CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75184

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 75-184 **Date of Submission: August 8, 2000**

Applicant's Name: Baker Norton

Established Name: Paclitaxel Injection, 6 mg/mL, Multiple dose vials

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (5 mL, 25 mL and 50 mL)-Satisfactory as of June 5, 2000 submission.

Carton Labeling: (1 x 5 mL, 1 x 25 mL and 1 x 50 mL) Satisfactory as of June 5, 2000 submission.

Professional Package Insert Labeling: Satisfactory as of August 8, 2000 submission.

Patient Information Leaflet: Satisfactory as of August 8, 2000 submission.

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes. Docket No. 97P-0058/CP1 for package size 150 mg/25 mL

What is the RLD on the 356(h) form: TAXOL® Injection

NDA Number: 20-262/S-033

NDA Drug Name: Paclitaxel Injection

NDA Firm: Bristol-Myers Squibb Pharmaceutical Research Institute

Date of Approval of NDA Insert and supplement #: October 25, 1999.(Physician's Insert; FPL 12-10-99)
December 10, 1999 (Patient Package Insert)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? Yes

If yes, give date of labeling guidance: Revised October 1997

Basis of Approval for the Container Labels: Container labels in file folder.

Basis of Approval for the Carton Labeling: Carton labeling in file folder.

Other Comments: S-036 was approved June 20, 2000, but is covered by exclusivity until June 20, 2003. For a 3-hour infusion of Taxol given every 3 weeks at a dose of 175 mg/m2 followed by cisplatin at a dose of 75 mg/m2 for the first line treatment of advanced ovarian carcinoma.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.			
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?	X		
Packaging			
Is this a new packaging configuration, never been approved by an AND or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**

Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does AND meet them?			X
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T □and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The reference listed drug for this product is TAXOL® (Bristol Myers Squibb; NDA#20-262/S-033; Approved October 25, 1999;FPL December 10, 1999). Patient Package insert S-032, approved December 10, 1999.
2. **Patent/ Exclusivities:**

Patent Data – NDA 20-262

No	Expiration	Use Code	Use	File
6096331	February 22, 2013		Methods and compositions useful for administration of chemotherapeutic agents. There are provided compositions and methods useful for the in vivo delivery of a pharmaceutically active agent, wherein the agent is associated with a polymeric biocompatible material.	P-IV
5496804	Mar 09,2013	U-204	Use of taxol in combination with g-csf for treatment of patients with aids-related kaposi's sarcoma	P-IV
5641803 5670537	Aug 03,2012	U-198	Treatment metastatic carcinoma of ovary after first-line failure or subsequent chemotherapy, treatment of breast cancer after failure of combination chemotherapy for metastatic disease and second-line treatment of aids-related kaposi's sarcoma	P-IV

Exclusivity Data– NDA 20-262

Code	Reference	Expiration
ODE	Treatment of AIDS-related Kaposi's Sarcoma	Aug 4,2004
D-57	3-hour infusion of taxol given every three weeks at a dose of 175mg/m2 followed by cisplatin at a dose of 75mg/m2 for the first-line treatment of advanced ovarian cancer	Jun 20,2003

I-230	In combination with cisplatin, for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation	Jan 08,2002
I-226	24 hour infusion -First-line therapy for the treatment of advanced carcinoma of the ovary in combination with cisplatin	Apr 09,2001
I-202	Second-line treatment of aids-related kaposi's sarcoma	Aug 04,2000
I-270	Adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy	Oct 25,2002

The firm is not seeking approval for any of the indications covered by the above listed exlcusivities. Although I-202 has expired, the ODE is for "the treatment of AIDS-related Kaposi's Sarcoma". It doesn't specify 1st or 2nd line and it doesn't expire until August 4, 2004. So the firm has not included second-line treatment in its labeling.

3. Storage/Dispensing Conditions:
   NDA: Store vials in original cartons between 20° to 25°C (68°to 77°F). Retain in the original package to protect from light.
   AND: Store between 20°to 25°C (68°to 77°F). Protect from light.
4. Product Line:
   The innovator markets their product in multiple dose vials containing 30 mg/5 mL ,100 mg/17 mL & 300 mg/50mL The applicant proposes to market their product in single dose vials containing 30 mg/5 mL, 150 mg/25 mL & 300 mg/50mL. See Suitability Petition Docket No. 97P-0058/CP1 for package size 150 mg/25 mL.
5. All manufacturing will be performed by Lederle Parenterals for Immunex Corporation. No outside firms are utilized for any manufacturing processes. See pages 321 and 328, Vol. 1.2.

****As of August 20, 1998, ownership of this ANDA was transferred to Baker Norton from Immunex. The product will now be manufactured by Faulding Pharmaceuticals. See Vol. 2.1, Letter dated August 20, 1998 and Vol. 3.1, Letter dated April 2, 1999.**

7. Container/Closure:
   The 30 mg/5 mL product will be packaged in 5 mL vials, flint glass with a grey rubber stopper and aluminum ring seal with a grey polypropylene flip off seal. See page 596, Vol. 1.3.
   The 150 mg/25 mL product will be packaged in 30 mL, 20 mm Clear, glass vial, w/ 20 mm, elastomeric closure and 20 mm aluminum w/blue plastic flip off cap 30 mL PVC

   The 300 mg/50 mL product will be packaged in 50 mL, 20 mm clear glass vial, w/ 20 mm, elastomeric closure and 20 mm aluminum w/blue plastic flip off cap. 50 mL PVC
   See Vol. 4.1, pages 100314 & 100315.
8. Components/Composition:
   Innovator:
   Active: Paclitaxel, 6 mg/mL
   Inactive: 527 mg/mL Cremophor® EL (polyoxyethylated castor oil), 49.7% (v/v) dehydrated alcohol USP
   Applicant
   Active: Paclitaxel, 6 mg/mL
   Inactive: 527mg/mL Polyoxyl 35 Castor Oil NF, 2 mg/mL Citric Acid, Anhydrous, USP, 49.7% (v/v) Dehydrated Alcohol USP, NF is used as headspace filler. See Vol. 4.1, page 100085 & 100086.
9. After discussion with Dianne Spellman (CSO) the innovator now only markets the multiple dose vials. They have supply left on the single dose vials until January 1988. The formulation for both products is the same. As of that date the firm will only market the multiple dose vials. Therefore, the generic products must be multiple dose also.
10. The firm has proposed a proprietary name, PAXENE®. It has been submitted to OPDRA for review on April 26, 2000.
11. The firm is no longer seeking approval for PAXENE®. It has submitted an alternate proposed proprietary name on May 10, 2000 for ONXOL™. This name has been sent to OPDRA for review on May 15, 2000.
12. The firm is no longer seeking approval for ONXOL™ per June 5, 2000 Submission.

Date of Review: August 14, 2000 **Date of Submission: August 8, 2000**
Reviewer: **Date:**
Team Leader: **Date:**

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cc:

AND 75-184
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)

Review

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

ANDA Number: 75-184 **Date of Submission: May 10, 2000 and June 5, 2000**
Applicant's Name: Baker Norton
Established Name: Paclitaxel Injection, 30 mg/5 mL, Multiple dose vials
Labeling Deficiencies:

1. GENERAL COMMENTS:
   a. We acknowledge that you are no longer seeking approval for the proposed proprietary name, ONXOL™.
   b. Please update your exclusivity statement. The reference listed drug received exclusivity D-57 which expires June 20, 2003.
2. CONTAINER- (5 mL, 25 mL, and 50 mL) Satisfactory as of June 5, 2000 submission.
3. CARTON – (1 x 5 mL, 1 x 25 mL, and 1 x 50 mL) Satisfactory as of June 5, 2000 submission.
4. PHYSICIAN'S INSERT
   a. CLINICAL PHARMACOLOGY -
      i. Revise to read "175 mg/m^2" in paragraph three of this section.
      ii. Penultimate Paragraph, penultimate sentence- BOLD the following:

      (See "PRECAUTIONS: Drug Interactions" section).

   b. INDICATIONS AND USAGE - Revise the first sentence of this section to read as follows:

      Paclitaxel is indicated as subsequent therapy for the treatment of advanced carcinoma of the ovary.
   c. WARNINGS - Second paragraph, last sentence) - Revise to read as follows:

      ...to a level of 1500 cells/mm^3 (>1000 cells/mm^3 for patients with KS) and platelets recover...
   d. ADVERSE REACTIONS -

      i. Following the sentence at the bottom of Table 4, Insert the following Subsection Heading:

      Disease Specific Adverse Event Experiences
      ii. Adverse Reactions By Body System (Cardiovascular) -Second paragraph, First Sentence Revise to read as follows:

      Significant cardiovascular events possibly related to single-agent paclitaxel occurred...

      iii. Adverse Reactions By Body System (Cardiovascular) -Fourth Paragraph; Revise the information contained in the parenthesis to read as follows:

      (See PRECAUTIONS: "Drug Interactions" section).

      iv. Adverse Reactions By Body System (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.

   e. DOSAGE AND ADMINISTRATION (Carcinoma of the Breast) - Revise the first sentence of this subsection to read as follows:

      For patients with carcinoma of the breast, the following regimen is recommended. (See

CLINICAL STUDIES: Breast Carcinoma section):

[Relocate (See **CLINICAL STUDIES: Breast Carcinoma** section) from the bottom of the paragraph]

4. PATIENT INFORMATION LEAFLET - Satisfactory in draft. [Note for computer generated insert labeling to be accepted as final print it must be printed front and back.]

Please revise your insert labeling, as instructed above, and submit 12 copies of final printed physician's insert and patient information leaflet labeling prior to expected full approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes: http//www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: (5 mL, 25 mL and 50 mL)-Satisfactory as of June 5, 2000 submission.
Carton Labeling: (1 x 5 mL, 1 x 25 mL and 1 x 50 mL) Satisfactory as of June 5, 2000 submission.
Professional Package Insert Labeling:
Patient Information Leaflet:
BASIS OF APPROVAL:
Was this approval based upon a petition? Yes. Docket No. 97P-0058/CP1 for intermediate package size 150 mg/25 mL
What is the RLD on the 356(h) form: TAXOL® Injection
NDA Number: 20-262/S-033
NDA Drug Name: Paclitaxel Injection
NDA Firm: Bristol-Myers Squibb Pharmaceutical Research Institute
Date of Approval of NDA Insert and supplement #: October 25, 1999.(Physician's Insert; FPL 12-10-99)
December 10, 1999 (Patient Package Insert)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? Yes
If yes, give date of labeling guidance: Revised October 1997
Basis of Approval for the Container Labels: Container labels in file folder.
Basis of Approval for the Carton Labeling: Carton labeling in file folder.
Other Comments: S-036 was approved June 20, 2000, but is covered by exclusivity until June 20, 2003. For a 3-hour infusion of Taxol given every 3 weeks at a dose of 175 mg/m2 followed by cisplatin at a dose of 75 mg/m2 for the first line treatment of advanced ovarian carcinoma.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.			
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?	X		
Packaging			
Is this a new packaging configuration, never been approved by an AND or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	

Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opecode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does AND meet them?			X
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T□ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD:

1. The reference listed drug for this product is TAXOL® (Bristol Myers Squibb; NDA#20-262/S-033; Approved October 25, 1999;FPL December 10, 1999). Patient Package insert S-032, approved December 10, 1999.
2. **Patent/ Exclusivities**:
   There three **patents** that exist for this product.
   Patent #5641803 - Methods for administration of Taxol. Expires: August 3, 2012.
   Applicant has filed a paragraph IV certification.
   Patent #5670537 – U-198 Treatment of metastatic carcinoma of the ovary after 1st line failure or subsequent chemotherapy and treatment of breast cancer after failure of combination chemotherapy for metastatic disease and second line treatment of AIDS related Kaposi's sarcoma.
   Expires: August 3, 2012
   Applicant has filed a paragraph IV certification.
   Patent #5496804 – U-204 Use of Taxol in combination with GCSF for treatment of patients with AIDS related kaposi's sarcoma. Expires: March 9, 2013
   Exclusivities:
   ODE-Treatment of AIDS-related Kaposi's sarcoma. Effective April 15, 1997 - Expires 2004 (7 years).
   I-202 – Second line treatment of AIDS-related Kaposi's Sarcoma. Expires: Aug. 4, 2000
   I-226 – 1st line treatment of advanced carcinoma of the ovary in combination with cisplatin.
   Expires: April 9, 2001
   I-230 – In combination with cisplatin, for the 1st line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation. Expires: June 8, 2002.
   I-270 –Adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. Expires: October 25, 2002.
   D-57-For a 3-hour infusion of Taxol given every 3 weeks at a dose of 175 mg/m2 followed by cisplatin at a dose of 75 mg/m2 for the first line treatment of advanced ovarian carcinoma.
   The three exclusivities that expired are:
   D-24 - For Ovarian Cancer The Recommended Regimen is 135 mg/m^2 or 175 mg/m^2. Expired on June 22, 1997.
   I-105- Treatment of Metastatic Carcinoma of the Breast After Failure of First-Line or Subsequent Chemotherapy. Expired on April 13, 1997.
   NCE-New Chemical Entity - Expired on December 29, 1997
   The firm is not seeking approval for any of the indications covered by the above listed exicusivities
3. Storage/Dispensing Conditions:
   NDA: Store vials in original cartons between 2□ to 25□C (36□ to 77□F). Retain in the original package to protect from light.
   AND: Store between 2□ to 25□C (36□ to 77□F). Protect from light.
4. Product Line:
   The innovator used to market their product in single dose vials containing 30 mg/5 mL and 100 mg/17 mL. Now they manufacture multiple dose vials.

The applicant proposes to market their product in single dose vials containing 30 mg/5 mL.

5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 152, Vol. 1.1.
6. All manufacturing will be performed by for Immunex Corporation. No outside firms are utilized for any manufacturing processes. See pages 321 and 328, Vol. 1.2.
   **As of August 20, 1998, ownership of this ANDA was transferred to Baker Norton from Immunex. The product will now be manufactured by Faulding Pharmaceuticals. See Vol. 2.1, Letter dated August 20, 1998 and Vol. 3.1, Letter dated April 2, 1999.
7. Container/Closure:
   This product will be packaged in 5 mL vials. flint glass with a grey rubber stopper and aluminum ring seal with a grey polypropylene flip off seal. See page 596, Vol. 1.3.
8. This firm utilizes The innovator utilizes Cremophor®EL and no I have referred these discrepancies to the chemist.
9. After discussion with Dianne Spellman (CSO) the innovator now only markets the multiple dose vials. They have supply left on the single dose vials until January 1988. The formulation for both products is the same. As of that date the firm will only market the multiple dose vials. Therefore, the generic products must be multiple dose also.
10. The firm has proposed a proprietary name, PAXENE®. It has been submitted to OPDRA for review on April 26, 2000.
11. The firm is no longer seeking approval for PAXENE®. It has submitted an alternate proposed proprietary name on May 10, 2000 for ONXOL™. This name has been sent to OPDRA for review on May 15, 2000.
12. The firm is no longer seeking approval for ONXOL™ per June 5, 2000 Submission.

Date of Review: August 2, 2000 **Date of Submission: May 10, 2000 and June 5, 2000**
Reviewer: **Date:**
Team Leader: **Date:**

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cc:

AND 75-184
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)

Review

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

ANDA Number: **75-184** Date of Submission: **December 9, 1999 and January 26, 2000**
Applicant's Name: **Baker Norton**
Established Name: **Paclitaxel Injection, 30 mg/5 mL, Multiple dose vials**

Labeling Deficiencies:

1. CONTAINER (5 mL) Satisfactory as of April 2, 1999 submission.
   (25 mL, and 50 mL) Satisfactory as of June 15, 1999 submission.

2. CARTON (1 x 5 mL) Satisfactory as of April 2, 1999 submission (
   (1 x 25 mL, and 1 x 50 mL) Satisfactory as of June 15, 1999 submission.

3. PHYSICIAN'S INSERT

   a. BOXED WARNINGS – We acknowledge your statement that the following is not appropriate as "Kaposi's sarcoma is not a labeled indication in this application." However, it is possible that this may not be utilized specifically to treat AIDS-related Kaposi's sarcoma, but the patient may have a concurrent disease state for which Paclitaxel Injection is indicated. Therefore, as a matter of safety, include this in your Boxed Warnings as requested.

      Revise the first sentence of paragraph three of this section to read as follows:

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

   b. CONTRAINDICATIONS

      See comment under BOXED WARNINGS.

   c. WARNINGS

      Revise the third sentence of paragraph two of this section to read as follows:

      ...than 1,500 cell/mm^3 (<1000 cell/mm^3 for patients with KS).

   d. PRECAUTIONS (Pediatric use) – You have inadvertently included the same information in two paragraphs of this subsection. Delete the information, beginning with sentence two of paragraph one until the end of the first paragraph.

   e. ADVERSE REACTIONS

      i. Second line Ovary (Table 5) –

         A. Revise the title to read as follows:

            TABLE 5: FREQUENCY[a] OF ADVERSE EVENTS...

         B. Hypersensitivity Reactions - Include "†" after "Severe".

4. PATIENT INFORMATION LEAFLET

The reference listed drug has received approval for a PATIENT INFORMATION LEAFLET (Bristol-Myers Squibb; NDA#20-262/S-032; approved December 10, 1999). Since this is part of the approved labeling for the reference listed drug, you are required to submit similar labeling. We have enclosed a copy for your convenience.

Please revise your insert labeling, as instructed above, and submit 12 copies of final printed physician's insert and patient information leaflet labeling prior to expected full approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes: http//www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes
Container Labels: (5 mL) Satisfactory as of April 2, 1999 submission.(Vol. 3.2) (25 mL and 50 mL) Satisfactory as of June 15, 1999 submission.
Carton Labeling: (1 x 5 mL) Satisfactory as of April 2, 1999 submission. (1 x 25 mL and 1 x 50 mL) Satisfactory as of June 15, 1999 submission.
Professional Package Insert Labeling:
Revisions needed post-approval:
BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: TAXOL□ Injection
NDA Number: 20-262/S-033
NDA Drug Name: Paclitaxel Injection
NDA Firm: Bristol-Myers Squibb Pharmaceutical Research Institute
Date of Approval of NDA Insert and supplement #: October 25, 1999.(Physician's Insert; FPL 12-10-99)
December 10, 1999 (Patient Package Insert)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? Yes
If yes, give date of labeling guidance: Revised October 1997
Basis of Approval for the Container Labels: Container labels in file folder.
Basis of Approval for the Carton Labeling: Carton labeling in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an AND or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		

Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does AND meet them?			X
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T □ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if	X		

none, please state.			

FOR THE RECORD:

1. The reference listed drug for this product is TAXOL® (Bristol Myers Squibb; NDA#20-262/S-033; Approved October 25, 1999;FPL December 10, 1999). Patient Package insert S-032, approved December 10, 1999.
2. **Patent/ Exclusivities:**
   There three **patents** that exist for this product.
   Patent #5641803 - Methods for administration of Taxol. Expires: August 3, 2012.
   Applicant has filed a paragraph IV certification.
   Patent #5670537 – U-198 Treatment of metastatic carcinoma of the ovary after 1st line failure or subsequent chemotherapy and treatment of breast cancer after failure of combination chemotherapy for metastatic disease and second line treatment of AIDS related Kaposi's sarcoma. Expires: August 3, 2012
   Applicant has filed a paragraph IV certification.
   Patent #5496804 – U-204 Use of Taxol in combination with GCSF for treatment of patients with AIDS related kaposi's sarcoma. Expires: March 9, 2013

   Exclusivities:
   ODE-Treatment of AIDS-related Kaposi's sarcoma. Effective April 15, 1997 - Expires 2004 (7 years).
   I-202 – Second line treatment of AIDS-related Kaposi's Sarcoma. Expires: Aug. 4, 2000
   I-226 – 1st line treatment of advanced carcinoma of the ovary in combination with cisplatin. Expires: April 9, 2001
   I-230 – In combination with cisplatin, for the 1st line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation. Expires: June 8, 2002.
   I-270 –Adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. Expires: October 25, 2002.
   The three exclusivities that expired are:
   D-24 - For Ovarian Cancer The Recommended Regimen is 135 mg/m^2 or 175 mg/m^2. Expired on June 22, 1997.
   I-105- Treatment of Metastatic Carcinoma of the Breast After Failure of First-Line or Subsequent Chemotherapy. Expired on April 13, 1997.
   NCE-New Chemical Entity - Expired on December 29, 1997
   The firm is not seeking approval for any of the indications covered by the above listed exlcusivities

3. Storage/Dispensing Conditions:
   NDA: Store vials in original cartons between 2□ to 25□C (36□ to 77□F). Retain in the original package to protect from light.
   AND: Store between 2□ to 25□C (36□ to 77□F). Protect from light.
   USP: Not a monograph in the USP.
4. Product Line:
   The innovator used to market their product in single dose vials containing 30 mg/5 mL and 100 mg/17 mL. Now they manufacture multiple dose vials.
   The applicant proposes to market their product in single dose vials containing 30 mg/5 mL.
5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 152, Vol. 1.1.
6. All manufacturing will be performed by for Immunex Corporation. No outside firms are utilized for any manufacturing processes. See pages 321 and 328, Vol. 1.2
   **As of August 20, 1998, ownership of this ANDA was transferred to Baker Norton from Immunex. The product will now be manufactured by Faulding Pharmaceuticals. See Vol. 2.1, Letter dated August 20, 1998 and Vol. 3.1, Letter dated April 2, 1999.

7. Container/Closure:
   This product will be packaged in 5 mL vials, [redacted] flint glass with a grey rubber stopper and aluminum ring seal with a grey polypropylene flip off seal. See page 596, Vol. 1.3.
8. This firm utilizes [redacted]. The innovator utilizes Cremophor□ EL and no[redacted]. I have referred these discrepancies to the chemist.
9. After discussion with Dianne Spellman (CSO) the innovator now only markets the multiple dose vials. They have supply left on the single dose vials until January 1988. The formulation for both products is the same. As of that date the firm will only market the multiple dose vials. Therefore, the generic products must be multiple dose also.

Date of Review: January 31, 2000
Date of Submission: December 9, 1999 and January 26, 2000

Reviewer: **Date:**

Team Leader: **Date:**

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cc:

AND 75-184
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)

Review

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

ANDA Number: **75-184** Date of Submission: **April 2, 1999 and June 15, 1999**

Applicant's Name: **Baker Norton**

Established Name: **Paclitaxel Injection, 30 mg/5 mL, Multiple dose vials**

Labeling Deficiencies:

1. CONTAINER (5 mL, 25 mL, and 50 mL)

   a. Satisfactory.

2. CARTON (1 x 5 mL, 1 x 25 mL, and 1 x 50 mL)

   a. Satisfactory.

3. INSERT

   a. Please note that the most recent labeling for the reference listed drug, TAXOL®, was approved January 8, 1999. Multiple supplements were approved at that time, and it should be noted that S-031 is subject of an exclusivity for "use in combination with cisplatin, for the 1st line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation". We have enclosed a copy of this labeling. Please revise your insert accordingly.

   b. BOXED WARNINGS

      i. Revise the first sentence of paragraph three of this section to read as follows:

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

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

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes: http//www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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.

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (5 mL) Satisfactory as of April 2, 1999 submission.(Vol. 3.2) (25 mL and 50 mL) Satisfactory as of June 15, 1999 submission.

Carton Labeling: (1 x 5 mL) Satisfactory as of April 2, 1999 submission. (1 x 25 mL and 1 x 50 mL) Satisfactory as of June 15, 1999 submission.

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No
What is the RLD on the 356(h) form: TAXOL® Injection

NDA Number: 20-262/S-031
NDA Drug Name: TAXOL® Injection
NDA Firm: Bristol-Myers Squibb Pharmaceutical Research Institute

Date of Approval of NDA Insert and supplement #: Jan 8, 1999.
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? Yes

If yes, give date of labeling guidance: Revised October 1997
Basis of Approval for the Container Labels: Container labels in file folder.
Basis of Approval for the Carton Labeling: Carton labeling in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the FF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

******NOTES/QUESTIONS TO THE CHEMIST:******

1. **The innovator markets this product as a multiple dose vial. The single dose and multiple dose vials have identical formulations. They will no longer market the single dose vials. Has this firm supported adequate data to label the product as a multiple-dose vial?**

2. **The innovator derives its Paclitaxel from . The applicant derives its Paclitaxel from Is this acceptable?**

FOR THE RECORD:

1. The reference listed drug for this product is TAXOL® (Bristol Myers Squibb; NDA#20-262/S-031; Approved January 8, 1999). Review based on the labeling guidance for Paclitaxel Injection; Revised October 1997.

2. **Patent/ Exclusivities:**

   There three **patents** that exist for this product.

   Patent #5641803 - Methods for administration of Taxol.
   Expires: August 3, 2012.
   Applicant has filed a paragraph IV certification.

   Patent #5670537 - U-198 Treatment of metastatic carcinoma of the ovary after 1st line failure or subsequent chemotherapy and treatment of breast cancer after failure of combination chemotherapy for metastatic disease and second line treatment of AIDS related Kaposi's sarcoma.
   Expires: August 3, 2012
   Applicant has filed a paragraph IV certification.

   Patent #5496804 - U-204 Use of Taxol in combination with GCSF for treatment of patients with AIDS related kaposi's sarcoma.
   Expires: March 9, 2013

Exclusivities:

ODE-Treatment of AIDS-related Kaposi's sarcoma.
Effective April 15, 1997 - Expires 2004 (7 years).

I-226 - 1st line treatment of advanced carcinoma of the ovary in combination with cisplatin.
Expires: April 9, 2001

I-230 - In combination with cisplatin, for the 1st line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation.
Expires: June 8, 2002.

The three exclusivities that expired are:

D-24 - For Ovarian Cancer The Recommended Regimen is 135 mg/m^2 or 175 mg/m^2. Expired on June 22, 1997.

I-105- Treatment of Metastatic Carcinoma of the Breast After Failure of First-Line or Subsequent Chemotherapy. Expired on April 13, 1997.

NCE-New Chemical Entity - Expired on December 29, 1997

3. Storage/Dispensing Conditions:

NDA: Store vials in original cartons between 2° to 25°C (36° to 77°F). Retain in the original package to protect from light.

AND: Store between 2° to 25°C (36° to 77°F). Protect from light.

USP: Not a monograph in the USP.

4. Product Line:

The innovator used to market their product in single dose vials containing 30 mg/5 mL and 100 mg/17 mL. Now they manufacture multiple dose vials.

The applicant proposes to market their product in single dose vials containing 30 mg/5 mL.

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 152, Vol. 1.1.

6. All manufacturing will be performed by for Immunex Corporation. No outside firms are utilized for any manufacturing processes. See pages 321 and 328, Vol. 1.2.

**As of August 20, 1998, ownership of this ANDA was transferred to Baker Norton from Immunex. The product will now be manufactured by Faulding Pharmaceuticals. See Vol. 2.1, Letter dated August 20, 1998 and Vol. 3.1, Letter dated April 2, 1999.

7. Container/Closure:

This product will be packaged in 5 mL vials, flint glass with a grey rubber stopper and aluminum ring seal with a grey polypropylene flip off seal. See page 596, Vol. 1.3.

8. This firm utilizes as a pH adjuster and Cremophor® EL-P*. The innovator utilizes Cremophor® EL I have referred these discrepancies to the chemist.

9. After discussion with Dianne Spellman (CSO) the innovator now only markets the multiple dose vials. They have supply left on the single dose vials until January 1988. The formulation for both products is the same. As of that date the firm will only market the multiple dose vials. Therefore, the generic products must be multiple dose also.

Date of Review: **April 7, 1999**
Date of Submission: **April 2, 1999**

Reviewer: **Date:**

Team Leader: **Date:**

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cc:
AND 75-184
DUP/DIVISION FILE
HFD-613/TWatkins/JGrace (no cc)
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Review

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

AND Number: **75-184**

Date of Submission: ~~September~~ July **22, 1997 and October 7, 1997**

Applicant's Name: **Immunex Corporation**

Established Name: **Paclitaxel Injection, 30 mg/5 mL, Multiple dose vials**

Labeling Deficiencies:

1. CONTAINER (5 mL)

   a. Revise the expression of strength to read as follows:

      6 mg/mL

      In addition, relocate the strength to appear immediately following the established name.

   b. Include the route of administration on the main panel and an "Each mL contains..." statement on the side panel.

   c. Relocate the "Protect from light" statement to appear in conjunction with the storage temperature recommendations. In addition include the following sentence:

      Retain in carton until time of use.

   d. Revise to read "Multiple-Dose" rather than

2. CARTON (1 x 5 mL)

   See comments under CONTAINER.

3. INSERT

   In addition to the comments below, we have prepared a

"mock-up" of your draft labeling outlining the necessary revisions needed. Please revise accordingly.

a. DESCRIPTION

Insert the following text as the second sentence of paragraph two:

...activity. Paclitaxel is obtained via a semi-synthetic process from *Taxus Baccata*.

b. CLINICAL PHARMACOLOGY

Ovarian Carcinoma - Insert the following text to appear as the last sentence of paragraph four:

...observed. These statistical analyses should be viewed with caution because of the multiple comparisons made.

c. WARNINGS

Revise the last paragraph to read as follows:

...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.

d. PRECAUTIONS

i. Drug Interactions - Insert the following text to appear as the penultimate paragraph:

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.

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility - Revise to read as follows:

...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/m^2 basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increase embryo- and fetotoxicity (See WARNINGS).

e. ADVERSE REACTIONS

Revise the second paragraph following the table to read as follows:

...812 patients with solid tumors treated in clinical studies. The frequency and severity of adverse events have been generally similar for patients receiving paclitaxel for the treatment of ovarian or breast carcinoma. The frequency and severity of important adverse events...

Please revise your container labels, carton and insert labeling, as instructed above, and submit final printed labels and 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.

_____

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

What is the RLD on the 356(h) form: TAXOL® Injection

NDA Number: 20-262

NDA Drug Name: TAXOL® Injection

NDA Firm: Bristol-Myers Squibb Pharmaceutical Research Institute

Date of Approval of NDA Insert and supplement #: S-022, Approved August 4, 1997
Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? Yes

If yes, give date of labeling guidance: Revised October 1997
Basis of Approval for the Container Labels:
Container labels in file folder.
Basis of Approval for the Carton Labeling:
Carton labeling in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?	X		
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does AND meet them?			X
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			X
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)	—		
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	—	X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

******NOTES/QUESTIONS TO THE CHEMIST:******

1. **This firms formulation contains for pH adjustment. The innovator does not contain this ingredient. Is this acceptable?**

2. **This firm utilizes "Cremophor® EL-P*" in their formulation. The innovator utilizes Cremophor® EL. Are these two ingredients the same?**

3. **The innovator markets this product as a multiple dose vial. The single dose and multiple dose vials have identical formulations. They will no longer market the single dose vials. Has this firm supported adequate data to label the product as a multiple-dose vial?**

FOR THE RECORD:

1. Review based on the labeling guidance for Paclitaxel Injection; Revised October 1997.

2. Patent/ Exclusivities:

   There is one patent that exists for this product. Patent 5641803 - Methods for administration of Taxol. Expires August 3, 2012. There is also two exclusivities that still exist for this product the other two have expired:

   NCE-New Chemical Entity - Expires on December 29, 1997

   ODE-Treatment of AIDS-related Kaposi's sarcoma. Effective April 15, 1997 - Expires 2004 (7 years).

   The two exclusivities that expired are:

   D-24 - For Ovarian Cancer The Recommended Regimen is 135 mg/m^2 or 175 mg/m^2. Expired on June 22, 1997.

   I-105- Treatment of Metastatic Carcinoma of the Breast After Failure of First-Line or Subsequent Chemotherapy. Expired on April 13, 1997.

3. Storage/Dispensing Conditions:

   NDA: Store vials in original cartons between 2° to 25°C (36° to 77°F). Retain in the original package to protect from light.

   AND: Store between 2° to 25°C (36° to 77°F). Protect from light.

   USP: Not a monograph in the USP.

4. Product Line:

   The innovator used to market their product in single dose vials containing 30 mg/5 mL and 100 mg/17 mL. Now they manufacture multiple dose vials.

   The applicant proposes to market their product in single dose vials containing 30 mg/5 mL.

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 152, Vol. 1.1.

6. All manufacturing will be performed by for Immunex Corporation. No outside firms are utilized for any manufacturing processes. See pages 321 and 328, Vol. 1.2.

7. Container/Closure:

   This product will be packaged in 5 mL vials, Type I flint glass with a grey rubber stopper and aluminum ring seal with a grey polypropylene flip off seal. See page 596, Vol. 1.3.

8. This firm utilizes ' as a pH adjuster and Cremophor® EL-P*. The innovator utilizes Cremophor® EL I have referred these discrepancies to the chemist.

9. After discussion with Dianne Spellman (CSO) the innovator now only markets the multiple dose vials. They have supply left on the single dose vials until January 1988. The formulation for both products is the same. As of that date the firm will only market the multiple dose vials. Therefore, the generic products must be multiple dose also.

Date of Review: **October 21, 1997 and November 20, 1997**

Date of Submission: **September 22, 1997 and October 7, 1997**

Reviewer: **Date:**

Team Leader: **Date:**