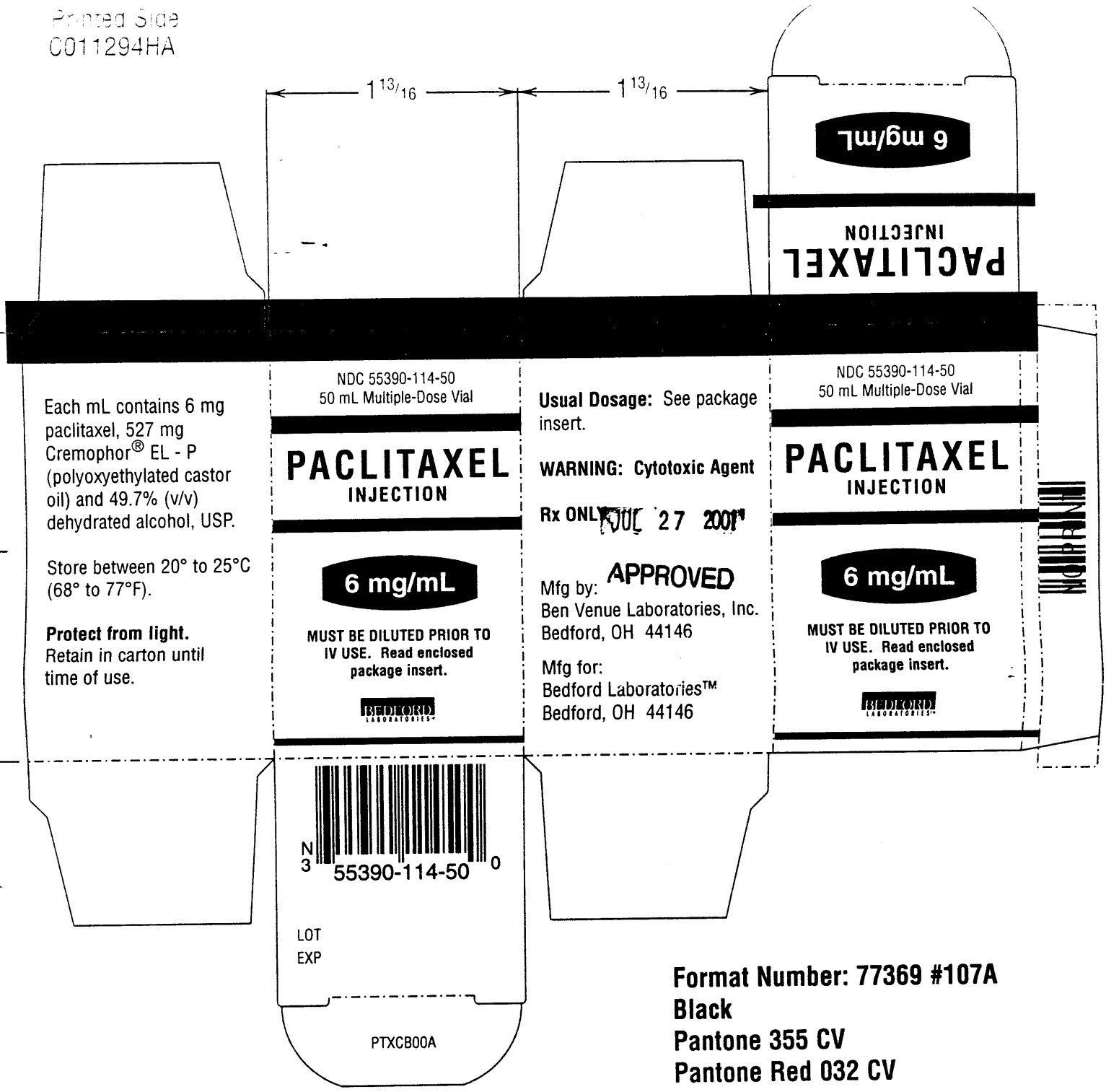

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75-190
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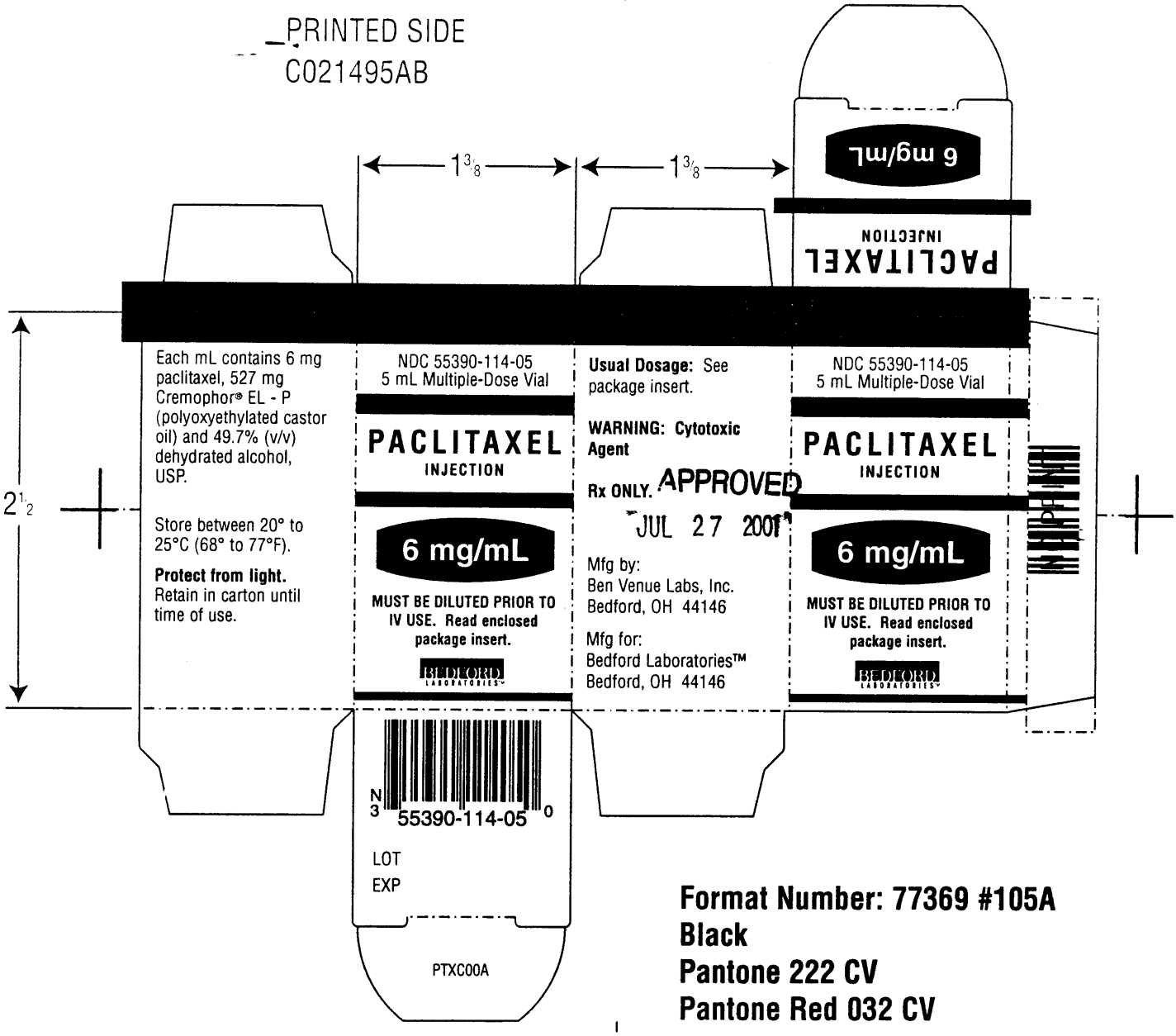

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APPROVED
JUL 27 2001

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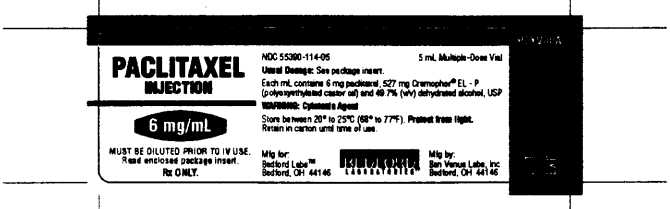

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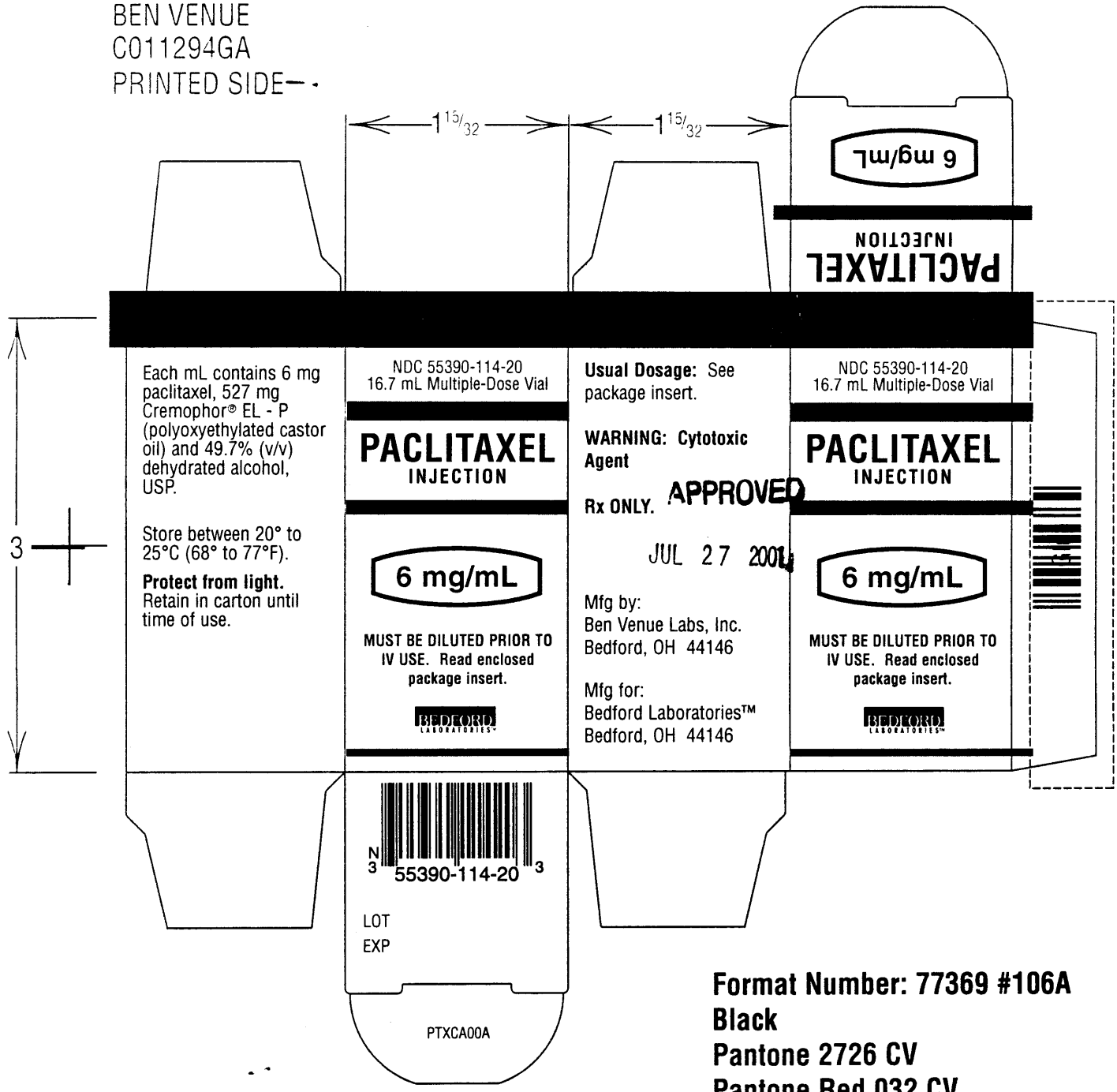

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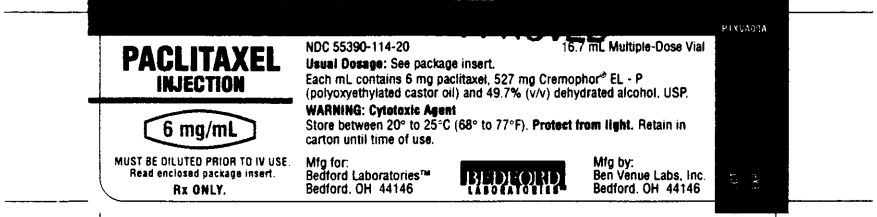

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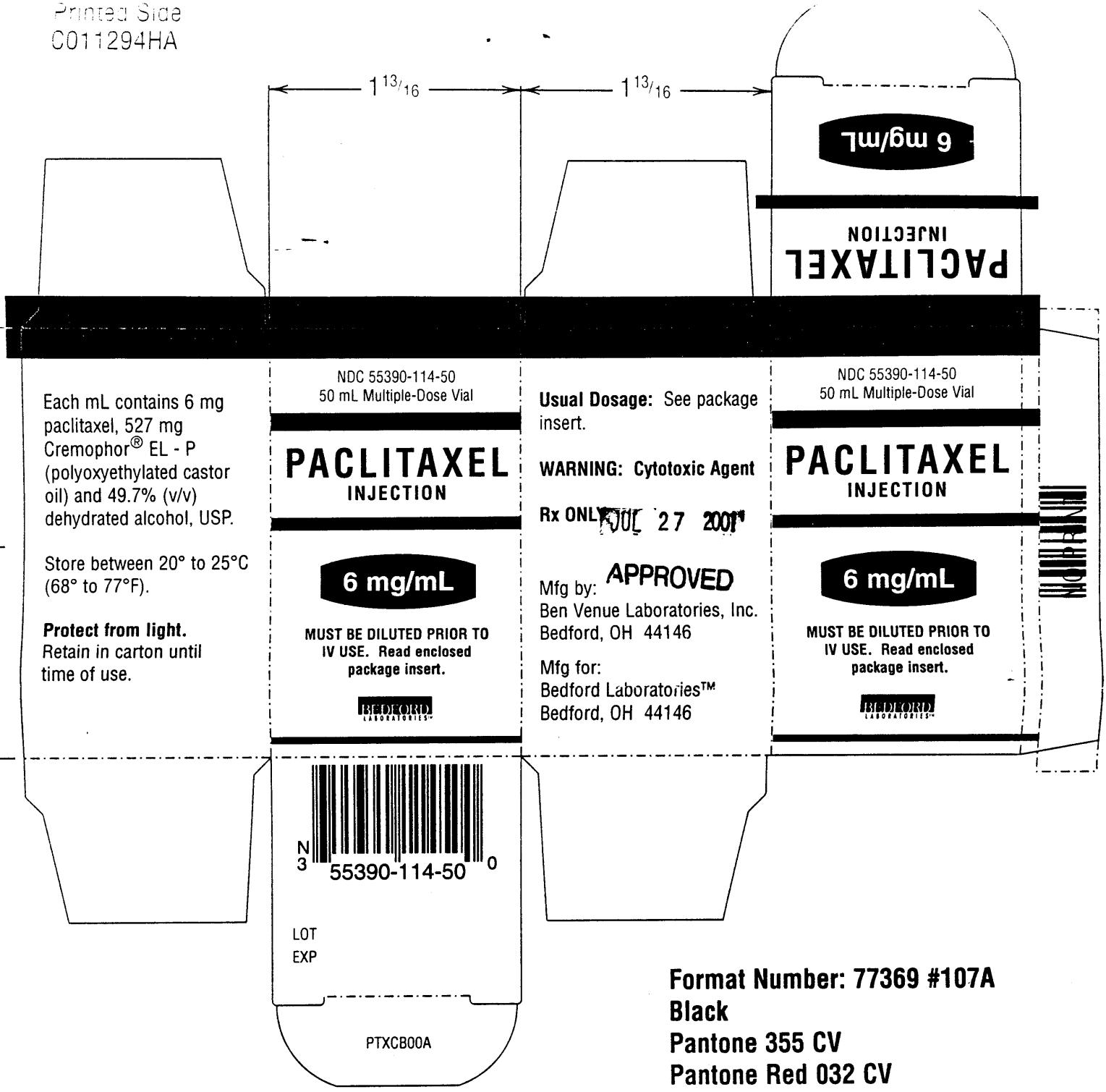

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75-190
AP 7/27/01

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C011294GA
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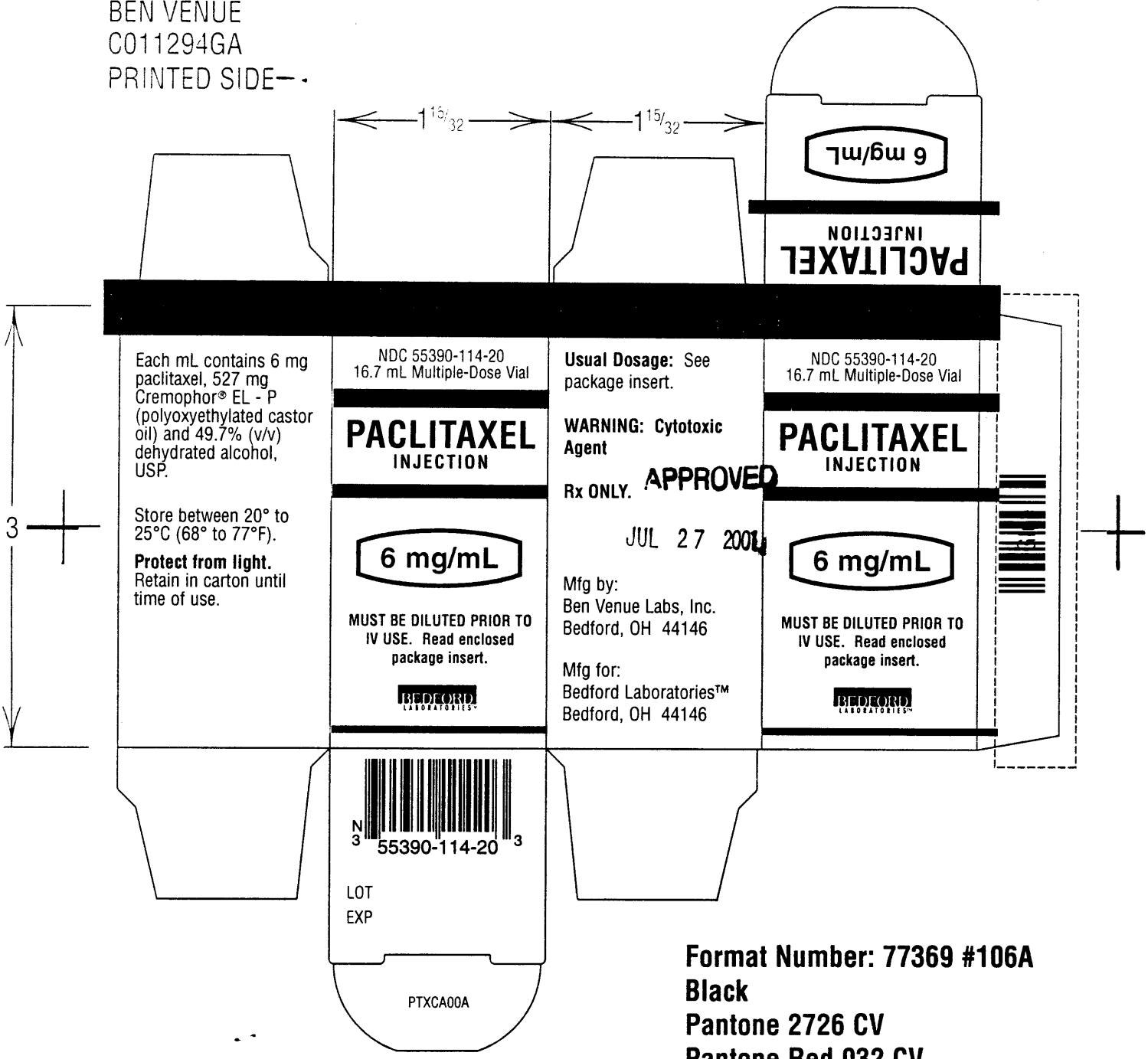

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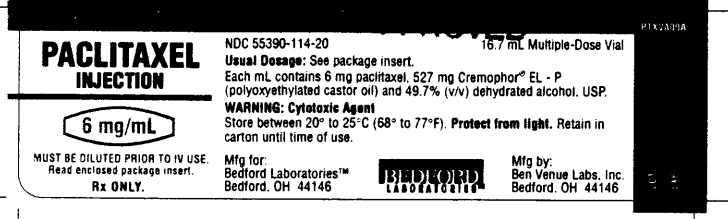


CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-190

CHEMISTRY REVIEW(S)

DW

1. CHEMISTRY REVIEW NO.: 1

2. ANDA #: 75-190

3. NAME AND ADDRESS OF APPLICANT:

Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
270 Northfield Road, Bedford, Ohio 44146

4. LEGAL BASIS FOR SUBMISSION:

Reference-listed drug:	Taxol® Injection Bristol-Myers Squibb, Inc. Application No. N20262 001
Dosage form:	Injectable
Strength:	6 mg/mL

- The active ingredient(Paclitaxel) is the same as the active ingredient in the listed drug.
- The conditions of use for the proposed drug product are the same as the conditions of use for the approved drug product.
- The route of administration, dosage form, and strength of the proposed drug product are the same as the route of administration, dosage form, and strength of the approved drug product

Marketing exclusivity:

Bedford stated that Patent NO. 5,641,803 assigned to Bristol Myers Squibb, Inc.(published on June 24, 1997) which claims the reduction of hematologic toxicity by administering a antineoplatically effective amount of about 135 mg/m^2 and 175 mg/m^2 of Taxol® over a period of three hours or the reduction of both hematologic and neurotoxicity by administering about 135 mg/m^2 over three hours is a prior art reported by Kris et al., Cancer treatment Rep., Vol 70, No.5(May 1986).

Based on the above information, Bedford Laboratories concluded that a marketing exclusivity for this product assigned to Bristol Myers Squibb, Inc. would expire on December 29, 1997.

Brief history:

21-AUG-97 Bedford's ANDA submission letter to FDA - This application was originally filed on December 30, 1996 with a Paragraph IV certification (Comparison between generic and referenced drug) for the 5,504,102 patent, which Bristol Myers chose not to list in the FDA's Orange book.

20-NOV-97 Bedford's Amendment to FDA - Bedford Lab. certified that notice has been provided to the patent holder, Bristol Myers Oncology that its unapproved ANDA 75-190 for Paclitaxel Injections, 6 mg/mL, 5 mL and 16.7 mL vials was submitted and accepted for filing and reviewing by the agency.

A copy of Bedford Lab. Paragraph IV certification was provided to the patent holder explaining the basis for Bedford Lab.'s opinion that patent number 5,641,803(expiring August 03, 2012), is invalid.

06-JAN-98 Bristol-Myers Squibb(BMS) letter to FDA - On December 17, 1997, BMS filed a lawsuit against Ben Venue Laboratories, Inc. and Bedford Lab. Alleging infringement of US patent No. 5,641,803.

20-JAN-98 Bristol-Myers Squibb(BMS) letter to FDA - Supplement to the letter dated 06-JAN-98.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Paclitaxel Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:: N/A

9. AMENDMENTS AND OTHER DATES:

21-AUG-97:	Date of ANDA submission
20-NOV-97:	Amendment to certify that notice has been provided to the patent holder, Bristol-Myers Oncology.
06-JAN-98:	Bristol-Myers Squibb letter to FDA informing a lawsuit filed against Ben Venue Laboratories.
26-JAN-98:	Amendment concerning the categorical exclusion claim and extraordinary circumstances.
05-FEB-98:	Update of 26-JAN-98 amendment.

10. PHARMACOLOGICAL CATEGORY: Antimicrotubule agent

11. Rx or OTC: Rx

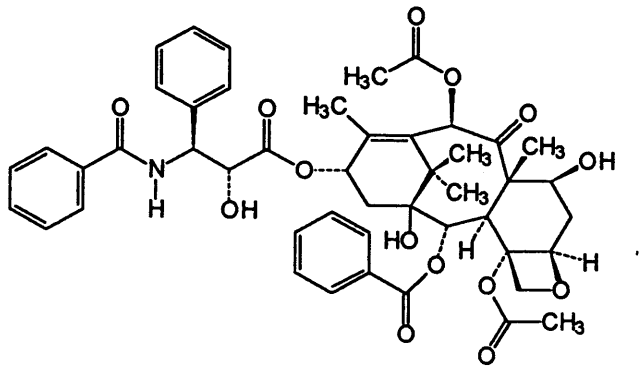
12. RELATED IND/NDA/DMF(s):

DMF #	TYPE	SUBJECT	HOLDER
[redacted]			

13. DOSAGE FORM: Injectable Sterile Solution

14. POTENCY: 6 mg/mL; 5 mL and 16.7 mL vials

15. CHEMICAL NAME AND STRUCTURE:
Benzenepropanoic acid, b-(benzoylamino)-a-hydroxy-, 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,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-9-yl ester, [2a*R*-[2aa,4b,4ab,6b,9a(a*R**,b*S**),11a,12a,12aa,12ba]]-.
$C_{47}H_{51}NO_{14}$, Mol. Wt. 853.93.



16. RECORDS AND REPORTS: N/A

17. COMMENTS: Comments are described in the review item No.38.

18. CONCLUSIONS AND RECOMMENDATIONS:

The application is not approvable.

19. REVIEWER: Gil Kang DATE COMPLETED: Feb 28, 1998

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1. **CHEMISTRY REVIEW NO.** 2

2. **ANDA #** 75-190

3. **NAME AND ADDRESS OF APPLICANT**

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
270 Northfield Road
Bedford, Ohio 44146

4. **LEGAL BASIS FOR SUBMISSION**

See Review #1.

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Paclitaxel

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

August 21, 1997	Original submission
November 20, 1997	Amendment (certifying that notice has been provided to patent holder)
January 6, 1998	Bristol-Myers Squibb's letter informing FDA that a lawsuit has been filed against Ben Venue.
January 26, 1998	Amendment (categorical exclusion claim and extraordinary circumstances)
February 5, 1998	Update of January 26, 1998 Amendment
March 26, 1998	Fax from Applicant requesting a telecon to discuss several FDA identified deficiencies
April 14, 1998	Telecon responding to applicant's March 26, 1998 FAX
May 6, 1998	New Correspondence (notification of patent litigation)
May 11, 1998	New Correspondence (Re: Patent Certification and revised Statement of Exclusivity)
June 3, 1998	New Correspondence (Re: Supplemental Patent Certification)
September 17, 1998	BMS Letter (Copy of Supplemental Complaint regarding alleged infringement of Patent)
February 5, 1999	FDA's Microbiology Deficiencies to Applicant
March 12, 1999	New Correspondence (notification of filing of Hatch/Waxman patent infringement actions)
*June 21, 1999	Amendment (Responding to FDA's Deficiencies per March 13, 1998 MAJOR amendment. Subject of this

review).

October 20, 1999 Amendment (Responding to Microbiology Deficiencies)

10. PHARMACOLOGICAL CATEGORY **11. Rx or OTC**

Antineoplastic Rx

12. RELATED IND/NDA/DMF(s)

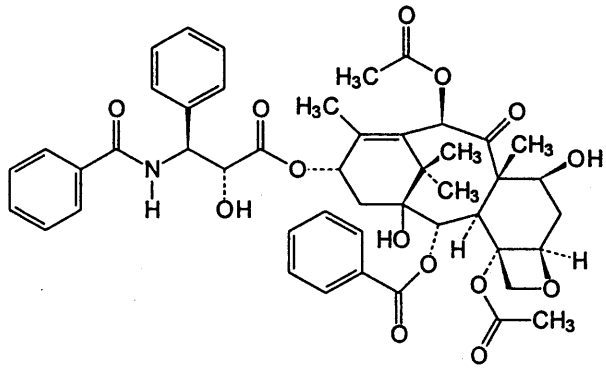
NDA 20-262 Bristol Myers Squibb
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM **14. POTENCY**

Injectable 6 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Paclitaxel. Benzenepropanoic acid, □-(benzoylamino)-□-hydroxy-, 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,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-9-yl ester, [2a*R*-[2a□,4□,4a□,6□,9□(□*R**,□*S**),11□,12□,12a□,12b□]]-. $C_{47}H_{51}NO_{14}$. 853.93. 33069-62-4. Antineoplastic. USAN 1995, page 499.



16. RECORDS AND REPORTS

N/A

17. COMMENTS

The applicant was asked to note and acknowledge the following:

1. **Firms referenced in this ANDA should be in compliance with current good manufacturing practices at the time of approval.**

   Response: The comment was acknowledged.

2. **The microbiology section is under review and you will be notified separately of any deficiencies.**

   Response: Comments from microbiology section were received under separate cover.

3. **Upon the resolution of the deficiencies of the method validation indicated above, the analytical methods will need to be validated by the FDA laboratories.**

   Response: The comment was acknowledged.

See item 38 of review for a listing of deficiencies.

18. **CONCLUSIONS AND RECOMMENDATIONS**

This ANDA is not approvable. Inform the applicant of deficiencies.

19. **REVIEWER:** **DATE COMPLETED:**

Shirley S. Brown October 27, 1999

APPEARS THIS WAY
ON ORIGINAL

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1. **CHEMISTRY REVIEW NO.** 3

2. **ANDA #** 75-190

3. **NAME AND ADDRESS OF APPLICANT**

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
270 Northfield Road
Bedford, Ohio 44146

4. **LEGAL BASIS FOR SUBMISSION**

See Review #1.

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Paclitaxel

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

August 21, 1997	Original submission
November 20, 1997	Amendment (certifying that notice has been provided to patent holder)
January 6, 1998	Bristol-Myers Squibb's letter informing FDA that a lawsuit has been filed against Ben Venue.
January 26, 1998	Amendment (categorical exclusion claim and extraordinary circumstances)
February 5, 1998	Update of January 26, 1998 Amendment
March 26, 1998	Fax from Applicant requesting a telecon to discuss several FDA identified deficiencies
April 14, 1998	Telecon responding to applicant's March 26, 1998 FAX
May 6, 1998	New Correspondence (notification of patent litigation)
May 11, 1998	New Correspondence (Re: Patent Certification and revised Statement of Exclusivity)
June 3, 1998	New Correspondence (Re: Supplemental Patent Certification)
September 17, 1998	BMS Letter (Copy of Supplemental Complaint regarding alleged infringement of Patent)
February 5, 1999	FDA's Microbiology Deficiencies to Applicant
March 12, 1999	New Correspondence (notification of filing of Hatch/Waxman patent infringement actions)
June 21, 1999	Amendment (Responding to FDA's MAJOR Deficiencies per March 13, 1998 NAL.

October 20, 1999	Amendment (Responding to Microbiology Deficiencies)
*May 16, 2000	Amendment (Responding to FDA's MAJOR Deficiencies per December 8, 1999 FAX)
May 23, 2000	NC (re: labeling telecon)
June 16, 2000	Amendment (Microbiology)
June 23, 2000	Amendment (Responding to telecon re: categorical exclusion)
*August 30, 2000	Amendment (Stability data. Supplemental Patent Certification responding to FDA telecon of August 15, 2000. Revised Exclusivity Statement responding to FDA telecon of August 23, 2000.)

*subject of this review

10. **PHARMACOLOGICAL CATEGORY** 11. **Rx or OTC**

Antineoplastic Rx

12. **RELATED IND/NDA/DMF(s)**

NDA 20-262 Bristol Myers Squibb
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM** 14. **POTENCY**

Injectable 6 mg/mL

15. **CHEMICAL NAME AND STRUCTURE**

See review 1.

16. **RECORDS AND REPORTS**

N/A

17. **COMMENTS**

The applicant was asked to note and acknowledge the following:

1. **The microbiologist's review of the October 20, 1999 submission for sterility assurance is pending.**

   Response: The comment was acknowledged.

2. **The drug product is not official in USP 23. Methods Validation**

will be requested following resolution of the testing issues.

Response: The comment was acknowledged.

3. **Your response must also address the labeling deficiencies.**

Response: The response to the labeling deficiencies is included in this amendment.

See item 38 of review for a listing of deficiencies.

18. **CONCLUSIONS AND RECOMMENDATIONS**

This ANDA is not approvable. Inform the applicant of deficiencies.

19. **REVIEWER:**	**DATE COMPLETED:**
Shirley S. Brown	November 13, 2000 November 28, 2000 (revised)

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pages of trade secret and /or confidential commercial information

1. **CHEMISTRY REVIEW NO.** 4

2. **ANDA #** 75-190

3. **NAME AND ADDRESS OF APPLICANT**

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
270 Northfield Road
Bedford, Ohio 44146

4. **LEGAL BASIS FOR SUBMISSION**

See Review #1.

5. **SUPPLEMENT(s)**

N/A

6. **PROPRIETARY NAME**

N/A

7. **NONPROPRIETARY NAME**

Paclitaxel

8. **SUPPLEMENT(s) PROVIDE(s) FOR:**

N/A

9. **AMENDMENTS AND OTHER DATES:**

August 21, 1997	Original submission
November 20, 1997	Amendment (certifying that notice has been provided to patent holder)
January 6, 1998	Bristol-Myers Squibb's letter informing FDA that a lawsuit has been filed against Ben Venue.
January 26, 1998	Amendment (categorical exclusion claim and extraordinary circumstances)
February 5, 1998	Update of January 26, 1998 Amendment
March 26, 1998	Fax from Applicant requesting a telecon to discuss several FDA identified deficiencies
April 14, 1998	Telecon responding to applicant's March 26, 1998 FAX
May 6, 1998	New Correspondence (notification of patent litigation)
May 11, 1998	New Correspondence (Re: Patent Certification and revised Statement of Exclusivity)
June 3, 1998	New Correspondence (Re: Supplemental Patent Certification)
September 17, 1998	BMS Letter (Copy of Supplemental Complaint regarding alleged infringement of Patent)
February 5, 1999	FDA's Microbiology Deficiencies to Applicant
March 12, 1999	New Correspondence (notification of filing of Hatch/Waxman patent infringement actions)
June 21, 1999	Amendment (Responding to FDA's MAJOR Deficiencies per March 13, 1998 NAL.

October 20, 1999	Amendment (Responding to Microbiology Deficiencies)
May 16, 2000	Amendment (Responding to FDA's MAJOR Deficiencies per December 8, 1999 FAX)
May 23, 2000	NC (re: labeling telecon)
June 16, 2000	Amendment (Microbiology)
June 23, 2000	Amendment (Responding to telecon re: categorical exclusion)
August 30, 2000	Amendment (Stability data. Supplemental Patent Certification responding to FDA telecon of August 15, 2000. Revised Exclusivity Statement responding to FDA telecon of August 23, 2000.)
December 12, 2000	NC (Request telecon)
*January 24, 2001	Amendment (Responding to FDA's MAJOR Deficiencies per December 8, 2000 Deficiencies)
*February 14, 2001	NC (Reclassifying the amendment as Minor)
*May 15, 2001	Telephone Amendment (responding to deficiency per review #4. The deficiency was corresponded to applicant April 30, 2001 by telephone.)
*May 25, 2001	Telephone Amendment (responding May 25, 2001 telecon.)

*subject of this review

10. **PHARMACOLOGICAL CATEGORY**

Antineoplastic

11. **Rx or OTC**

Rx

12. **RELATED IND/NDA/DMF(s)**

NDA 20-262 [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. **DOSAGE FORM**

Injectable

14. **POTENCY**

6 mg/ml, 5 mL, 16.7 mL, 50 mL.

15. **CHEMICAL NAME AND STRUCTURE**

See review 1.

16. **RECORDS AND REPORTS**

N/A

17. **COMMENTS**

The applicant was asked to note and acknowledge the following:

1. **The microbiologist's review for the 50-mL container and the June 16, 2000 submission for sterility assurance is pending. Labeling and Bioequivalence reviews for the 50-ml container are also pending.**

   Response: The comment was acknowledged.

2. **The review of your request for categorical exclusion per the June 23, 2000 amendment is pending.**

   Response: The comment was acknowledged.

3. **The drug product is not official in USP 23. Methods Validation will be requested following resolution of the testing issues.**

   Response: The comment was acknowledged.

4. **Your response must also address the labeling deficiencies.**

   Response: The labeling deficiencies are addressed in Part C of this amendment.

5. **Per the April 30, 2001 telecon, the applicant was asked to "Commit to resolve any MV issues per the MV report".**

   Response: The commitment was made.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable. Pending - Updated EER. MVP has been issued to Philadelphia.

19. REVIEWER:

/S/

Shirley S. Brown

/S/
6/15/01

DATE COMPLETED:

June 15 2001
May 29, 2001
March 28, 2001
April 11, 2001 (revised)
May 18, 2001 (May 15, 2001 Telephone Amendment)
May 29, 2001 (May 25, 2001 Telephone Amendment)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-190

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS
Microbiologists Review #1
November 18, 1998

A. 1. ANDA: **75-190**

APPLICANT: Bedford Laboratories
A division of Ben Venue
Laboratories, Inc.
300 Northfield Road
Bedford, Ohio 44146

2. PRODUCT NAMES: Paclitaxel Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 6 mg/ml in 5 ml (30 mg) and 16.7 ml (100 mg)vials, Single-dose vials, Intravenous

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antitumor Agent

B. 1. DATE OF INITIAL SUBMISSION: August 21, 1997
Subject of this Review

2. DATE OF AMENDMENT:
Amendment dated June 5, 1998. Supplemental patent certifications for U.S. Patent 5,670,537 and 5,496,804.
Amendment dated May 12,1998. Patent Certification for U.S. patent 5,670,537, 5,496,804 and revised Statement of Exclusivity.
Amendment dated Feb. 10, 1998. Environmental Assessment statement.

3. RELATED DOCUMENTS: DMF [redacted] DMF [redacted]
DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted]

4. ASSIGNED FOR REVIEW: 10/26/98

C. REMARKS:

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and a Microbiologist's draft of deficiencies to be provided to the Applicant found at the end of the review.

/S/ 12/23/98
Lynne A. Ensor, Ph.D.

/S/ 12/31/98

cc:

Original ANDA
Duplicate ANDA
Division Copy
Field Copy
Drafted by L. Ensor, HFD 640 x:wp\microrev\75190
Initialed by M. Fanning, P. Cooney /S/ 1/5/99

APPEARS THIS WAY
ON ORIGINAL

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OFFICE OF GENERIC DRUGS, HFD-620
Microbiologists Review #2
May 17, 2000

A. 1. ANDA: 75-190

APPLICANT: Bedford Laboratories
A division of Ben Venue Labs., Inc.
300 Northfield Road
Bedford, Ohio 44146

2. PRODUCT NAMES: Paclitaxel Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 6 mg/ml in 5 ml (30 mg) and 16.7 ml (100 mg)vials, Single-dose vials, Intravenous

4. METHOD OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antitumor Agent

B. 1. DATE OF INITIAL SUBMISSION: August 21, 1997

2. DATE OF AMENDMENT: October 20, 1999
Subject of this Review (Received October 21, 1999)

3. RELATED DOCUMENTS: none
4. ASSIGNED FOR REVIEW: May 5, 2000

C. REMARKS: The subject amendment provides responses to the microbiology deficiencies provided to the applicant September 24, 1999.

D. CONCLUSIONS: The submission is **not recommended** for approval on the basis of sterility assurance. The [redacted] Specific comments are provided in "E. Review Notes" and a Microbiologist's draft of deficiencies to be provided to the Applicant found at the end of the review.

/S/ 5/17/00
Lynne A. Ensor, Ph.D.

cc:
Original ANDA
Duplicate ANDA
Division Copy
Field Copy
Drafted by L. Ensor, HFD 600 v:microrev\75190a
Initialed by M. Fanning /S/ 5/19/00

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pages of trade secret and/or confidential commercial information

MHM

3.1

OFFICE OF GENERIC DRUGS, HFD-620
Microbiologists Review #3
December 13, 2000

A. 1. ANDA: 75-190

APPLICANT: Bedford Laboratories
A division of Ben Venue Labs., Inc.
300 Northfield Road
Bedford, Ohio 44146

2. PRODUCT NAMES: Paclitaxel Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 6 mg/ml in 5 ml vial (13mm, 30 mg/vial), 16.7 ml in 20 cc vials (13mm, 100 mg/vial) and 48 mL (20mm, 290 mg/vial) in 50 cc vials MULTIPLE-dose vials, Intravenous

4. METHOD OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antitumor Agent

B. 1. DATE OF INITIAL SUBMISSION: August 21, 1997

2. DATE OF AMENDMENTS: October 20, 1999

May 16, 2000
Subject of this Review (Received May 17, 2000)

June 16, 2000
Subject of this Review (Received June 19, 2000)

3. RELATED DOCUMENTS: none
4. ASSIGNED FOR REVIEW: December 6, 2000

C. REMARKS: The first subject amendment (5/16/00) is an amendment for chemistry and labeling deficiencies. However, a microbiology review was prepared because the amendment contained Antimicrobial Preservative Effectiveness Test data and provides for the addition of a 50 mL dosage form.

The second subject amendment (6/16/00) provides responses to the microbiology deficiencies provided to the applicant May 23, 2000. A telecon held with the applicant 6/16/00 is also referenced in the amendment.

D. CONCLUSIONS: The submission **is recommended** for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".

/S/ 12/19/00
Lynne A. Ensor, Ph.D.

/S/ 12/19/00

cc:

Original ANDA
Duplicate ANDA
Division Copy
Field Copy
Drafted by L. Ensor, HFD 600 v:microrev\75190a2
Initialed by A. High

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pages of trade secret and/or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-190

BIOEQUIVALENCE REVIEW

Paclitaxel Injection, 6 mg/mL
5 mL, 16.7 mL and 50 mL Vials
ANDA #75-190
Reviewer: Moheb H. Makary
W. 75190W.500

Bedford Laboratories
Bedford, Ohio
Submission Date:
May 16, 2000

Review of a Waiver Request

I. Objective:

The firm has requested a waiver of *in vivo* bioequivalence study requirements for its product Paclitaxel Injection, 6 mg/mL, 50 mL vial. This represents the addition of a new dosage to this unapproved application. The reference listed drug is Taxol[R] Injection, 6 mg/mL, manufactured by Bristol-Myers Squibb. Paclitaxel Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion.

Paclitaxel is a natural product with antitumor activity. Taxol[R] (paclitaxel) is obtained via a semi-synthetic process from Taxus baccata.

Taxol[R] is available in 30 mg (5 mL), 100 mg (16.7 mL) and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor[R] EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

II. Background:

On August 21, 1997, Bedford submitted a request for a waiver of *in vivo* study requirements to the Division of Bioequivalence for its Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials. The information submitted by the firm demonstrates that Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials falls under 21 CFR 320.22 (b)(1). The waiver of *in vivo* study requirements for Bedford's Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials, was granted (review dated December 31, 1997).

III. Formulation: (Not to be released under FOI)

The formulations of Bedford's Paclitaxel Injection and Bristol-Myers Squibb's Taxol[R] Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL vials are shown below:

Listed Drug Taxol[R]		Proposed Drug	
Paclitaxel	6 mg/mL	Paclitaxel	6 mg/mL
Cremopher[R] EL-P	527 mg/mL	Cremopher[R] EL-P	527 mg/mL
Dehydrated Alcohol	49.7%(v/v)	Dehydrated Alcohol	49.7%(v/v)

IV. Comments:

1. The active and inactive ingredients and their concentrations for the test product are the same as those of the innovator's Taxol[R] Injection 6 mg/mL; 5 mL, 16.7 mL and 50 vials, manufactured by Bristol-Myers Squibb.

2. Waiver of *in vivo* bioequivalence study requirements may be granted based on 21 CFR 320.22(b)(1).

V. Recommendation:

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories, demonstrates that Paclitaxel Injection, 6 mg/mL; 50 mL vial falls under 21 CFR 320.22 (b)(1). The waiver of *in vivo* bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation 6 mg/mL; 50 mL vial, to be bioequivalent to Taxol[R] Injectable, 6 mg/mL; 50 mL vial, manufactured by Bristol-Myers Squibb.

The firm should be informed of the above recommendation.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III /S/ 1/9/01

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT /S/ Date: 1/10/01

Concur: /S/ Date: 1/11/2001
for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-190 SPONSOR : **Bedford Laboratories**

DRUG AND DOSAGE FORM : Paclitaxel Injection, 6 mg/mL

STRENGTH(S) : 6 mg/mL, 50 mL vial

TYPES OF STUDIES : Amendment

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : The waiver is granted
Dissolution: N/A

DSI INSPECTION STATUS

Inspection needed: (NO)	Inspection status:	Inspection results:
First Generic ____ New facility _____ For cause _____ other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : 3

INITIAL : _ /S/ _____ DATE : 1/9/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : 3

INITIAL : _ /S/ _____ DATE : 1/10/01

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for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 1/11/2001

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-140 SPONSOR: Bedford Lab
DRUG: Paclitaxel
DOSAGE FORM: Injection
STRENGTH(s): 6 mg/mL, 5 mL and 16.7 Vials
TYPE OF STUDY: Single/Multiple N/A Fasting/Fed
STUDY SITE: N/A

STUDY SUMMARY:

Waiver is granted based on 320.22(b)(1).

DISSOLUTION: N/A

PRIMARY REVIEWER: Mahtab N. Mahdy BRANCH: ~~III~~

INITIAL: /S/ DATE: 12/23/97

BRANCH CHIEF: BRANCH:

INITIAL: /S/ DATE: 12/23/97

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 12/31/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

Paclitaxel Injection, 6 mg/mL
5 mL and 16.7 mL Vials
ANDA #75-190
Reviewer: Moheb H. Makary
WP. 75190W.897

Bedford Laboratories
Bedford, Ohio
Submission Date:
August 21, 1997

Review of a Waiver Request

I. Objective:

The firm has requested a waiver of bioequivalence study requirements for its product Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL Vials. Innovator product is Taxol® Injection 6 mg/mL; 5 mL and 16.7 mL Vials, manufactured by Bristol-Myers Squibb. Paclitaxel Injection is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Taxol^{R} is available in 30 mg (5 mL) and 100 mg (16.7 mL) single-dose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP. Paclitaxel is a natural product with antitumor activity. Taxol^{R} (paclitaxel) is obtained via a semi-synthetic process from Taxus baccata.

II. Formulation: **(Not to be released under FOI)**

The formulations of Bedford's Paclitaxel Injection and Bristol-Myers Squibb's Taxol^{R} Injection, 6 mg/mL; 5 mL and 16.7 mL Vials are shown below:

Listed Drug Taxol^{R}	**Proposed Drug**
Paclitaxel, 6 mg/mL	Paclitaxel, 6 mg/mL
Cremopher^{R} EL, 527 mg/mL	Cremopher^{R} EL, 527 mg/mL
Dehydrated Alcohol, 49.7%(v/v)	Dehydrated Alcohol, 49.7%(v/v)

III. Comments:

1. The active and inactive ingredients and their concentrations for the test product are the same as those of the innovator's Taxol^{R} Injection 6 mg/mL; 5 mL and 16.7 mL Vials, manufactured by

Bristol-Myers Squibb.

2. Waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR 320.22(b)(1).

IV. Recommendation:

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories, demonstrates that Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL Vials falls under 21 CFR 320.22 (b)(1). The waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation 6 mg/mL; 5 mL and 16.7 mL Vials to be bioequivalent to Taxol[R] Injectable, 6 mg/mL; 5 mL and 16.7 mL Vials, manufactured by Bristol-Myers Squibb.

The firm should be informed of the above recommendation.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 12/23/97

Concur: /S/ Date: 12/31/97
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/11-17-97, 12-23-97 wp 75190W.897
cc: ANDA #75-190, original, HFD-658(Makary), Drug File, Division File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 75-190 APPLICANT: Bedford Laboratories

DRUG PRODUCT: Paclitaxel Injection, 6 mg/mL; 50 mL Vial

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 75-190 APPLICANT: Bedford Laboratories

DRUG PRODUCT:Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL Vials

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #75190
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements: (Draft and Final with Dates)
HFD-658/Reviewer Moheb Makary 12/23/97
HFD-658/Bio Team Leader Ramakant Mhatre 12/23/97
HFD- /Project Manager Nancy Chamberlin
HFD-600/Division Sign Off Rabindra Patnaik 12/31/97

X:\NEW\FIRMSAM\BEDFORD\LTRS&REV\75190W.897
BIOEQUIVALENCY - ACCEPTABLE

WAIVER (WAI)

Strengths: 6mg/ml (5 ml and 16.7 ml vials)
Outcome: **AC** **IC** **UN** **NC**

Outcome Decisions:
AC - Acceptable
NC - No Action

UN - Unacceptable (fatal flaw)
IC - Incomplete

APPEARS THIS WAY
ON ORIGINAL

MESSAGE CONFIRMATION

12/08/99 07:35
ID=OGD/CDER DOC RM1

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT	
12/08	06'23"	4402322772	CALLING	14	OK	0000

12/08/99 07:27 OGD/CDER DOC RM1 → 914402322772 NO.136 P01

MAJOR AMENDMENT

DEC 8 [illegible]

ANDA 75-190

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
PHONE: (440) 232-3320

ATTN: Shahid Ahmed
FAX: (440) 232-2772

FROM: Michelle Dillahunt
PROJECT MANAGER (301) 827–5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 21, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Paclitaxel Injection, 6 mg/mL, 5 mL and 16.7 mL vials.

Reference is also made to your amendment(s) dated June 21, 1999.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons

MESSAGE CONFIRMATION

12/08/99 10:20
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12/08/99 10:19 OGD/CDER DOC RM1 → 914402322772 NO.137 P01

DEC 8

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-190 APPLICANT: Bedford Laboratories, Inc.

DRUG PRODUCT: Paclitaxel Injection, 6 mg/mL

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Drug Master File [redacted] for the active ingredient is deficient. The Drug Master Holder has been notified.

2. The specifications for the drug substance are not acceptable. We acknowledge your statement that (1) you are in the process of revising current specifications and test methods to include the individual chemical names and limits for the known impurities and (2) following updating the specifications and test method, the application will be amended. Please provide this information.

3. You [redacted] supporting this ANDA in order to compensate for out of [redacted] No investigation/discussion is provided as to why there was a failure in the first place. The [redacted] and is not acceptable

ANDA 75-190

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 27, 2001

FROM: Gary J. Buehler /S/ 9/27/01
Director
Office of Generic Drugs

SUBJECT: ANDA 75-190, Bedford Laboratories, Inc. (Bedford), Paclitaxel Injection

TO: The Record

These are the facts underlying the approval of ANDA 75-190, paclitaxel injection, an ANDA submitted by Bedford Laboratories on August 21, 1997, and the record upon which the decision to approve the ANDA was based:

ANDA 75-190 seeks approval of a generic version of paclitaxel, the brand name of which is Taxol, a drug manufactured by Bristol Myers Squibb (BMS). ANDA 75-190 was received by FDA on August 25, 1997.

On July 21, 1997, BMS listed patent 5,641,803 (patent '803) with FDA, on August 29, 1997, BMS listed patent 5,496,804 and on October 9, 1997, BMS listed patent 5,670,537 (patent '537) with

the agency, asserting that these patents cover Taxol. Bedford filed PIV certifications to patents '803, '804 and '537, claiming the patents were invalid, unenforceable, or not infringed. See 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(12)(i)(A)(4). Because Bedford was sued by BMS within 45 days of giving BMS notice of its paragraph IV certifications, approval of Bedford's ANDA was stayed for 30 months, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii). Bedford did not provide proof of notification for the '537 patent and the '804 patent to the Agency. Therefore, the Agency based the 30-month stay of approval of Bedford's ANDA beginning from July 17, 1998, the date that BMS filed a supplemental complaint against Bedford (Civil Action No 97cv6050), United States District Court of New Jersey. The Agency considers the 30 months to have expired on January 17, 2001.

On August 1, 2000, the Patent and Trademark Office issued a new patent to American Bioscience Inc. (ABI), U.S. Patent Number 6,096,331 (the '331 patent). ABI claimed that this patent covered BMS's Taxol product.

On August 11, 2000, ABI obtained a temporary restraining order (TRO) from a district court in California directing BMS to list

the patent with FDA in Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). That order stated that, should ABI fail to prevail in the underlying litigation, BMS would be required to take all steps necessary to delist the patent.

On August 11, 2000, BMS listed the patent in the Orange Book pursuant to the court order. This was an extremely unusual condition for patent listing and the first time it was requested that a patent be listed pursuant to a court order.

On August 30, 2000 Bedford submitted a Paragraph I certification to the '331 patent. See 21 U.S.C. § 355(j)(2)(A)(vii)(I); 21 C.F.R. § 314.94(a)(12)(i)(A)(1). This certification was incorrect. The effect of this submission is discussed below.

On September 7, 2000, the district court in California dissolved the TRO, dismissed ABI's complaint, and ordered BMS to delist the '331 patent from the Orange Book to restore the status quo. The court stayed its order until September 13, 2000.

BMS submitted another listing for the patent on September 11, 2000. This listing made no mention of the original court-ordered August 11, 2000, listing.

In its September 7, 2000 Order, the California district court recommended that FDA "toll the period in which BMS may timely cause such listing." OGD did not follow this recommendation for four reasons: (1) FDA was not a party to the California litigation in which the order was issued, and therefore, FDA's views were not presented to the court nor did the court have jurisdiction over the agency; (2) the 30-day time period is a statutory limit for timely submission, and it is not clear that the agency has the authority to extend that period; rather FDA believes that the 30 day period represents a Congressional determination that 30 days is sufficient; (3) even if the agency did have the authority to toll the deadline, it would set an undesirable precedent that future holders of pioneer applications could use to try to obtain extensions of the 30 day period, thereby blocking the approval of generic applications; and (4) the agency saw no reason why BMS could not have voluntarily listed the '331 patent within 30 days of its issuance if BMS

thought the listing was appropriate under the Federal Food, Drug, and Cosmetic Act.

On September 14, 2000, BMS submitted a letter to FDA to comply with the court order to delist the patent. The letter states "BMS hereby withdraws the Original Listing to the extent that listing was compelled by the TRO."

Because the court order directing BMS to submit the patent to FDA was dissolved, and BMS withdrew the original submission made pursuant to the TRO, FDA considered BMS's first submission of the patent on August 11, 2000, to be without effect. The September 11, 2000 submission by BMS was given effect. However, patents must be listed with FDA within 30 days of their issuance. See 21 U.S.C. § 355(c)(2). An FDA regulation, the "late-listing regulation," directly applies to patents submitted to FDA more than 30 days after they are issued. 21 C.F.R. § 314.94(a)(12)(vi). That regulation provides that pending ANDAs need not certify to patents that are listed beyond the 30-day interval set out in the statute. Here, because BMS withdrew the August 11 listing, the only listing remaining for the '331 patent was the September 11 listing, which was submitted more than 30

days after the patent's August 1, 2000, issuance, and was therefore, untimely.

On December 14, 2000, BMS listed an additional patent in the Orange Book. U.S. Patent Number 6150398 ('398) is a use patent identified by the patent use code U-380 in the Orange Book. U-380 is for "combinations of Taxol (paclitaxel)and cisplatin which are suitable for the treatment of ovarian and non-small cell lung carcinomas."

On April 21, 2001, the 180-day generic drug exclusivity period granted to ANDA 75-184, Baker Norton, paclitaxel injection, expired.

On May 30, 2001, Bedford submitted a method of use statement to the '398 patent pursuant to 21 C.F.R.§ 314.94(a)(12)(iii) indicating that they were not claiming the use covered by the '398 patent.

On June 8, 2001, Bedford amended their patent certification to the '331 patent to state that the patent was not timely filed

pursuant to 21 CFR 314.94(a)(12)(vi), and requested full approval of this ANDA.

OGD has resolved all the scientific and technical issues related to the approval of ANDA 75-190

The 30 month stay had expired for patents '803, '804, and '537. Patent '398 was addressed by a method of use statement pursuant to 21 C.F.R. § 314.94(a)(12)(iii).

With respect to the Paragraph I certification to the '331 patent, Bedford argues in a July 2, 2001 letter from counsel Marty Pavane to OCC attorney Annamarie Kempic that its ANDA should be approved under the late-listing regulation for three reasons:

1. The U.S. District Court has held that the '331 patent was not listed within the thirty day statutory period and, therefore, Bedford is entitled to the benefit of this holding, especially in light of agency's approval of another generic under the late-listing regulation (Zenith Goldline).

2. The late listing regulation applies only to listings concerning other patents, not the patent that is the trigger for the application of the regulation.

3. Bedford could not find the listing when it searched the online and hard copy versions of the Orange Book on August 15, 2000.

The late-listing regulation states the following:

> If a patent on the listed drug is issued and the holder of the approved application for the listed drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an abbreviated new drug application for that drug *that contained an appropriate patent certification before the submission of the patent information is not required to submit an amended certification.*

21 C.F.R. § 314.94(a)(12)(A) (emphasis added).

At issue here is whether the Paragraph I certification that Bedford filed precludes the application of the late listing

regulation to its ANDA, in that the Paragraph I certification would not be an "appropriate" certification.

While Bedford is correct in stating that the district court has determined that the '331 patent was late listed, the court's holding in and of itself does not compel the approval of the Bedford ANDA. Rather, the issue is whether Bedford needs to file a certification to the '331 patent.

The fact that the district court did find that the patent was late-listed, however, is significant in that it supports the application of the late-listing regulation to other generic applicants who had "appropriate" certifications at the time of the September 11 listing. The district court found that FDA was not arbitrary and capricious in finding that the August 11 listing was null, in that the district court in California never had the authority to issue the order and, therefore, BMS's TRO-compelled listing was without effect. Particularly compelling in this regard is the fact that BMS clearly had its own doubts about the validity of the August 11 listing; there is no other explanation for its September 11 listing. In addition, BMS could have listed voluntarily before August 31, and plainly chose not

to do so. Therefore, the fact that the valid listing is that of September 11, rather than August 11, is clearly supported by the agency record and by the district court's holding.

The next step, then, is to assess what effect, if any, the Bedford Paragraph I certification should play. Bedford should be treated consistently with the other generic applicants, but patent-holder ABI should not be prejudiced. Bedford's contention that it could not find evidence of a "listing" in the on-line or hard copy of the Orange Book and, therefore, its Paragraph I listing should be viewed as appropriate, is wrong. The applicable regulation, 21 C.F.R § 314.53(d)(5), clearly states that a listing is deemed to be effective when it is received by FDA. This accounts for delays in publishing and transcribing information. Given the clear language of the regulation, and the fact that FDA notified Bedford of a new listing on August 15, 2000, and the fact that at least two other generic applicants filed Paragraph IV certifications – Bedford is plainly incorrect in defending its Paragraph I listing on this grounds.

Bedford's remaining argument, that the late listing regulation should not be applied to the patent that is the trigger for the

application of the regulation is, however, more compelling. This is the first time that a court has ordered a pioneer to list a patent. The tenuous wording of the August 11 court order (stating that the patent should be immediately delisted if patent-holder ABI failed to prevail in its lawsuit), as well as jurisdictional questions that surfaced almost immediately, caused an unprecedented situation with respect to pending ANDAs. FDA views the August 11 listing as null from the time it was issued, and the district court has supported the agency's view. Moreover, that fact that Bedford may have made a mistake, coupled with the uncertainty written into the August 11 court order, the obvious reluctance of BMS to list, and the jurisdictional challenges to the order, should not prejudice its product. Because the August 11 listing is null, the only valid listing is the September 11 listing, and that listing is beyond the 30 day time period set out in the FDCA. Therefore, under the late-listing regulation, pending ANDA applicants are not required to certify to that patent. Because Bedford is not required to file *any* certification, its Paragraph I certification should not impede application of the late listing regulation.

To find otherwise would be illogical, for the trigger for the certification (the August 11 TRO-ordered listing) was later found to be invalid. In the typical, orderly listing process, the patent that triggers the application of the late-listing regulation has not, by definition, yet been listed. It cannot, therefore, affect the application of the late-listing regulation. Because the August 11 listing is without effect, it cannot trigger obligations that would not otherwise exist.

This interpretation is consistent with FDA analysis concerning the BNP approval and ABI's challenge to the application of the late-listing regulation, and is consistent with the agency's approach to other, similarly situated, generic applicants. Moreover, given the unique factual circumstances giving rise to this case, it is doubtful that another patent will act as both trigger for the application of the late-listing regulation and the actual listed patent. While ABI may contend that an incorrect paragraph citation results in a "inappropriate" certification, that argument does not hold up under the facts in this case, for that would mean that the same patent would be late listed and timely listed and both cannot be true. Moreover, a

triggering event that is later found to be void should not impose obligations which would not independently exist.

ABI may contend that the listing was "continued and continuous" and, therefore, "validates" the August 11 listing, requiring all other generic applicants to file paragraph IV certifications. Given the tentative wording of the August 11 court order, the fact that BMS itself acted in a manner inconsistent with a belief that the August 11 listing was valid, and, most importantly, the district court's support of FDA's conclusion that the August 11 listing is not valid, FDA does not view the August 11 listing as imposing any obligations on Bedford or any other generic applicant.

ABI also may contend that it is prejudiced in that it did not have an opportunity to sue Bedford for patent infringement following a paragraph IV certification. This contention falls short for two reasons: first, Bedford could have (even under ABI's analysis) "*appropriately*" filed a Paragraph III certification, which does not carry a trigger for litigation. Or they could have filed no certification at all until the status of the patent listing was resolved, as was the case with Mylan. ABI

cannot, therefore, state with any certainty that it has been deprived of a right to pursue patent litigation against Bedford. Second, ABI could still bring suit against Bedford and, if successful, would be eligible for treble damages, so ABI plainly is not without remedy. Finally, Bedford should be treated no worse than other applicants with pending ANDAs at the time of the September 11 listing, and none of those applicants were compelled to file a Paragraph IV certification and raise the potential for a significant delay in approval while awaiting the resolution of patent litigation. In addition, as has been revealed in the ABI litigation against FDA, the transcript of the proceedings in the district court in California make clear that ABI - far from propelling the TRO proceedings along - acted in a manner that further delayed the ultimate resolution of the court's jurisdiction and voluntarily chose to have that issue resolved *after* the August 31 deadline for listing the '331 patent.

Given that Bedford's Paragraph I certification was unnecessary to begin with, non-prejudicial to ABI, triggered by an invalid listing pursuant to a subsequently dismissed order by a court without jurisdiction, holding Bedford to an added obligation of filing a Paragraph IV certification is unnecessary under the law

and harmful to Bedford, while treating other pending ANDA applicants in a more favorable fashion. For the reasons discussed above, FDA does not believe that ABI is prejudiced by Bedford's approval.

All of the scientific and regulatory issues have been resolved for Bedford's ANDA 75-190, and it is otherwise ready for approval. Therefore, it is OGD's view, based upon the facts outlined above that Bedford ANDA's, 75-190, paclitaxel injection, may be approved under the late-listing regulation, 21 C.F.R. § 314.94(a)(12)(A).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-190

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-190** Date of Submission: **June 21, 1999**

Applicant's Name: **Bedford Laboratories**

Established Name: **Paclitaxel Injection, 6 mg/mL**

Labeling Deficiencies:

1. CONTAINER (5 mL and 16.7 mL vials)

   a. Please note that the statement MUST BE DILUTED PRIOR TO IV USE must appear in red in accord with the reference listed drug's labels and labeling.

2. CARTON (1 x 5 mL and 1 x 16.7 mL vials)

   See comments under CONTAINER.

3. INSERT

   Due to changes in the insert labeling of the reference listed drug, TAXOL® (Bristol-Myers Squibb; approved January 8, 1999), please revise your insert labeling to be in accord with the enclosed copy of this labeling. In addition, please update your Patent Certification and Statement of Exclusivity.

Please revise your container labels, carton and insert labeling, as instructed above, and submit 12 copies of final printed container labels along with 12 copies of final printed carton labeling and 4 copies of draft insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-190** Date of Submission: **May 16, 2000**
Applicant's Name: **Bedford Laboratories**
Established Name: **Paclitaxel Injection, 6 mg/mL**
Labeling Deficiencies:

1. CONTAINER (5 mL, 16.7 mL and 50 mL vials) - Delete the word [redacted] from the established name of this product.
2. CARTON (1 x 5 mL, 1 x 16.7 mL, and 1 x 50 mL vials) - See comments under CONTAINER.
3. INSERT
   a. BOXED WARNINGS – Revise the first sentence of paragraph two of this section to read as follows:

      ...less than 1500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil counts of less than 1000 cells/mm^3.

      NOTE: We acknowledge you are not seeking approval for Kaposi's sarcoma. However, it is possible that patients may have a concurrent disease state for which paclitaxel is indicated, therefore, as a matter of safety, please include this information.

   b. CONTRAINDICATIONS – Revise the last sentence of this section to read as follows:

      ...of 1500 cells/mm^3 or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm^3.

   c. PRECAUTIONS (Hepatic) – Delete the word " [redacted] from the first sentence of this subsection.

   d. ADVERSE REACTIONS- Include the following to appear just before the subsection heading "Second-Line Ovary". In addition, **BOLD** this heading.:

      Disease Specific Adverse Event Experiences

   e. ADVERSE REACTIONS (Adverse Event Experiences by Body System). Include the following to appear as sentence three of this subsection:

      In addition, rare events have been reported from postmarketing experience or from other clinical studies.

   f. ADVERSE REACTIONS (Other Clinical Events)- Include the following to appear as the last sentence of this subsection:

      Reports of asthenia and malaise have been received as part of the continuing surveillance of paclitaxel safety.

4. PATIENT INFORMATION LEAFLET – Satisfactory as of May 16, 2000 submission.

Please revise your container labels, carton and insert labeling, as instructed above, and submit 12 copies of final printed container labels along with 12 copies of final printed carton labeling and 4 copies of draft insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ANDA NUMBER 75-190

FIRM: Bedford Laboratories

DOSAGE FORM: Injection

STRENGTH: 6 mg/ml

DRUG: Paclitaxel

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 5/14/99.
Update - Acceptable as of 6/1/01.

BIO STUDY: The waiver of an *in vivo* bioequivalence study for the drug product was granted per the Division of Bioequivalence for the 5 ml vial and 16.7 ml vial on 12/13/97 and for the 50 ml vial on 1/11/01.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

MV is pending - ——— Per RECEIPT OF SAMPLES statement, the lab received the samples on 5/1/01.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Yes except for the crimp seals. Commercial batches will use blue ones.

5 ml and 16.7 ml

Component	Item ID No.	Type	Manufacturer/supplier	DMF No.	BVL RM #
———	———	———	———	DMF ———	———
	———	———	———	DMF ———	———

				DMF	
				N/A	

50-mL

Component	Item ID No.	Type	Manufacturer/Supplier	DMF No.	BVL RM #
				DMF	
				DMF	

Data are provided for exhibit lots:

5-ml vial: lot 818-44-216718
16.7-ml vial: lot 818-00-216717
50-ml vial: lot 818-57-216719

3-month data for samples stored upright and inverted at 40° C/75% RH and tested at 0, 1, 2 and 3-months. Accelerated data tentatively support the proposed 24-month expiry date.

6-month data for samples stored upright and inverted at 22.5° C ± 2.5° C and tested at 0, 3 and 6-months. Future studies will be at 25° ± 5°C/60° ± 5% RH.

LABELING: Satisfactory per the March 13, 2001 review.

STERILIZATION VALIDATION (IF APPLICABLE):

The microbiologist's review #3 (December 13, 2000) recommended the submission for approval on the basis of sterility assurance for all 3 vial sizes.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?): (Yes. DMF ——— ——— used for the three fill sizes.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA SAME PROCESS):

Same Process

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Same Process

Review Chemist: Shirley S. Brown/5/25/01 /S/ 6/15/01
Team Leader: Michael Smela
Date: May 25,2001 /S/ 6/15/01

V:\FIRMSAM\BEDFORD\LTRS&REV\CHECK75.190

F/T by: gp/6/12/01

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-190

CORRESPONDENCE

BEDFORD LABORATORIES™

January 25, 2002

Minor Amendment

NC TO FAX (Am)

NEW CORRESP

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **ANDA 75-190 /Minor Amendment**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL, and 50 mL per vials**

Dear Sir:

We wish to amend our tentatively Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials in response to the tentative approval letter received January 25, 2002. Form 356H is provided in Attachment I.

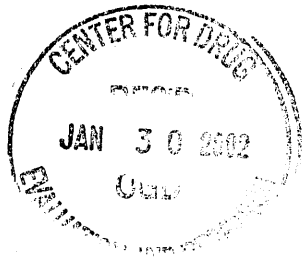
As requested, this minor amendment is being submitted in order to obtain final approval on ANDA 75-190. Bedford Laboratories™ believes that ANDA 75-190 is eligible for final approval based on the fact that Bristol Myers Squibb withdrew the listing of U.S. Patent No. 6,096,331 from the Orange Book for the reference listed drug, Taxol®. A copy of the current electronic Orange Book Patent Listing is provided for your review. Because this patent has been delisted, no patent certification is required for final approval under section 505(j)(2)(A)(vii) of the Act. In addition, the indications and methods of use covered by exclusivity, D-57, I-270, I-226, I-230, and Orphan Drug, are not claimed in the Bedford Laboratories™ labeling for Paclitaxel Injection 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials.

There have been no changes to the chemistry, manufacturing, controls, or labeling since the issue of this tentative approval, or the previous final approval (issued on July 27, 2001 and rescinded on January 25, 2002). In addition, a supplement for a [redacted] had been filed to this application on January 14, 2002 and has been withdrawn under separate cover. Bedford Laboratories™ understands that such withdrawal is without prejudice to refiling.

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 201-3576.

Sincerely,
for BEDFORD LABORATORIES™

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.



A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD
LABORATORIES™

January 25, 2002

Supplement Withdrawal

NEW CORRESP

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **ANDA 75-190 /Withdrawal of a Changes Being effected Supplement**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL, and 50 mL per vials**

Dear Sir:

We wish to amend our tentatively Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials. Bedford Laboratories™ is withdrawing a supplement which had been filed to this application on January 14, 2002 and provided for the use of a _____. Bedford Laboratories™ understands that such withdrawal is without prejudice to refiling.

Form 356H is provided in Attachment I.

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 201-3576.

Sincerely,
for BEDFORD LABORATORIES™

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 28 2002

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD LABORATORIES™

January 14, 2002

Special Supplement - Changes Being Effected in 30 Days

Mr. Gary Buehler
Office of Generic Drugs
Center for Drug Evaluation and Resea
Food and Drug Administration
Metro Part II
7500 Standish Place, Room 150
Rockville, MD 20855

DRUG AMENDMENT
N- Am

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 22 2002

RE: **Special Supplement – Changes Being Effected in 30 Days**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials**

Dear Mr. Buehler,

In accordance with 21 CRF 314.70(c)(2)(C), this Special Supplement – Changes Being Effected in 30 Days, is being filed to provide an [redacted] for the production of Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials. Previously, a Global Supplement dated March 6, 2001, was submitted for use of this [redacted] for all of Bedford's approved liquid products, both [redacted] An approval letter was issued on April 3, 2001 for this Global Supplement. The Paclitaxel ANDA was in the review process and could not be included in the Post Approval Global Supplement. Based on the November 1999 Guidance for Industry, "Changes to an approved NDA or ANDA", this supplement is being submitted as a CBE-30 based on point IV.C.1.b. Located in Attachment I is the FDA Form 356h. Located in Attachment II are the Global Supplement and its corresponding Approval Letter.

Ben Venue Laboratories, Inc., has upgraded the [redacted] to include [redacted], which [redacted] identical to Ben Venue Laboratories' existing [redacted]

Please note, Cincinnati District Investigator Fredrick Lochner conducted an inspection of the [redacted] from October 17, 2000 to October 24, 2000; an FDA-483 was issued with a commitment from BVL to have all items to be corrected within 30 days of issuance. A copy of the Cincinnati District Inspector's report as well as BVL's response is included in Attachment III of this supplement.

Pursuant to this PAI, Bedford Laboratories™ submitted a Supplement – Changes Being Effected in 30 Days to NDA 50-731 for Daunorubicin Hydrochloride Injection, on November 9, 2000; a response to a microbiological deficiency letter was provided to the Division of Oncology Drug Products on January 25, 2001. Copies of both of these correspondences are located in Attachment IV. This supplement was subsequently approved on March 5, 2001. A copy of this letter is located in Attachment V.

BEDFORD
LABORATORIES™

We trust that this meets with your approval. If you have any question or comments, please contact the undersigned at (440) 201-3576.

Sincerely,
For Bedford Laboratories™

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

ANDA 75-190

JUL 27 2001

Bedford Laboratories
Attention: Molly Rapp
270 Northfield Road
Bedford, Ohio 44146

Dear Ms. Rapp:

This is in reference to your abbreviated new drug application dated August 21, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Paclitaxel Injection, 6 mg/mL, (packaged in 30 mg/5 mL, 100 mg/16.7 mL, and 300 mg/50 mL multiple-dose vials).

By separate letter, you are receiving approval for the (ANDA) identified above. This letter provides background on the ANDA and addresses regulatory issues related to U.S. Patent Number 6,096,331.

ANDA 75-190 seeks approval of a generic version of paclitaxel, the brand name of which is Taxol, a drug manufactured by Bristol Myers Squibb (BMS). ANDA 75-190 was received by FDA on August 25, 1997.

On July 21, 1997, BMS listed patent 5,641,803 (patent '803) with FDA; on August 29, 1997, BMS listed patent 5,496,804 (patent '804); and on October 9, 1997; BMS listed patent 5,670,537 (patent '537) with the agency, asserting that these patents cover Taxol. Bedford filed Paragraph IV certifications to patents '803, '804, and '537, claiming the patents were invalid, unenforceable, or not infringed. (See 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(12)(i)(A)(4)). Because Bedford was sued by BMS within 45 days of giving BMS notice of its paragraph IV certifications, approval of Bedford's ANDA was stayed for 30 months, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii). Bedford did not provide proof of notification for the '537 patent and the '804 patent to the Agency. Therefore, the Agency calculated the 30 month stay of approval of Bedford's ANDA beginning from July 17, 1998, the date that BMS filed a supplemental complaint (Civil Action No. 97cv6050) against Bedford in the United States District Court of

New Jersey. The Agency considers the 30 months to have expired on January 17, 2001.

On August 1, 2000, the Patent and Trademark Office issued a new patent to American Bioscience Inc. (ABI), U.S. Patent Number 6,096,331 (the '331 patent). ABI claimed that this patent covered BMS's Taxol product. On August 11, 2000, ABI obtained a temporary restraining order (TRO) from a district court in California directing BMS to list the patent with FDA in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). This order stated that, should ABI fail to prevail in the underlying litigation, BMS would be required to take all steps necessary to delist the patent. On August 11, 2000, BMS listed the patent in the Orange Book pursuant to the court order. This was an extremely unusual condition for patent listing and the first time FDA had received a request that a patent be listed pursuant to a court order.

On September 7, 2000, the district court in California dissolved the TRO, dismissed ABI's complaint, and ordered BMS to delist the '331 patent from the Orange Book to restore the status quo. The court stayed its order until September 13, 2000.

On September 11, 2000, BMS submitted another listing for the patent. This listing made no mention of the original court-ordered August 11, 2000, listing. In its September 7, 2000, Order, the California district court recommended that FDA "toll the period in which BMS may timely cause such listing." OGD did not follow this recommendation for four reasons: (1) FDA was not a party to the California litigation in which the order was issued, and therefore, FDA's views were not presented to the court nor did the court have jurisdiction over the agency; (2) the 30-day time period is a statutory limit for timely submission, and it is not clear that the agency has the authority to extend that period; rather FDA believes that the 30 day period represents a Congressional determination that 30 days is sufficient; (3) even if the agency did have the authority to toll the deadline, it would set an undesirable precedent that future holders of pioneer applications could use to try to obtain extensions of the 30 day period, thereby blocking the approval of generic applications; and (4) the agency saw no reason why BMS could not have voluntarily listed the '331 patent within 30 days of its issuance if BMS thought the listing was appropriate under the Federal Food, Drug, and Cosmetic Act.

On September 14, 2000, BMS submitted a letter to FDA to comply with the court order to delist the patent. The letter states "BMS hereby withdraws the Original Listing to the extent that listing was compelled by the TRO." Because the court order directing BMS to submit the patent to FDA was dissolved, and BMS withdrew the original submission made pursuant to the TRO, FDA considered BMS's first submission of the patent on August 11, 2000, to be without effect.

The September 11, 2000 submission of the '331 patent by BMS was given effect. However, patents must be listed with FDA within 30 days of their issuance. See 21 U.S.C. § 355(c)(2). An FDA regulation, the "late-listing regulation," directly applies to patents submitted to FDA more than 30 days after they are issued. 21 C.F.R. § 314.94(a)(12)(vi). That regulation provides that pending ANDAs that contain appropriate patent certifications before the late patent is submitted need not be amended to contain certifications to patents that are listed beyond the 30-day interval set out in the statute. Here, because BMS withdrew the August 11 listing, the only listing remaining for the '331 patent was the September 11 listing, which was submitted more than 30 days after the patent's August 1, 2000, issuance.

On August 30, 2000, Bedford submitted a Paragraph I certification to the '331 patent. However, because the August 11, 2000, submission was a nullity, Bedford was not required to file any certification to that submission. Because Bedford was not required to file any certification to the August 11, 2000, submission, its paragraph I certification did not render its certification inappropriate.

The late-listing regulation states the following:

> If a patent on the listed drug is issued and the holder of the approved application for the listed drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an abbreviated new drug application for that drug *that contained an appropriate patent certification before the submission of the patent information is not required to submit an amended certification.*
>
> 21 C.F.R. § 314.94(a)(12)(vi)(A) (emphasis added).

Under this regulation, Bedford's ANDA contained an appropriate certification prior to submission of the '331 patent on September 11, 2000, because no certification to the August 11, 2000, submission was necessary. A certification to this nullity does not result in and "inappropriate" certification. To conclude otherwise would mean that the same patent would be listed late and would be timely listed. The August 11, 2000, listing is without effect, and cannot trigger obligations that do not otherwise exist. The district court found FDA was not arbitrary and capricious in finding that the August 11 listing was a nullity, in that the district court in California never had the authority to issue the August 11, 2000 order directing the patent listing and, therefore, BMS's TRO-compelled listing was without effect. The fact that the valid listing is that of September 11, 2000, rather than August 11, 2000, is clearly supported by the agency's own record and by the district court's holding.

Other applicants with ANDAs pending at the time of the August 11, 2000, submission of the '331 patent responded with a variety of certifications, including a paragraph IV certification and no certification whatsoever. There is no requirement in the regulations or the statute that an ANDA applicant submit a certification to a newly listed patent within a certain time period. ABI and BMS were not prejudiced by Bedford's submission of a paragraph I certification.

On December 14, 2000, BMS submitted an additional patent for listing in the Orange Book. U.S. Patent Number 6,150,398 ('398) is a use patent identified by the patent use code U-380 in the Orange Book. U-380 is for "combinations of Taxol (paclitaxel)and cisplatin which are suitable for the treatment of ovarian and non-small cell lung carcinomas."

On April 21, 2001, the 180-day exclusivity period granted to ANDA 75-184, Baker Norton, paclitaxel injection, expired.

On May 30, 2001, Bedford submitted a method of use statement pursuant to the section 505(j)(2)(a)(vii) of Act to the '398 patent indicating they were not seeking approval for the use covered by the '398 patent.

On June 8, 2001, Bedford amended its patent certification to the '331 patent to state that the patent was not timely filed pursuant to 21 CFR 314.94(a)(12)(vi), and requested full approval of this ANDA.

The agency has concluded that Bedford is not required to submit a certification to the '331 patent under the late listing regulation, 21 C.F.R. § 314.94(a)(12)(vi), since the '331 patent was not listed in a timely manner. Bedford has properly addressed all remaining patent and exclusivity issues.

Sincerely yours,

/S/

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

7/27/01

APPEARS THIS WAY
ON ORIGINAL

BEDFORD
LABORATORIES™

July 25, 2001

Telephone Amendment

Cecelia Parise
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

W CORRESP

RE: **ANDA 75-190**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL, and 50 mL per vials**

Dear Ms. Parise:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials. This is in reference to a telephone message left with Ms. Molly Rapp on July 25, 2001, by Ms. Cecelia Parise of the Agency. Because of the departure of Mr. Shahid Ahmed from Ben Venue Laboratories, Inc., the responsibility for the ANDA has transferred to Ms. Molly Rapp, Supervisor of Regulatory Affairs for Ben Venue Laboratories, Inc.

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 201-3576.

Sincerely,
for BEDFORD LABORATORIES

M L Rapp

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
JUL 27 2001
OGD

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD
LABORATORIES™

June 13, 2001

Telephone Amendment

Michelle Dillahaunt
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

N/AM
ORIG AMENDMENT

RE: **ANDA 75-190**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL, and 50 mL per vials**

Dear Ms. Dillahaunt:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials. This is in reference to a telephone message left with Mr.Shahid Ahmed on June 13, 2001, by Ms. Michelle Dillahaunt of the Agency regarding returned receipt of the certified mail and also copy of the summary judgement from the United States Court.

Attached, please find the copy of the envelope, which was sent to Ben Venue Laboratories by Bristol Myers Squibb Company on November 13, 1997 (post marked by the U.S Postal Office on November 13, 1997). Unfortunately, returned certified mail receipt never made it to Ben Venue Laboratories. I hope this fulfills the Agency's request.

Also, a copy of the summary judgement from the United States Court is provided in this amendment for your review.

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 201-3333.

Sincerely,
for BEDFORD LABORATORIES

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
JUN 14 2001
OGD

/S/
Returning to office
Friday June 22nd

ANDA 75-190

JUL 27 2001

Bedford Laboratories
Attention: Molly Rapp
270 Northfield Road
Bedford, Ohio 44146

Dear Madam:

This is in reference to your abbreviated new drug application dated August 21, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Paclitaxel Injection, 6 mg/mL, (packaged in 30 mg/5 mL, 100 mg/16.7 mL, and 300 mg/50 mL multiple-dose vials).

Reference is also made to your amendments dated October 20, 1999; June 16, 2000; and January 24, May 15, May 25, May 30, June 8, June 13, and July 25, 2001.

The listed drug product (RLD) referenced in your application, Taxol Injection of Bristol Myers Squibb Co. Pharmaceutical Research Institute, is subject to periods of patent protection which expire on August 3, 2012, [U.S. Patent No. 5,641,803 (the '803 patent), and U.S. Patent No. 5,670,537 (the '537 patent], March 9, 2013 [U.S. Patent No. 5,496,804 (the '804 patent)], May 8, 2011 [U.S. Patent No. 6,150,398 (the '398 patent)], and February 22, 2013 [U.S. Patent No. 6,096,331 (the '331 patent)].

Your application contains patent certifications under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on the '804, '803, or the '537 patents. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received by the owner of the new drug application (NDA) for the referenced listed drug product and the patent holder. You have notified FDA that Bedford Laboratories (Bedford) has complied with the requirements of Section 505(j)(2)(B) of the Act and that Bristol-Myers Squibb initiated a patent infringement suit in the United States District Court for the District of New Jersey (Bristol-Myers Squibb Company v. Boehringer Ingelheim Corp., Ben Venue Laboratories, Inc. and Bedford Laboratories, Civil Action No. 97CV-6050(WHW).

With regard to the litigation noted above, the Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act during which time FDA is precluded from approving your application, has expired.

We also note that your application contains a patent statement under Section 505(j)(2)(A)(viii) of the Act indicating that the '398 patent is a method of use patent, and that this patent does not claim any of the proposed indications for which you are seeking approval. Furthermore, please see the accompanying letter for a description of FDA's resolution of issues related to U.S. Patent Number 6,096,331.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Paclitaxel Injection, 6 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Taxol® Injection, 6 mg/mL, of Bristol Myers Squibb Co. Pharmaceutical Research Institute).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies, which may be identified.

Sincerely yours,

/S/

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

7/27/01

MAJOR AMENDMENT

DEC 8 1999

ANDA 75-190

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
PHONE: (440) 232-3320

ATTN: Shahid Ahmed
FAX: (440) 232-2772

FROM: Michelle Dillahunt
PROJECT MANAGER (301) 827–5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 21, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Paclitaxel Injection, 6 mg/mL, 5 mL and 16.7 mL vials.

Reference is also made to your amendment(s) dated June 21, 1999.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (14 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

CMC and Labeling Comments Included.

X:\new\ogdadmin\macros\faxmaj.frm

12/7/99

COHEN, PONTANI, LIEBERMAN & PAVANE
COUNSELLORS AT LAW
PATENTS, TRADEMARKS & COPYRIGHTS
551 FIFTH AVENUE
NEW YORK, NEW YORK 10176

TEL: (212) 687-2770
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KENT H. CHENG, PH.D.
GEORGE G. WANG, PH.D.
GERALD J. CECHONY
ROGER S. THOMPSON
JEREMY A. KAUFMAN
GEORGE J. BRANOT, JR.
TEODOR J. HOLMBERG
F. BRICE FALLER

July 2, 2001

VIA TELEFAX NO. (301) 443-0933

Annamarie Kempic, Esq.
General Counsel's Office
Food and Drug Administration
5600 Fishers Lane
GCF-1
Rockville, MD 20856

Re: ANDA 75-190 of Ben Venue Laboratories, Inc./Bedford Laboratories
For: Paclitaxel Injection
Our File No. 4764-2L

Dear Ms. Kempic:

We are counsel for Ben Venue Laboratories, Inc./Bedford Laboratories ("Ben Venue"), the applicant in ANDA 75-190 for Paclitaxel Injection.

Last week, the undersigned spoke with you concerning the status of Ben Venue's ANDA. We particularly discussed the question of whether Vivorx Pharmaceuticals, Inc.'s U.S. Patent No. 6,096,331 ("'331 patent") posed any obstacle to final approval of Ben Venue's ANDA. You advised that the matter was under active consideration by the general counsel's office, and that you expected a resolution shortly. Based on the undersigned's conversation with you, it is Ben Venue's understanding that the issue concerns Ben Venue's compliance with the "late listing" regulation, 21 C.F.R. § 314.94(a)(12)(vi). The following comments are offered in the hope of expediting a favorable resolution of this issue.

But or Approval

As your office is undoubtedly aware, the very issue of whether the '331 patent was timely listed was addressed and resolved in *American Bioscience, Inc. v. Tommy T. Thompson*, Civil Action No. 00-2247(CKK)(DDC 2001). In an April 19, 2001 memorandum opinion, Judge Kollar-Kotelly squarely held that the '331 patent was not listed within the thirty (30) day statutory period and, therefore, that applicants with pending ANDAs were not required to file a patent certification for the '331 patent. Ben Venue's ANDA was filed before the '331 patent ☆

ignore August Listing

even issued and, therefore, is entitled to the benefit of the holding in the *American Bioscience, Inc.*

The "late listing" regulation is discussed in the District Court's opinion and quoted at footnote 10 of that opinion. For ease of reference, it reads as follows:

> The "late listing" regulation provides as follows:
>
> > If a patent on the listed drug is issued and the holder of the approved application for the listed drug does not submit the required information on the patent within 30 days of issuance of the patent, an applicant who submitted an abbreviated new drug application for that drug that contained an appropriate patent certification before the submission of the patent information is not required to submit an amended certification. An applicant whose abbreviated new drug application is submitted after a later submission of patent information, or whose pending abbreviated application was previously submitted but did not contain an appropriate patent certification at the time of the patent submission, shall submit a certification under paragraph (a)(12)(i) of this section or a statement under paragraph (a)(12)(iii) of this section as to that patent.

blf Sept 11

Based on the undersigned's telephone conversation with you, it appears that FDA is considering the significance of the phrase "an appropriate patent certification" in the above-quoted regulation. For several reasons, Ben Venue believes that this language poses no impediment to approval of its ANDA.

By its very terms, the regulation speaks of "an appropriate patent certification [submitted] *before* the submission of the [late-listed] patent information" (emphasis added). It is plain, therefore, that the "appropriate patent certification" referenced in the regulation is not a patent certification for the late-listed patent, but a patent certification previously submitted by the ANDA applicant concerning other listed patents, if any. Put another way, an ANDA applicant could not possibly submit "an appropriate patent certification" with respect to a late-listed patent before patent information concerning the late-listed patent is submitted to the FDA.

* SA can't apply patent that is late-listed

On August 15, 2000, the FDA requested that Ben Venue submit a certification with respect to the '331 patent. *See* attached letter of August 30, 2000 from Shahid Ahmed of Ben Venue

COHEN, PONTANI, LIEBERMAN & PAVANE

(Exhibit A). On the same day as this request, in-house counsel for Ben Venue searched both the on line and hard copy versions of the Orange Book and did not find the '331 patent listed against paclitaxel. Accordingly, Ben Venue submitted a "Paragraph I Certification" with respect to the '331 patent. 21 C.F.R. § 314.94(a)(12)(A). That certification was correct when made, as there was no evidence that information concerning the '331 patent had been submitted to FDA as evidenced from its absence from the Orange Book. Subsequently, in June, 2001, in response to a specific request from FDA, a "telephone amendment" to Ben Venue's application was made. *See* attached June 8, 2001 letter from Shahid Ahmed of Ben Venue (Exhibit B) to Gregory Davis at FDA confirming the telephone amendment wherein Ben Venue states:

> "In the opinion of the applicant and to the best of its knowledge, Patent 6,096,331 was not filed in a timely manner by the patent holder. Therefore, in accordance with 21CFR 314.94 B12(vi)(sic), Bedford Laboratories™ would like to seek full approval of this ANDA."

The foregoing statement was also true when made, and remains true today, as the *American Bioscience* decision confirms that the '331 patent was not listed with FDA in a timely manner.

Ben Venue has also obtained a copy of FDA's March 27, 2001 approval letter to Zenith Goldline Pharmaceuticals, Inc.("Zenith") for Zenith's generic paclitaxel injection product. A copy of that letter is attached as Exhibit C. In that letter, FDA states:

> We note that U.S. Patent No. 6,096,331 also references Taxol Injection. However, in accordance with 21 CFR 314.94(a)(12)(vi), Zenith Goldline Pharmaceuticals, Inc. ("Zenith Goldline") is not required to submit a certification to this patent.

This is consistent with the District Court's opinion in *American Bioscience* wherein the District Court stated:

> In this case, it appears that the FDA may never have had occasion to prompt BNP to provide the requisite notification. At the time BNP submitted its certification amendment, *see* AR 8, the FDA had determined that Bristol-Myers' original listing had been withdrawn and that a separate late-listing had been submitted. *See* Buehler Decl. §§ 15-16. Accordingly, because FDA understood that there had been no timely listing of the '331 patent, BNP was not required to provide notice under the late-listing regulation. *See* 21 C.F.R. § 314.94(a)(12)(vi).

Civil Action No. 00-2247, p. 26, n. 11.

COHEN, PONTANI, LIEBERMAN & PAVANE

Of course, this reasoning also applies to Ben Venue, which also had a pending ANDA before the '331 patent was late-listed. Consequently, Ben Venue was entitled to the benefit of the regulation and not required to provide any certification with respect to the '331 patent. Under these circumstances, there is no reason, logical or otherwise, why Ben Venue's submission of a Paragraph I Certification in August, 2000 should in any way affect FDA's approval of Ben Venue's ANDA. And, as noted above, at the time Ben Venue submitted its Paragraph I Certification, it was accurate, as the '331 patent did not appear in the Orange Book.] NOT correct

CONCLUSION

It is evident that the reference to "an appropriate patent certification" in the subject regulation refers to a certification for other than the late-listed patent, and for this reason alone Ben Venue's submissions to FDA with respect to the '331 patent are not affected by the regulation and pose no obstacle to FDA's approval of Ben Venue's ANDA. Furthermore, Ben Venue's submissions to FDA with respect to the '331 patent are accurate, as at the time Ben Venue submitted its Paragraph I Certification, the '331 patent was not listed in the Orange Book, and for this additional reason Ben Venue's submissions to FDA with respect to the '331 patent do not pose an obstacle to FDA's approval of Ben Venue's ANDA. Finally, and in any event, the court in *American Bioscience* has specifically held that applicants with pending ANDAs at the time the '331 patent was late-listed were not required to submit *any* patent certification with respect to the '331 patent, and for this independent reason Ben Venue's submissions to FDA concerning the '331 patent pose no obstacle to approval of Ben Venue's ANDA.

Ct. holds was ltd, from this

Prompt and favorable consideration of Ben Venue's ANDA is solicited.

Very truly yours,
COHEN, PONTANI, LIEBERMAN & PAVANE

Martin B. Pavane

MBP/aw/encs.

Exhibit A

APPEARS THIS WAY
ON ORIGINAL

BEDFORD LABORATORIES™

August 30, 2000

Gratuitous Amendment

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **ANDA 75-190 /Gratuitous Amendment**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials, by providing three months accelerated and room temperature stability data per our commitment to the Major Amendment, dated May 16, 2000 as well as Supplemental Paragraph I Certification and revised Exclusivity Statement.

FDA 356h form is provided in Attachment I.

Three months stability testing under accelerated temperature and proposed label temperature have been completed and stability data are provided in Attachment II. This is in reference to the telephone conversation between Shahid Ahmed and Mr. Mike Smela, Ms. Shirley Brown and Ms. Michelle Dillahunt from the Agency on April 3, 2000.

Moreover, we have provided Supplemental Patent Certification to this ANDA regarding the new Patent 6,096,331 in Attachment III. This is in reference to the telephone conversation between Ms. Molly Rapp of Ben Venue and Ms. Beth Fritsch from the Agency on August 15, 2000.

Also, we have provided revised Exclusivity Statement in this amendment due to current update in Orange Book. This is in reference to the telephone conversation between Ms. Pratima Patel of Ben Venue and Mr. Greg Davis from the Agency on August 23, 2000.

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 232-3320, ext.3333

Sincerely,
for BEDFORD LABORATORIES

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

Exhibit B

APPEARS THIS WAY
ON ORIGINAL

BEDFORD LABORATORIES™

June 8, 2001

Telephone Amendment

Gregory Davis
Branch Chief,
Regulatory Support Branch, HFD-615
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-190
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL, and 50 mL per vials**

Dear Mr. Davis:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials. This is in reference to a telephone message left with Mr.Shahid Ahmed on June 7, 2001, by Ms. Michelle Dillahaunt of the Agency regarding Patent 6,096,331. This is also in reference to a telephone conversation on June 8, 2001 between Mr. Gregory Davis of the Agency and Mr. Shahid Ahmed of Ben Venue Laboratories, Inc.

In the opinion of the applicant and to the best of its knowledge, Patent 6,096,331 was not filed in a timely manner by the patent holder. Therefore, in accordance with 21CFR 314.94 B12(vi), Bedford Laboratories™ would like to seek full approval of this ANDA.

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 201-3333.

Sincerely,
for BEDFORD LABORATORIES

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

Exhibit C

ANDA 75-297

March 27, 2001

Zenith Goldline Pharmaceuticals, Inc.
Attention: Karen Rocco
140 Legrand Avenue
Northvale, NJ 07647

Dear Madam:

This is in reference to your abbreviated new drug application dated December 30, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Paclitaxel Injection, 6 mg/mL (packaged in 30 mg/5 mL, 100 mg/16.7 mL, and ~~~~~ multiple-dose vials).

Reference is also made to the Tentative Approval letter issued by this office on October 10, 2000, and to your amendments dated March 5, and March 14, 2001.

The listed drug product (RLD) referenced in your application, Taxol Injection of Bristol Myers Squibb Co. Pharmaceutical Research Institute, is subject to periods of patent protection which expire on August 3, 2012, [U.S. Patent No. 5,641,803 (the '803 patent), and U.S. Patent No. 5,670,537 (the '537 patent], and March 9, 2013 [U.S. Patent No. 5,496,804 (the '804 patent)]. We note that U.S. Patent No. 6,096,331 also references Taxol Injection. However, in accordance with 21 CFR 314.94(a)(12)(vi), Zenith Goldline Pharmaceuticals, Inc. (Zenith Goldline) is not required to submit a certification to this patent.

Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of this drug product will not infringe on these patents. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received by the owner of the new drug application (NDA) for the referenced listed drug product and the patent holder. You have notified

FDA that Zenith Goldline has complied with the requirements of Section 505(j)(2)(B) of the Act and that Bristol-Myers Squibb initiated a patent infringement suit in the United States District Court for the District of New Jersey

(Bristol-Myers Squibb Company v. Zenith Goldline Pharmaceuticals, Inc. and Ivax Corporation, Civil Action No. 98-1412). You have also informed us that a judgement of invalidity was rendered on April 7, 2000 and that this judgement was appealed by Bristol-Myers Squibb Company to the Court of Appeals for the Third Circuit on April 17, 2000. The appellate proceeding remains pending.

With regard to the litigation, the Agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act during which time FDA is precluded from approving your application, has expired. Furthermore, we acknowledge that Baker Norton Pharmaceuticals, Inc. (BNPI), is the holder of 180-day exclusivity for this drug product in accordance with the Hatch-Waxman Amendments to the Act. We also acknowledge that on
March 5, 2001, BNPI selectively waived the remainder its exclusivity to Zenith Goldline.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Paclitaxel Injection, 6 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Taxol® Injection, 6 mg/mL, of Bristol Myers Squibb Co. Pharmaceutical Research Institute).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your

initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

BEDFORD
LABORATORIES™

June 8, 2001

Telephone Amendment

'331 was late filed.
OK! /S/ 13-JUN-2001
/S/
NEW CORRESP
NC

Gregory Davis
Branch Chief,
Regulatory Support Branch, HFD-615
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: **ANDA 75-190**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL, and 50 mL per vials**

Dear Mr. Davis:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials. This is in reference to a telephone message left with Mr.Shahid Ahmed on June 7, 2001, by Ms. Michelle Dillahaunt of the Agency regarding Patent 6,096,331. This is also in reference to a telephone conversation on June 8, 2001 between Mr. Gregory Davis of the Agency and Mr. Shahid Ahmed of Ben Venue Laboratories, Inc.

In the opinion of the applicant and to the best of its knowledge, Patent 6,096,331 was not filed in a timely manner by the patent holder. Therefore, in accordance with 21CFR 314.94 B12(vi), Bedford Laboratories™ would like to seek full approval of this ANDA.

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 201-3333.

Sincerely,
for BEDFORD LABORATORIES

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG
RECD
JUN 11 2001
OGD
EVALUATION

BEDFORD
LABORATORIES™

May 30, 2001

Patent Amendment

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

MOU for 380 # OK! /S/ 13-JUN-2001 NEW CORRESP /S/ NC

RE: **ANDA 75-190**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL, and 50 mL per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials. This is in reference to a telephone message left with Mr.Shahid Ahmed on May 30, 2001 by Ms. Michelle Dillahaunt of the Agency regarding the Certification of new U.S. Patent 6,150,398.

FDA 356h form is provided.

The U.S. Patent 6,150,398, which was published in current Orange Book Supplement (May 7, 2001, copy attached) concerning Paclitaxel with Use Code of U-380, deals with synergistic combinations of Cisplatin and Taxol for use in treating cancer in humans. However, our proposed labeling does not claim the listed treatment regimen. Therefore, in accordance with 21 CFR 314.94 (a) (12) (iii), Bedford Laboratories would like to seek a regulatory approval of the proposed drug product claiming that above indication is not listed in the proposed drug product labeling, which is covered by the U.S. Patent 6,150,398.

The current package insert labeling is provided for your review in this amendment.

We trust this meets your approval. If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 201-3333.

Sincerely,
for BEDFORD LABORATORIES

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 31 2001
OGD

BEDFORD
LABORATORIES™

May 25, 2001

Telephone Amendment
Chemistry Deficiencies

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AM

RE: **ANDA 75-190**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL, and 50 mL per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials in response to the deficiencies cited in the Telephone Amendment, dated May 25, 2001. This is in reference to a telephone conversation on May 25, 2001 between Mr. Michael Smela, Jr., Ms. Shirley Brown of the Agency and Ms. Pratima Patel of Ben Venue Laboratories, Inc.

FDA 356h form is provided.

As discussed, Bedford Laboratories commits to conduct the long term stability studies at controlled temperature of 25° ± 2°C/60% ± 5% RH for the first three commercial production batches and all annual stability batches of each strength. This change has been reflected to our Post-Approval Stability Protocol, which is provided in this amendment.

Also, we would like to revise our Active Drug Substance Specifications for [redacted] This is in reference to a telephone conversation in February of this year between Mr. Shahid Ahmed of Ben Venue Laboratories and Dr. Rashmikant Patel and Dr. David Gill of the Agency in general to revise the [redacted], for all pending unapproved Applications. Revised Active Drug Substance Specifications are provided for your review.

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 201-3333.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 29 2001
OGD

Sincerely,
for BEDFORD LABORATORIES

P. Patel for

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD
LABORATORIES™

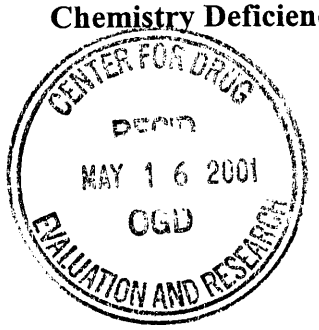
May 15, 2001

Telephone Amendment
Chemistry Deficiencies

ORIG AMENDMENT

N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855



RE: **ANDA 75-190**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL, and 50 mL per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials in response to the deficiencies cited in the Telephone Amendment, dated April 30, 2001. This is in reference to a telephone conversation on April 30, 2001 between Mr. Michael Smela, Jr., Ms. Shirley Brown of the Agency and Ms. Pratima Patel of Ben Venue Laboratories, Inc.

FDA 356h form is provided.

The Agency has requested to include all possible impurities in the current Finished Product Release and Stability Specifications. We have amended our Finished Product Release and Stability Specifications by including [redacted] with the Specifications of not more than [redacted] (same limits as active drug substance). The other two impurities, [redacted] have not been included in the current Specifications due to the fact, these impurities were not observed in the active drug substance (refer to attached PPD Report 96-0107).

Revised Finished Product Specifications and Stability Specifications are provided in this amendment for your review.

Also, Bedford Laboratories commits to provide full cooperation to resolve any problem, which may arise during method validation testing as part of "Post-Approval" process for the above listed drug product.

BEDFORD LABORATORIES™

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 201-3333.

Sincerely,
for BEDFORD LABORATORIES

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

BEDFORD LABORATORIES™

February 14, 2001

Gary Buehler
Director, Office of Generic Director
CDER, FDA
7500 Standish Place
Rockville, MD 20855

Reference: ANDA 75-190, Paclitaxel Injection 6mg/mL; 5mL, 16.7mL and 50mL per vials

Dear Mr. Buehler:

I would like to take this opportunity to express our profound disappointment over the handling of Bedford Laboratories pending ANDA for Paclitaxel Injection by the Agency.

Following is a brief summary of events which took place during the last four years.

On December 29, 1996, Bedford Laboratories hand delivered the original application with a paragraph IV certification to the Agency since the NCE on Paclitaxel was to expire on December 29, 1997. To our dismay, application was sent back to Bedford Laboratories after approximately four weeks in the original boxes ..thout any written communication from OGD. On August 21, 1997, Bedford Laboratories re-filed the ANDA with a paragraph IV certification. Later it was discovered that IVAX Corporation had also filed an ANDA for Paclitaxel in the first week of August and hence will be granted 180 days exclusivity.

Bedford Laboratories received the first Major Amendment on March 13, 1998, along with CMC, labeling and Bioequivalence comments. The application holder responded to the major amendment on June 21, 1999, and numerous correspondences were sent to the Agency regarding revised patent certifications and 180 days exclusivity during this period as well. Additionally, a written response to the Agency was also sent on October 20, 1999, regarding issues related to the microbiological review of the application. Regretfully, we received the second Major Amendment from the Agency on December 8, 1999. Since this was a second Major Amendment, we requested a teleconference with the Agency personnel on March 27, 2000, to resolve the technical issues. On April 3, 2000, we were able to speak to Mr. Mike Smela, Ms. Shirley Brown, and Ms. Michelle Dillahunt and after brief discussion, we agreed to the Agency's proposal regarding manufacture of a new exhibit batch. Bedford Laboratories forwarded a written response to the second major amendment on May 16, 2000, Agency followed by a submission of a gratuitous amendment on August 30, 2000, which contained stability data from the new exhibit batch, as well as new patent certification and exclusivity statement.

Surprisingly, we received a third Major Amendment on our pending application on December 8, 2000. When I contacted Ms. Dillahunt regarding the third Major Amendment, she informed me that the Team Leader had suggested that this should be a minor amendment, however, the Deputy Division Director changed the classification to a major amendment. I requested a teleconference with the Agency personnel on December 12, 00, in order to resolve all outstanding issues. On January 12, 2001, I spoke with Mr. Smela, Ms. Brown and s. Dillahunt and informed them that we have finalized our written response to the Agency's letter and will be

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD
LABORATORIES™

sending the written communication to the Agency fairly soon. Moreover, we will be requesting that the major amendment be reclassified to a minor amendment since the information provided to the Agency could be reviewed in less than an hour. A written response to the third Major amendment was sent to the FDA on January 24, 2001. However, I received a voice mail message from Michelle Dillahunt on February 7, 2001, informing me that Bedford Laboratories's request for reclassification of the amendment has been denied by Dr. Schwartz.

Suffice to say, we were extremely disappointed with the denial of reclassification of this amendment. Particularly, because of the minimal review time the amendment represents and the significant negative impact it may have on the approval of our ANDA since we will not be able to know the outcome of the regulatory review for the next 6 months.

In light of the above mentioned facts and on behalf of Bedford Laboratories, I am requesting your assistance and help in obtaining an expedited review of our pending application.

Looking forward to hearing from you soon. However, if you have any questions or comments, please contact me at (440) 201-3333.

Sincerely,
For Bedford Laboratories

Jahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories

APPEARS THIS WAY
ON ORIGINAL

BEDFORD LABORATORIES™

January 24, 2001

Major Amendment
Chemistry and Labeling

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

N/AC

ORIG AMENDMENT

RE: **ANDA 75-190 /Major Amendment**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL, and 50 mL per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials in response to the deficiencies cited in the Major Amendment, dated December 8, 2000.

Bedford Laboratories™ would like to request that the Agency reclassify this Major Amendment to a Minor Amendment as discussed between Ms. Michelle Dillahunt, Mr. Michael Smela, Jr., and Ms. Shirley Brown from the Agency and Mr. Shahid Ahmed of Ben Venue Laboratories, Inc., during the conference call dated January 12, 2001.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356H is provided in Attachment I.

A. CHEMISTRY DEFICIENCIES

1. The Reference Listed drug does include a 50 mL vial. Please refer to page 425 of the previous amendment which lists the 50mL vial in the "How Supplied Section" of the package insert from Bristol Myers Squibb. Furthermore, the vial label and carton for the 50 mL dosage of the Reference Listed Drug is provided in Attachment II.

2. The DMF holder has responded to the deficiencies cited for DMF ——— The confirmation letters are provided in Attachment III for you reference.

3. The ——— specification for the drug substance has been revised to NMT ——— ——— Please refer to Attachment IV for the revised specifications.

4a. An additional identification test by ——— is proposed for the drug product release. The revised specification including this test is provided in Attachment V.

4b. ———

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4c.

4d. Per the Agency's request and upon review of the current stability data, the specification for Individual Unknown Impurities has been revised to NMT — from — for the drug product release. The revised specifications for the drug product are provided in Attachment V.

5a. Per the Agency's request, the assay specification for the drug product stability has been revised to —— from —— which is identical to the release specifications. The revised Pre-Approval and Post-Approval Stability Protocols are provided in Attachment VI.

5b. Please refer to Response 4c.

5c. The Individual Unknown Impurities specification has been revised to NMT — The revised protocols are provided in Attachment VI.

5d. The innovator drug product sample and the Bedford Laboratories drug product samples stored for 6 months at 25 °C were analyzed using the —— method for known impurities. Results of the analyses are provided in the following table:

Lot Number	——	——
818-00-216717(5mL Vial)	——	——
818-44-216718(16.7mL Vial)	——	——
818-57-216719(50mL vial)	——	——
Innovator (5mL vial) Lot Number OD 22426 Expiration Date: 04/02	——	——

6. Bedford Laboratories™ commits to providing a prior approval supplement in order to change the source or grade of the ———————————, if it becomes necessary in the future.

7. The certificate of analysis for the lot of active drug substance used in the new batch is provided in Attachment VII.

8. Apparent pH of the drug product solution was measured using the stability samples stored for six months at 25 °C and there was no significant change in the apparent pH over time. The updated stability data is provided in Attachment VIII.

B. ACKNOWLEDGEMENTS

1. Bedford Laboratories™ acknowledges that the microbiologist's review for sterility assurance is still pending, as well as the Labeling and Bioequivalence reviews.

2. Bedford Laboratories™ acknowledges that the request for categorical exclusion is pending.

3. Bedford Laboratories™ acknowledges that a method validation will be requested following resolution of the testing issues.

4. The labeling deficiencies are addressed in Part C of this amendment.

C. LABELING DEFICIENCIES

1. All deficiencies cited have been corrected. Please refer to Attachment IX for copies of final printed vial labels, cartons, and package insert labeling for review. Also located in Attachment IX are annotated side-by-side comparisons of the final printed package insert with the last draft package insert.

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If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 201-3333.

Sincerely,
for BEDFORD LABORATORIES

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

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Paclitaxel Injection
ANDA 75-190
6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials

Table of Contents

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August 30, 2000

Gratuitous Amendment

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

received PI for 331 + revised exclusiv. certification (clarification) 9/25/00

NDA ORIG AMENDMENT
AA
/S/

RE: **ANDA 75-190 /Gratuitous Amendment**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials, by providing three months accelerated and room temperature stability data per our commitment to the Major Amendment, dated May 16, 2000 as well as Supplemental Paragraph I Certification and revised Exclusivity Statement.

FDA 356h form is provided in Attachment I.

Three months stability testing under accelerated temperature and proposed label temperature have been completed and stability data are provided in Attachment II. This is in reference to the telephone conversation between Shahid Ahmed and Mr. Mike Smela, Ms. Shirley Brown and Ms. Michelle Dillahunt from the Agency on April 3, 2000.

Moreover, we have provided Supplemental Patent Certification to this ANDA regarding the new Patent 6,096,331 in Attachment III. This is in reference to the telephone conversation between Ms. Molly Rapp of Ben Venue and Ms. Beth Fritsch from the Agency on August 15, 2000.

Also, we have provided revised Exclusivity Statement in this amendment due to current update in Orange Book. This is in reference to the telephone conversation between Ms. Pratima Patel of Ben Venue and Mr. Greg Davis from the Agency on August 23, 2000.

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 232-3320, ext.3333

CENTER FOR DRUG EVALUATION AND RESEARCH
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SEP 0 1 2000
OGD

Sincerely,
for BEDFORD LABORATORIES

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

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300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD
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June 23, 2000

SUPPL AMENDEMENT
N/AA.

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-190/Gratuitous Amendment
Product: Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL, 5 mL and 16.7 mL vials, in response to the telephone communication of June 22, 2000, between Ms. Nancy Sager of the Agency and Ms. Laurel Benyo of Ben Venue Laboratories, Inc. In accordance with 21 CFR 25.15 (d) and 25.31 (b), Bedford Laboratories is seeking categorical exclusion due to the following:

1. [redacted]

2. The paclitaxel active pharmaceutical ingredient is manufactured by a semi-synthetic process and obtained exclusively from *Taxus baccata* [redacted]

3. [redacted]

4. [redacted]

To the applicant's knowledge, no extraordinary circumstances exist.

We trust this meets with your approval. If the Agency has any further questions or comments, we welcome direct contact at (440) 232-3320, ext. 333 or (440) 232-2772 (facsimile).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

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May 23, 2000

New Correspondence

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

RE: **ANDA 75-190**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials**

Dear Sir:

We wish to amend our response to the Major Amendment submitted to the Agency on May 16, 2000 to our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials. This is in reference to the telephone conversation between Ms. Teresa Watkins of the Agency and Ms. Laurel Benyo of Ben Venue on May 23, 2000. Per the discussion, we have updated our statement that Bedford Laboratories has no intention to claim the indication regarding the

FDA 356h form is provided in this amendment.

The revised statement reads as "Bedford Laboratories has no intention to claim the indication in the labeling regarding , therefore, the Patent Certification and Exclusivity Statement remains unchanged.

If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 232-3320, ext.333

Sincerely,
for BEDFORD LABORATORIES

P. Patel for
Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

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MAY 24 2000
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ISR 6-26-00

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June 16, 2000

Microbiology Deficiencies

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AS

RE: **ANDA 75-190**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials to remove the deficiencies communicated in your letter dated May 23, 2000. Also, this is in reference to the telephone conversation between Mr. Joe Buccine and Dr. Lynn Ensore of the Agency and Mr. Shahid Ahmed, Ms. Pratima Patel and Ms. Angela Boss of Ben Venue on June 16, 2000.

FDA 356h form is provided in this amendment.

The endotoxin limit for the Paclitaxel Injection was calculated as follows:

The recommended dosage of paclitaxel in the proposed drug product labeling is 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours every week; therefore,

$$175\ mg/m^2 \times \frac{1.8M^2}{70\ kg\ (Body\ wt)} = 45\ mg/kg/3\ hour = 1.5\ mg/kg/hour$$

$$\text{Based on LAL Guideline, } K/M = \frac{5.0\ EU/kg}{1.5\ mg/kg} = 3.3\ EU/mg$$

Based on the above calculations, we would like to keep the LAL specification to NMT for Finished Product Release and Stability Specifications, as we have proposed in the previous deficiency response.

We trust this meets your approval. If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 232-3320, ext.333

Sincerely,
for BEDFORD LABORATORIES™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

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JUN 19 2000
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May 16, 2000

Major Amendment/Chemistry and Labeling Deficiencies

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA 075-190 AMENDMENT
AC

RE: **ANDA 75-190 /Major Amendment**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL, 16.7 mL and 50 mL per vials, in response to your letter dated December 8, 1999.

FDA 356h form is provided in Attachment I.

The number identifying the responses in this amendment correspond to the deficiencies cited in your letter.

A. Deficiencies:

1. The DMF holder has responded to their deficiency letter on April 12, 2000. Please note that the [redacted] The DMF [redacted] has been updated with this change. Please refer to Attachment II for a correspondence letter and U.S. Agent letter.

2. The current active drug substance Specifications and Test Method have been updated to include the individual chemical names and limits for the known impurities. Please refer to Attachment III for revised Paclitaxel Drug Substance Specifications and Test Method.

3. We acknowledge the Agency's comment. We have updated the [redacted]

[redacted]

FOR DRUG
REC'D
MAY 17 2000
OGD
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by providing three months accelerated temperature stability data per the telephone conversation between Shahid Ahmed and Mr. Mike Smela, Ms. Shirley Brown and Ms. Michelle Dillahunt from the Agency on April 3, 2000.

4. Our Proposed Specifications (release and stability) for Appearance are adopted from Current USP <788>, which reads as "Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, should be essentially free from particles that can be observed on visual inspection".

5. Please refer to Attachment IV for revised Finished Product and Stability Specifications, where the sample preparation for the pH determination has been included.

6. Updated Pre- and Post-Approval Stability Protocols are provided in Attachment IV with the inclusion of pH and [redacted] content.

7. Please refer to Attachment V for the General Test Method 999-00-020 for color test.

8. Antimicrobial Preservative Effectiveness Test data is provided in Attachment VI.

B. In addition to the other comments, we would like to acknowledge the following:

1. The microbiologist's review of our amendment dated October 20, 1999 for sterility assurance is pending.

2. The drug product samples for method validation will be requested under separate cover following resolution of the testing issues.

3. The response to the labeling deficiencies is included in this amendment.

Labeling deficiencies:

We have updated vial labels and carton labeling based on the Agency's comments. Please note that the proposed package insert labeling has been updated in accordance with the recently updated reference listed drug package insert labeling (revised October 1999) . Twelve copies of final printed labels and labeling are provided in Attachment VI. The final printed vial labels and carton labeling are compared with previously submitted draft labels and carton labeling, where as final printed package insert has been compared with recently revised reference listed drug package insert. Please refer Attachment VI for side-by-side comparison of labels and labeling .

Please note that Bedford Laboratories has no intention to claim the indication in the labeling regarding [redacted] therefore, the Patent Certification and Exclusivity Statement remain unchanged.

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If the Agency has any comments or further requests, we welcome direct and immediate telephone contact at (440) 232-3320, ext.333

Sincerely,
for BEDFORD LABORATORIES

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

A DIVISION OF BEN VENUE LABORATORIES, INC.

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October 20, 1999

Response to Microbiology Deficiencies

NDA ORIG AMENDMENT
N/As

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-190
PRODUCT: Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL per vials

Dear Sir/Madam:

We would like to amend our unapproved Abbreviated New Drug Application, Paclitaxel Injection; 6 mg/mL; 5 mL and 16.7 mL by responding the Agency's letter dated September 24, 1999.

FDA 356h form is provided in Attachment I.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication.

Microbiology Deficiencies:

1. [redacted]

RECD
OCT 2 1 1999
OGD

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

Redacted 0

pages of trade secret and/or confidential commercial information

numbers for contact are (440)-232-3320, ext.333 (direct) and (440)-232-2772 (fax).

Sincerely,
for Bedford Laboratories

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

A DIVISION OF BEN VENUE LABORATORIES, INC.

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June 21, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
N/Ac

RE: **ANDA 75-190 /Major Amendment**
Product: **Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL per vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 and 16.7 mL per vials, in response to your letter dated March 13, 1998.

FDA 356h form is provided in Attachment I.

The number identifying the responses in this amendment correspond to the deficiencies cited in your letter.

Section VIII. Raw Material Control

1. The DMF holder has responded to their deficiency letter on June 5, 1998.

2. The drug product contains [redacted]

   Also, this issue was discussed with Dr. Gill and Mr. Buccine of the Agency and Shahid Ahmed of Ben Venue on April 4, 1998.

3. Ben Venue is in the process of revising current specifications and test method to include the individual chemical names and limits for known impurities. As soon as the specifications and test method are updated, this application will be amended.

4. The Bacterial Endotoxin limit for the finished product and stability sample is not more than [redacted] of paclitaxel; therefore, current Bacterial Endotoxin limit of [redacted] of paclitaxel for active drug substance is not high. Also, [redacted] the DMF holder has a

Section XI. Manufacturing & Processing Instructions

5. The actual amount of paclitaxel will be listed on Formula Card of Compounding Instructions.

A DIVISION OF BEN VENUE LABORATORIES, INC.
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March 12, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

RE: **ANDA 75-190/ New Correspondence**
Product: **Paclitaxel Injection, 6 mg/mL; 5 and 16.7 mL per vial**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 and 16.7 mL per vial, by requesting 180-day generic drug marketing exclusivity.

FDA 356h form is provided in this amendment.

Attached, please find a notification letter of the filing of Hatch/Waxman patent infringement actions to the Agency.

If the Agency has any comments, we welcome direct and immediate telephone contact at (440) 232-3320, ext.333 (phone) and (440) 232-2772 (fax).

Sincerely,
for BEDFORD LABORATORIES

P. Patel for

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.
/pp

RECEIVED
MAR 1 5 1999
GENERIC DRUGS

Bristol-Myers Squibb Company
345 Park Avenue New York, NY 10154-0037 212 546-4000

NEW CORRESP
NDC

NAI
PD initiation of
civil action

September 17, 1998

/S/
11/7/98

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
7500 Standish Place, Room 150
Rockville, MD 20855

75-190

RE: Bristol-Myers Squibb Company v. Boehringer Ingelheim, Ben Venue Laboratories and Bedford Laboratories

Gentlemen:

This supplements our January 6, 1998 letter (copy enclosed). We want to formally advise the Food and Drug Administration ("FDA") that on July 17, 1998, Bristol-Myers Squibb Company ("BMS") filed a Supplemental Complaint against Boehringer Ingelheim, Ben Venue Laboratories and Bedford Laboratories ("Ben Venue") in federal district court in Newark, New Jersey, alleging infringement of U.S. Patent Nos. 5,641,803, 5,670,537 and 5,496,804. A copy of the Supplemental Complaint is enclosed (Civil Action No. 97cv 6050 (WHW), United States District Court, District of New Jersey).

BMS filed this action within 45 days of receipt of notice of the certification concerning U.S. Patent Nos. 5,670,537 and 5,496,804. As indicated in our January 6, 1998 letter, BMS had previously received certification concerning U.S. Patent No. 5,641,803 and had filed a lawsuit against Ben Venue within 45 days of that certification. Pursuant to the Federal Food, Drug and Cosmetic Act, § 505 (j) (4) (B) (iii), the FDA cannot approve ANDA 75-190 until "the expiration of the thirty-month period beginning on the date of the receipt of the notice . . .or such shorter or longer period as the court may order. . . ."

It is noted that BMS is not required to provide this notification to the FDA, but is doing so out of an abundance of caution to ensure that the FDA is fully informed concerning the status of Ben Venue's ANDA 75-190.

Should any questions concerning this matter arise, please feel free to contact me directly.

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SEP 21 1998
GENERIC DRUGS

Very truly yours,

Francis S. Rossi

/S/
11-23-98

BEDFORD
LABORATORIES™

June 3, 1998

NEW CORRESP
NC

Office of Generic Drugs
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-190
Product: Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials to provide the Supplemental Patent Certifications for U. S. Patent 5,670,537, and 5,496,804.

FDA 356h form is provided.

Attached herewith is Supplemental Paragraph IV Certifications.

If you have any questions or comments, the phone numbers for contact are (440) 232-3320, ext. 333 direct and (440) 439-6398 (fax).

Sincerely,
for Bedford Laboratories

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

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JUN 05 1998
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A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD LABORATORIES™

NAT
/S/

May 11, 1998

Office of Generic Drugs
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP
NC

RE: ANDA 75-190
Product: Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials to provide the Patent Certification for U. S. Patent 5,670,537, 5,496,804 and revised Statement of Exclusivity. FDA 356h form is provided.

Attached herewith is revised Paragraph IV Certification and revised Statement of Exclusivity.

If you have any questions or comments, the phone numbers for contact are (440) 232-3320, ext. 333 direct and (440) 439-6398 (fax).

Sincerely,
for Bedford Laboratories

Shahid Ahmed

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
MAY 12 1998
GENERIC DRUGS

/S/

BEDFORD
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May 6, 1998

NAI
(S)

Greg Davis
Office of Generic Drugs
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NC

RE: ANDA 75-190
Product: Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials

Dear Mr. Davis:

This is to confirm that the law firm Cohen, Pontani, Lieberman & Pavane in New York City, and specifically Martin B. Pavane, William A. Alper and Myron Cohen of that firm, are representing Bedford Laboratories, a division of Ben Venue Laboratories, Inc. in certain patent litigation relating to Paclitaxel Injection and have been authorized by Bedford Laboratories, to communicate with you and other representatives of the U.S. Food and Drug Administration from time to time with respect to Bedford Laboratories' pending ANDA 75-190 for approval to market Paclitaxel Injection. We would appreciate any assistance you can give them.

If you have any questions or comments, the phone numbers for contact are (440) 232-3320, ext. 333 direct and (440) 439-6398 (fax).

Sincerely,
for Bedford Laboratories

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

cc: Cohen, Potani, Lieberman & Pavane
(By Facsimile)

RECEIVED
MAY 0 8 1998
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

BEDFORD
LABORATORIES™

February 5, 1998

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 75-190
Product: Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL, 5 mL and 16.7 mL vials in response to a facsimile from the Agency dated 12/10/97 concerning the categorical exclusion claim and extraordinary circumstances for the environmental assessment. In accordance with 21 CFR 25.15(d) and 25.31(b) Bedford Laboratories, Inc., is seeking categorical exclusion due to the following :

1. The paclitaxel active pharmaceutical ingredient is manufactured by a semi-synthetic process and obtained exclusively from the *Taxus Baccata* [redacted]

2. [redacted]

3. [redacted]

A written statement from the [redacted] is provided with this letter and also to the applicant's knowledge, no extraordinary circumstances exist. This statement is updated based on my telephone conversation with Nancy Sager.

If the Agency has any comment or further requests, or if we could be of any assistance in the review, we welcome direct and immediate telephone contact at (440) 232-3320, ext.333.

Sincerely,
for Bedford Laboratories™

P. Patel for SA

Shahid Ahmed
Director, Regulatory Affairs

RECEIVED
FEB 10 1998
GENERIC DRUGS

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A DIVISION OF BEN VENUE LABORATORIES, INC.

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February 5, 1998

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Dear Sir/Madam:

Enclosed, please find the revised Environmental Assessment statement to our ANDA 75-190. This statement has been updated based on my telephone conversation with Nancy Sager.

Sincerely,
for Bedford Laboratories

P. Patel

Pratima Patel
Senior Regulatory Affairs Associate
Ben Venue Laboratories, Inc.

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FEB 10 1998
GENERIC DRUGS

/S/

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

BEDFORD
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January 26, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

Re: ANDA 75-190
Product: Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL, 5 mL and 16.7 mL vials in response to a facsimile from the Agency dated 12/10/97 concerning the categorical exclusion claim and extraordinary circumstances for the environmental assessment. In accordance with 21 CFR 25.15(d) and 25.31(b) Bedford Laboratories, Inc., is seeking categorical exclusion due to the following :

1. The paclitaxel active pharmaceutical ingredient is manufactured by a semi-synthetic process and obtained exclusively from the *Taxus Baccata*

2.

3.

A written statement from the is provided with this letter.

If the Agency has any comment or further requests, or if we could be of any assistance in the review, we welcome direct and immediate telephone contact at (440) 232-3320, ext.333.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

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JAN 27 1998
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

Bristol-Myers Squibb Company
P.O. Box 4000 Princeton, NJ 08543-4000
609 252-4328 Fax: 609 252-4526

NEW CORR
NC

Donald J. Barrack
Chief Counsel - Patents

January 20, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Bristol-Myers Squibb Company v. Ben Venue Laboratories

Gentlemen:

This letter will supplement my letter dated January 6, 1998 regarding ANDA 75-190 filed by Ben Venue Laboratories' Bedford Laboratories division ("Ben Venue") directed to its paclitaxel injection generic version of Bristol-Myers Squibb's ("BMS") Taxol®.

As stated in my January 6 letter, BMS filed a patent infringement action against Ben Venue within 45 days of receipt of notice of a patent certification by Ben Venue and pursuant to the Federal Food, Drug and Cosmetic Act ("FFDCA"), §505(j)(4)(B)(iii), the FDA cannot approve ANDA 75-190 until "the expiration of the thirty (30) month period beginning on the date of the receipt of the notice. . . or such shorter or longer period as the court may order . . . ." BMS now calls the FDA's attention to §505(j)(4)(D)(ii) of the FFDCA which provides that because Ben Venue provided notice of its patent certification to BMS prior to the expiration of the five (5) year data exclusivity period enjoyed by BMS pursuant to that section, the thirty (30) month period is "extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of [BMS's paclitaxel new drug application]".

Should any questions concerning this matter arise, please feel free to contact me directly.

RECEIVED
JAN 2 1 1998
GENERIC DRUGS

Sincerely,

1 Cy

Bristol-Myers Squibb Company

P.O. Box 4000 Princeton, NJ 08543-4000
609 252-4328 Fax: 609 252-4526

January 6, 1998

HAL S!
1/15/98
Note Bedford did not challenge -537 Patent

Donald J. Barrack
Chief Counsel - Patents

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs, HFD-600
7500 Standish Place, Room 150
Rockville, Maryland 20855

NEW CORRESP

RE: Bristol-Myers Squibb Company v. Ben Venue Laboratories

Gentlemen:

ANDA 75-190 filed by Ben Venue Laboratories' Bedford Laboratories division ("Ben Venue") is directed to its paclitaxel injection generic version of Bristol-Myers Squibb's ("BMS") Taxol® and contains a certification under 21 U.S.C. §355(j)(2)(A)(vii)(IV) asserting that United States Patent No. 5,641,803 is invalid. Notice of the certification was received by BMS on a date after November 3, 1997, the date of the postmark on the notice sent by Ben Venue to BMS.

This letter is to advise the Food and Drug Administration ("FDA") that on December 17, 1997, BMS filed a lawsuit against Ben Venue Laboratories, Inc. and Bedford Laboratories in federal district court in Newark, New Jersey, alleging infringement of United States Patent No. 5,641,803. A copy of the complaint is enclosed (Civil Action No. 97cv 6050 (WHW), United States District Court, District of New Jersey).

Because BMS has filed its action within 45 days of receipt of notice of the certification, pursuant to the Federal Food, Drug and Cosmetic Act, §505(j)(4)(B)(iii), the FDA cannot approve ANDA 75-190 until "the expiration of the thirty-month period beginning on the date of the receipt of the notice. . . or such shorter or longer period as the court may order . . . ."

It is noted that BMS has not received from Ben Venue notice of a patent certification with regard to BMS's United States Patent No. 5,670,537 which is listed in the Orange Book as a covering patent for paclitaxel. In the absence of a patent certification directed to United States Patent No. 5,670,537, ANDA 75-190 cannot be approved.

Should any questions concerning this matter arise, please feel free to contact me directly.

Sincerely,

BEDFORD
LABORATORIES™

NEW CORRESP

NC

Noted
NAT 12/5/97

November 20, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 75-190
Product: Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials

Dear Sir/Madam:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-190, for Paclitaxel Injection, 6 mg/mL, 5 mL and 16.7 mL vials, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and 21 CFR 314.95.

Bedford Laboratories™ is amending its application to certify that notice has been provided to the patent holder, Bristol-Myers Oncology, that its unapproved ANDA 75-190 for Paclitaxel Injection, 6 mg/mL, 5 mL and 16.7 mL vials, was submitted and accepted for filing and review by the Agency. A copy of Bedford Laboratories™ Paragraph IV Certification, which was submitted to the Agency in the original application, was provided to the patent holder explaining the basis for our opinion that Patent Number 5,641,803 (expiring August 03, 2012), is invalid.

Additionally, please refer to the attached copy of confirmation letter, which was sent by Bristol-Myers Squibb Company that the patent holder has received the Paragraph IV Certification notice.

If the Agency has any comment or further requests, or if we could be of any assistance in the review, we welcome direct and immediate telephone contact at (216) 232-3320, ext.333.

Sincerely,
for Bedford Laboratories™

P. Patel for

Shahid Ahmed
Manager, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
NOV 2 1 1997
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

BEDFORD
LABORATORIES™

August 21, 1997

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: Abbreviated New Drug Application
PRODUCT: Paclitaxel Injection; 6 mg/mL; 5 mL and 16.7 mL vials

Dear Sir/Madam:

In accordance with Section 505 (j) (1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Paclitaxel Injection, 6 mg/mL; 5 mL and 16.7 mL vials. Please note that the field copy has been sent directly to the FDA District Office in Cincinnati, Ohio.

Please note that this application was originally filed on December 30, 1996 by the applicant with a Paragraph IV certification for the 5,504,102 patent, which Bristol Myers

Bedford Laboratories requests the Agency to date this application as of December 30, 1996 for purposes of Waxman/Hatch patent challenge process.

The drug product which is a subject of this application will be manufactured by Ben Venue Laboratories, Inc., located at 270 Northfield Road, Bedford, Ohio, 44146.

This abbreviated new drug application contains the information required by Section 505 (j)(2)(A)(i), (ii)(I), (iv), (v) and (vi) respectively. This application is provided in the format suggested by your office, and contains a copy of the package insert of the "reference listed drug" (Bristol-Myers, Taxol® Injection) as well as copies of the relevant pages of the **Approved Drug Products with Therapeutic Equivalence Evaluations, 17th edition and supplements.**

In accordance with Title 21 CFR 320.22 Bedford Laboratories requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug product that is the subject of this application

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-2772

(Paclitaxel Injection, 6mg/mL; 5mL and 16.7mL vials). The drug product is a sterile solution and is intended solely for intravenous administration and contains the active ingredient in the same concentration as in the reference listed drug.

Bedford Laboratories certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection 3 (cGMP Certification).

Three copies of analytical methods which were used to test this product and the analytical method validation reports are enclosed separately along with this application.

One copy of the Microbiological Validation, along with the drug product specification, stability protocol, and the package insert are enclosed separately with this application. This drug product was aseptically filled.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (216)-232-3320, ext. 218 (direct) and (216)-232-2772 (fax).

Sincerely,
for Bedford Laboratories

Robert V. Kasubick, Ph. D.
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

ANDA 75-190

Bedford Laboratories,
Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
270 Northfield Road
Bedford, OH 44156

OCT 15 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Paclitaxel Injection 6 mg/mL,
5 mL and 16.7 mL vials

DATE OF APPLICATION: August 21, 1997

DATE OF RECEIPT: August 25, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sheila O'Keefe
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FILE IN ANDA 75-190

BEDFORD LABORATORIES™

CBER CORRESP

AL

Response to Telephone Request

ANDA 75-190

From: Molly Rapp
Supervisor Regulatory Affairs
Ben Venue Laboratories

Φ (440) 201-3576 (Direct)
(440) 232-2772 (Fax)

To: Mr. Peter Rickman
OGD/CDER/FDA
Document Control Room,
Metro Park, North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Φ (301) 827 - 5840
(301) 827 - 5991 (Fax)

75911

Product: Paclitaxel Injection, 6 mg/mL

Date: Jan. 18, 2002

Comments:

Please find attached the May 30, 2001 amendment which contained a method of use statement for patent 6,150,398.

Should you need hard copies of this amendment or any further information, please give me a call.

Pages: 6, including this cover sheet

Noted,
/S/
1/28/2002