

**CENTER FOR DRUG
EVALUATION AND RESEARCH**

Approval Package for:

APPLICATION NUMBER:

76-233

Generic Name: Paclitaxel Injection, 6 mg/ mL

Sponsor: NaPro BioTherapeutics, Inc.

Approval Date: August 1, 2002

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APPLICATION NUMBER:
76-233

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EVALUATION AND RESEARCH**

APPLICATION NUMBER:

76-233

APPROVAL LETTER

AUG 1 2002

NaPro BioTherapeutics, Inc.
Attention: Kip Vought
6304 Spine road, Unit A
Boulder, CO 80301

Dear Sir:

This is in reference to your abbreviated new drug application dated August 31, 2001, 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, 150 mg/25 mL, and 300 mg/50 mL multiple-dose vials).

Reference is also made to your amendments dated April 5, June 12, June 13, and July 9, 2002. We also acknowledge receipt of your correspondence addressing patent notification and legal issues dated March 11, April 4, June 28, and July 25, 2002. Reference is also made to the Suitability Petition submitted under Section 505(j)(2)(C) of the Act and approved on June 10, 1997, permitting you to seek approval for the 150mg/25 mL package size. This package size is not included in the labeling for the reference listed drug product (RLD).

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)]; May 08, 2011, [U.S. Patent No. 6,150,398 (the '398 patent)]; and March 9, 2013 [U.S. Patent No. 5,496,804 (the '804 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 Paclitaxel Injection will not infringe on the '803, '804, or '537 patents, or that these patents are invalid or unenforceable. Your application also contains an amended statement under Section

505(j)(2)(A)(viii) of the Act indicating that the '398 patent is a method of use (MOU) patent, and that your labeling does not claim any of the indications or methods of use covered by this patent.

Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against NaPro BioTherapeutics (NaPro) for infringement of one or more of the patents that are the subject of the certifications. This action must be brought against NaPro prior to the expiration of forty-five (45) days from the date the notice provided by NaPro under paragraph (2)(B)(i) is received by the NDA and patent holders. You have informed the Agency that NaPro has complied with the requirements of Section 505(j)(2)(B) of the Act and that no action for patent infringement was brought against NaPro within the 45-day period. You have also notified the agency that NaPro has entered into a non-exclusive cross license agreement with the Bristol Myers Squibb Company (BMS). The agreement grants NaPro a license under BMS patents to market Paclitaxel Injection, pursuant to an ANDA approval.

The reference listed drug product, Taxol® Injection, is also subject to periods of Waxman-Hatch exclusivity, [i.e., D-57, I-270, and Orphan Drug Exclusivity (ODE)] that are listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book". You have stated that your labeling for this drug product will not claim these indications or methods of use until the exclusivity expires.

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,

A handwritten signature in black ink, appearing to be 'G Buehler', with a stylized 'S' or 'B' symbol above it.

Gary Buehler 8/1/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

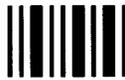
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RESEARCH**

APPLICATION NUMBER:

76-233

Final Printed Labeling

AUG 1 2002



APPROVED

5 mL Vial **Multiple-dose**
PACLITAXEL Injection
30 mg/5 mL (6 mg/mL)

NDC 0074-5088-01
Store between 20° to 25°C (68° to 77°F). Each mL contains 6 mg paclitaxel, 527 mg of Cremophor® EL (Polyoxyl 35 Castor Oil, NF), 49.7% (w/v) Dehydrated Alcohol, USP and 2 mg Citric Acid, USP.
Cremophor® EL is the registered trademark of BASF Aktiengesellschaft. Manufactured by Abbott Laboratories, North Chicago, IL 60064, USA. PAC6364-2/R2-11/01

CAUTION: DILUTION REQUIRED PRIOR TO IV INFUSION. Rx only
WARNING: Cytotoxic agent Rx only
Retain in carton until contents are used.
Protect from light. Usual Dosage: See insert.

AUG - 1 2002

16.7 mL Vial Multiple-dose

**PACLITAXEL
Injection**

100 mg/16.7 mL (6 mg/mL)

**CAUTION: DILUTION REQUIRED
PRIOR TO IV INFUSION.**

Rx only

**WARNING: Cytotoxic agent
Retain in carton until contents are used.
Protect from light. Usual Dosage: See insert.**



NDC 0074-5088-02

Store between 20° to 25°C (68° to 77°F).
Each mL contains 6 mg paclitaxel,
527 mg of Cremophor® EL (Polysaxyl
35 Castor Oil, NF), 43.7% w/v
Dehydrated Alcohol, USP and 2 mg
Citric Acid, USP.
Cremophor® EL is the registered
trademark of BASF Aktiengesellschaft,
Manufactured by Abbott Laboratories,
North Chicago, IL 60064, USA.

RAO6367-2/R2-11/01



(01) 0 030074 508802 9

APPROVED

AUG - 1 2002

25 mL Vial Multiple-dose



NDC 0074-5088-03

Store between 20° to 25°C (68° to 77°F).
Each mL contains 6 mg paclitaxel, 527 mg of Cremophor® EL (Polyoxyyl 35 Castor Oil, NFI, 48.7% (w/v) Dehydrated Alcohol, USP and 2 mg Citric Acid, USP. Cremophor® EL is the registered trademark of BASF Aktiengesellschaft. Manufactured by Abbott Laboratories, North Chicago, IL 60064, USA

CAUTION: DILUTION REQUIRED PRIOR TO IV INFUSION.
WARNING: Cytotoxic agent Retain in carton until contents are used.
Protect from light. Usual Dosage: See package insert.

Rx only



(01) 0 030074 508803 6

APPROVED

RA06365-2-R2-11/01
NDC 0074-5088-01
5 mL Vial Multiple-dose
PACLITAXEL Injection
30 mg/5 mL (6 mg/mL)

APPROVED

**PACLITAXEL
Injection**

30 mg/5 mL (6 mg/mL)

Each mL contains 6 mg
paclitaxel, 527 mg of
Cremophor® EL
(Polyoxyl 35 Castor Oil,
NF), 49.7% (v/v)
Dehydrated Alcohol,
USP and 2 mg Citric
Acid, USP.

Cremophor® EL is the
registered trademark of BASF
Aktiengesellschaft.

Manufactured by
Abbott Laboratories,
N. Chicago, IL 60064, USA

Usual Dosage: See insert for
detailed dosage, directions
for use and precautions.

AUG - 1 2002



5 mL NDC 0074-5088-01
Vial Multiple-dose

**PACLITAXEL
Injection**

30 mg/5 mL (6 mg/mL)

**CAUTION: DILUTION
REQUIRED PRIOR TO
IV INFUSION.**

**WARNING: Cytotoxic Agent
Retain in carton until
contents are used.
Protect from light.**

Store vials between 20° to
25°C (68° to 77°F). only

RAO6366-2/R2-11/01
16.7 mL NDC 0074-5088-02
Multiple-dose Vial
PACLITAXEL Injection
100 mg/16.7 mL
(6 mg/mL)

PACLITAXEL Injection
100 mg/16.7 mL
(6 mg/mL)

Each mL contains 6 mg paclitaxel, 527 mg of Cremophor® EL (Polyoxyl 35 Castor Oil, NF), 49.7% (v/v) Dehydrated Alcohol, USP and 2 mg Citric Acid, USP.

Cremophor® EL is the registered trademark of BASF Aktiengesellschaft.
Manufactured by Abbott Laboratories, North Chicago, IL 60064, USA

Usual Dosage: See insert for detailed dosage, directions for use and precautions.

APPROVED
AUG 17 2002



16.7 mL NDC 0074-5088-02
Multiple-dose Vial

PACLITAXEL Injection
100 mg/16.7 mL
(6 mg/mL)

CAUTION: DILUTION REQUIRED PRIOR TO IV INFUSION.

WARNING: Cytotoxic Agent
Retain in carton until contents are used.
Protect from light.
Store vials between 20° to 25°C (68° to 77°F).

R_x only



25 mL NDC 0074-5088-03
Multiple-dose Vial

RA06369-2/R2-11/01



Each mL contains 6 mg paclitaxel, 527 mg of Cremophor® EL (Polyoxyl 35 Castor Oil, NF), 49.7% (v/v) Dehydrated Alcohol, USP and 2 mg Citric Acid, USP.

Cremophor® EL is the registered trademark of BASF Aktiengesellschaft. Manufactured by Abbott Laboratories, North Chicago, IL 60064, USA

Usual Dosage: See insert for detailed dosage, directions for use and precautions.

AUG - 1 2002
APPROVED



(01) 0 030074 508803 6

25 mL NDC 0074-5088-03
Vial Multiple-dose



CAUTION: DILUTION REQUIRED PRIOR TO IV INFUSION.

WARNING: Cytotoxic Agent
Retain in carton until contents are used.
Protect from light.

Store vials between 20° to 25°C (68° to 77°F).

R_x only

RA06371-2/R2-11/01
50 mL NDC 0074-5088-04
Multiple-dose Vial
PACLITAXEL Injection
300 mg/50 mL
(6 mg/mL)

PACLITAXEL Injection
300 mg/50 mL
(6 mg/mL)

Each mL contains 6 mg paclitaxel, 527 mg of Cremophor® EL (Polyoxyl 35 Castor Oil, NF), 49.7% (v/v) Dehydrated Alcohol, USP and 2 mg Citric Acid, USP.

Cremophor® EL is the registered trademark of BASF Aktiengesellschaft.

Manufactured by Abbott Laboratories, North Chicago, IL 60064, USA

Usual Dosage: See insert for detailed dosage, directions for use and precautions.

APPROVED
AUG - 1 2002



50 mL NDC 0074-5088-04
Multiple-dose Vial

PACLITAXEL Injection
300 mg/50 mL
(6 mg/mL)

CAUTION: DILUTION REQUIRED PRIOR TO IV INFUSION.

WARNING: Cytotoxic Agent
Retain in carton until contents are used.
Protect from light.

Store vials between 20° to 25°C (68° to 77°F).

R_x only

**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

76-233

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1
2. ANDA # 76-233
3. NAME AND ADDRESS OF APPLICANT

NaPro BioTherapeutics, Inc.
6304 Spine Road, Unit A
Boulder, CO 80301

4. LEGAL BASIS FOR SUBMISSION

Based on TAXOL[®] (Paclitaxel) Injection, 6 mg/mL (Bristol-Myers Squibb, NDA 20-262.

The patent for TAXOL[®] (Paclitaxel) Injection, held by Bristol-Myers Squibb, expires May 8, 2011, August 3, 2012, February 22, 2013, March 9, 2013 and August 3, 2013.

TAXOL[®] (Paclitaxel) Injection is entitled to a period of marketing exclusivity.

NaPro Bio Therapeutics, Inc. certifies that the following five patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Paclitaxel injection for which this application is submitted.

Patent No.	6150398
Patent Expiration	May 8, 2011

Patent No.	5670537
Patent Expiration	August 3, 2012

Patent No.	5496804
Patent Expiration	March 9, 2013

Patent No.	5641803
Patent Expiration	August 3, 2012

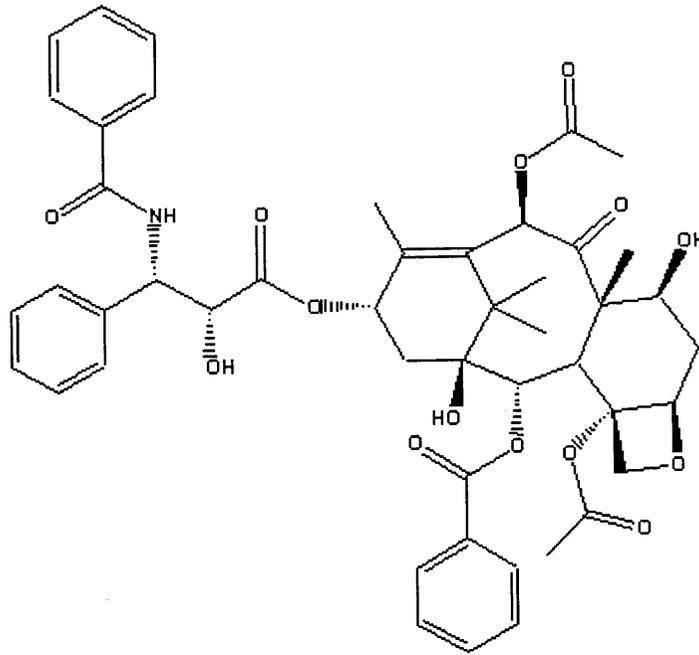
Patent No.	6096331
Patent Expiration	February 22, 2013

The reference listed drug is entitled to the following six periods of marketing exclusivity. None of these exclusivities would bar the approval of this application because NaPro Bio Therapeutics, Inc. does not seek inclusion of those indications in the labeling of its product before the expiration of the exclusivity applicable to each indication.

5. SUPPLEMENT (s) N/A

6. PROPRIETARY NAME
Paclitaxel
7. NONPROPRIETARY NAME
N/N
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Original 8/31/01
Correspondence 10/19/01
Amendment 12/21/01
10. PHARMACOLOGICAL CATEGORY
Treatment of advanced carcinoma of the ovary.
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
DMF's ~~_____~~
13. DOSAGE FORM
Injection
14. POTENCIES
30, 100, 150 and 300 mg/vial
15. CHEMICAL NAME AND STRUCTURE
(2aR, 4aS, 6R, 9S, 11S, 12SS, 12aR, 12bS)-1, 2a, 12b-Dodecahydro-4, 6, 9, 1, 1, 12, -12b-hexahydroxy-4a, 8, 13, 13-tetramethyl-7, 11-methano-5H-cyclodeca[3, 4]benz[1, 2-b]oxet-5-one 6, 12b-diacetate, 12-benzoate, 9ester with (2R, 3s)-N-benzoyl-3-phenylisoserine

**APPEARS THIS WAY
ON ORIGINAL**

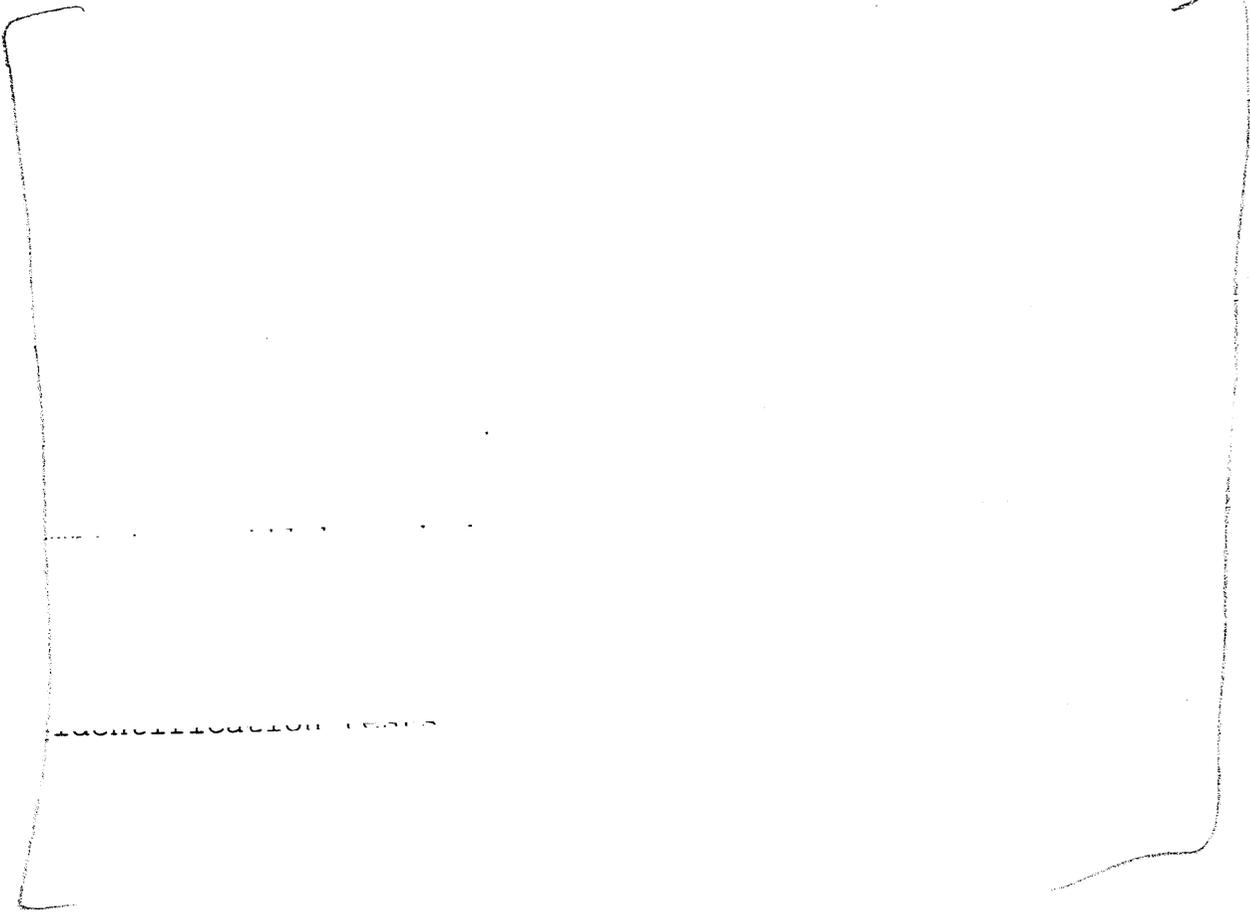


16. RECORDS AND REPORTS

17. COMMENTS

[]

heavy metals.



18. CONCLUSIONS AND RECOMMENDATIONS

The application is deficient.

19. REVIEWER: **/S/** DATE COMPLETED:
Nashed E. Nashed, Ph.D. 2/25/02
1/29/02

Supervisor: James M. Fan 1/29/02

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1. CHEMISTRY REVIEW NO. 2
2. ANDA # 76-233
3. NAME AND ADDRESS OF APPLICANT

NaPro BioTherapeutics, Inc.
6304 Spine Road, Unit A
Boulder, CO 80301

4. LEGAL BASIS FOR SUBMISSION

Based on TAXOL[®] (Paclitaxel) Injection, 6 mg/mL (Bristol-Myers Squibb, NDA 20-262.

The patent for TAXOL[®] (Paclitaxel) Injection, held by Bristol-Myers Squibb, expires May 8, 2011, August 3, 2012, March 9, 2013 and August 3, 2013.

TAXOL[®] (Paclitaxel) Injection is entitled to a period of marketing exclusivity.

NaPro Bio Therapeutics, Inc. certifies that the following five patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of Paclitaxel injection for which this application is submitted.

Patent No. 6150398
Patent Expiration May 8, 2011

Patent No. 5670537
Patent Expiration August 3, 2012

Patent No. 5496804
Patent Expiration March 9, 2013

Patent No. 5641803
Patent Expiration August 3, 2012

The reference listed drug is entitled to the following six periods of marketing exclusivity. None of these exclusivities would bar the approval of this application because NaPro Bio Therapeutics, Inc. does not seek inclusion of those indications in the labeling of its product before the expiration of the exclusivity applicable to each indication.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

Paclitaxel

7. NONPROPRIETARY NAME

N/N

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

9. AMENDMENTS AND OTHER DATES:

Original 8/31/01
Correspondence 10/19/01
Amendment 12/21/01
Amendment 3/11/02 (patent amendment)
Amendment 4/5/02 (Minor Amendment)
New Corr. 4/4/02 (Patent amendment)
Amendment 6/13/02 (Micro)
Amendment 7/9/02 (Labeling)
New Corr. 7/25/02 (Patent)

10. PHARMACOLOGICAL CATEGORY

Treatment of advanced carcinoma of the ovary.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's _____

13. DOSAGE FORM

Injection

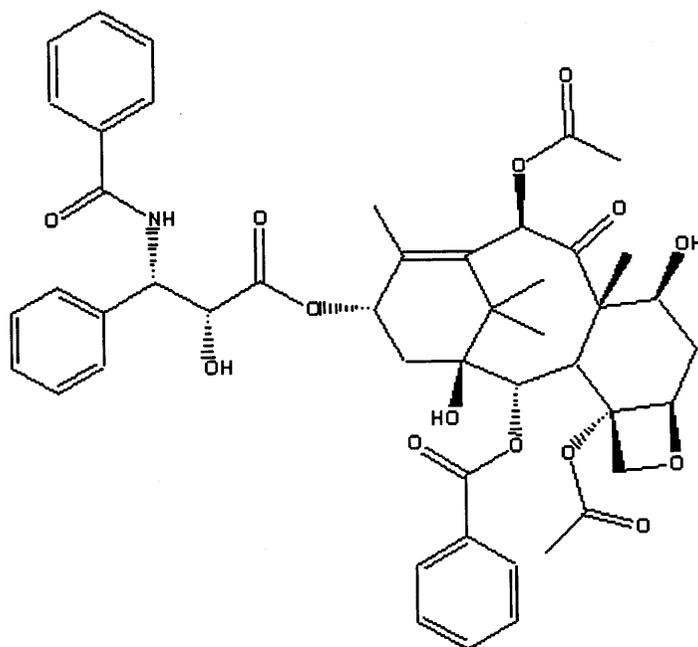
14. POTENCIES

30, 100, 150 and 300 mg/vial

15. CHEMICAL NAME AND STRUCTURE

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

**APPEARS THIS WAY
ON ORIGINAL**



16. RECORDS AND REPORTS

17. COMMENTS - See individual review section.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is Approvable

19. REVIEWER: */S/*

DATE COMPLETED:

Nashed E. Nashed, Ph.D.

7/26/02

4/25/02

Supervisor: James M. Fan

5/19/02

cc: ANDA 76-233
Division File
Field Copy

Endorsements:

HFD-627/NNashed

HFD-627/JFan

F/t by: gp/7/26/02

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/S/ 7/26/02
/S/ 7/27/02

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**CENTER FOR DRUG EVALUATION
AND RESEARCH**

APPLICATION NUMBER:

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MICROBIOLOGY REVIEW

Product Quality Microbiology Review

Review for HFD-620

12 June 2002

ANDA: 76-233

Drug Product Name

Proprietary: N/A

Non-proprietary: Paclitaxel Injection

Drug Product Classification: Anti Neoplastic

Review Number: 1

Subject of this Review

Submission Date: August 31, 2001 and June 12, 2002 (Telephone amendment)

Receipt Date: September 5, 2001 and June 13, 2002)

Consult Date: N/A

Date Assigned for Review: May 23, 2002

Submission History (for amendments only)

Date(s) of Previous Submission(s): N/A

Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor

Name: NaPro Bio Therapeutics, Inc

Address: 6304 Spine Road, Unit A, Boulder, CO 80301

Representative: Kip Vought

U.S. Agent: N/A

Telephone: 303-516-8500

Name of Reviewer: Nrapendra Nath

Conclusion: The submission is **recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUPPLEMENT:** N/A
- 2. **SUPPLEMENT PROVIDES FOR:** N/A
- 3. **MANUFACTURING SITE:**
 Abbott Laboratories
 Hospital Products Division
 1776 N. Centennial Drive
 McPherson, Kansas 67460
- 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 30, 100, 150 and 200 mg /vial (multiple dose vials); Intravenous infusion with buffered solution.
- 5. **METHOD(S) OF STERILIZATION:** _____
- 6. **PHARMACOLOGICAL CATEGORY:** Anti-neoplastic.

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:** The subject drug product is manufactured by Abbott Laboratories at their McPherson, Kansas facility and _____

A telecon was held on June 11, 2002 at the initiative of the reviewer seeking clarification of the conditions of _____
 The applicant's telephone amendment dated 6/12/02 has been incorporated in the subject review.

filename: V:\Microrev\ 76-233.doc

**APPEARS THIS WAY
ON ORIGINAL**

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **recommended** for approval on the basis of sterility assurance. Specific comments are provided in the "Product Quality Microbiology Assessment".

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -

The subject drug product is _____

**B. Brief Description of Microbiology Deficiencies -
None.**

**C. Assessment of Risk Due to Microbiology Deficiencies -
None.**

III. Administrative

A. Reviewer's Signature _____ **/S/** _____ 6/18/02

B. Endorsement Block
Microbiologist / Nrapendra Nath
Microbiology Supervisor/Lynne Ensor **/S/** 6/18/02
6/18/02

C. CC Block
cc:
Original ANDA 76-233
HFD- 600/Division File/ANDA 76-233
filename: V:\Microrev\ 76-233.doc

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**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

76-233

BIOEQUIVALENCE REVIEW

**OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE**

ANDA # : 76-233

SPONSOR : Napro Biotherapeutics, Inc.

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

STRENGTH(S) : 6 mg/mL; 30 mg, 100 mg, 150 mg and 300 mg Vials

TYPES OF STUDIES : Original ANDA

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY : The waivers are granted

Dissolution: N/A

DSI INSPECTION STATUS

Inspection needed: <u>NO</u>	Inspection status:	Inspection results:
First Generic <u>ND</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
other _____		

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

INITIAL : MS DATE : 11/6/01

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

INITIAL : MS DATE : 11/9/01

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

INITIAL : MS DATE : 11/15/01

1.1 Azk

Paclitaxel Injection, 6 mg/mL
5, 16.7, 25 and 50 mL Vials
ANDA #76-233
Reviewer: Moheb H. Makary
W 76233W.801

Napro Biotherapeutics
Boulder, CO.
Submission Date:
August 31, 2001

Review of Waiver Requests

I. Background

The firm has requested a waiver of *in vivo* bioequivalence study requirements for its proposed product, Paclitaxel Injection, 6 mg/mL; 30 mg/5 mL, 100 mg/16.7 mL, 150 mg/25 mL and 300 mg/50 mL vials. The reference listed drug is Taxol^R (paclitaxel) Injection, NDA# 20262, 6 mg/mL; 30 mg/5 mL, 100 mg/16.7 mL and 300 mg/50 ml multi-dose vials, manufactured by Bristol-Myers Squibb. The 150 mg/25 mL vial was approved by the Agency based on the suitability petition granted to Fujisawa USA, Inc. on June 10, 1997 (Docket No. 97P-0058/CP1). The proposed product differs from the reference listed drug by the presence of citric acid as a _____ and use of Cremophor^R EL as the _____ instead of the purified Cremophor^R EL.

Paclitaxel Injection is a viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. It is indicated for the subsequent therapy for the treatment of advanced carcinoma of the ovary.

The reference product, Taxol^R (paclitaxel) Injection, is to be administered by the intravenous route. The same route of administration applies for the proposed product, Paclitaxel Injection.

II. Formulation comparison

The test and reference formulations are compared as shown below.

Ingredients	Reference: Taxol ^R (paclitaxel) Injection, per mL	Test: Paclitaxel Injection, per mL
Paclitaxel	6 mg	6 mg
*Purified Cremophor ^R	527 mg	527 mg

citric acid is a ~~_____~~. See attachment #2.

6. The presence of citric acid in the test product is in accordance with 21 CFR 314.94 (a)(9)(iii), which allows for change in ~~_____~~ provided that the change does not affect the safety of the proposed drug product.

7. The two products are deemed bioequivalent under 21 CFR 320.24 (b)(6).

Recommendation

The Division of Bioequivalence agrees that the information submitted by Napro Biotherapeutics, Inc. demonstrates that Paclitaxel Injection, 6 mg/mL; 30 mg, 100 mg, 150 mg and 300 mg vials, falls under 21 CFR section 320.24 (b)(6) of the Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence deems the test product, Paclitaxel Injection, 6 mg/mL (30 mg, 100 mg, 150 mg and 300 mg vials), to be bioequivalent to the reference product, Taxol^R (paclitaxel) Injection, 6 mg/mL, manufactured by Bristol-Myers Squibb.

The firm should be informed of the recommendation.

~~_____~~ /S/
Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

Date: 11/14/01

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT

11/14/01 /S/

Date 11/14/01

Concur ~~_____~~ /S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 11/15/01

Mmakary/ 11-6-01, 11-9-01, 76233W.801
cc: ANDA #76-233, original, HFD-658 (Makary), Drug File,
Division File.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA #76-233 APPLICANT: Napro Biotherapeutics, Inc.

DRUG PRODUCT: Paclitaxel Injection, 6 mg/mL; 30 mg, 100 mg, 150 mg and 300 mg 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,



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

**APPEARS THIS WAY
ON ORIGINAL**

CC: ANDA #76-233
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

V:\FIRMSNZ\NAPRO BT\LTRS&REV\76233W.801
Printed in final on 11/9 /01

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary *MS/ 11/15/01*
HFD-658/ Bio team Leader B. Davit *MS/ 11/15/01*
HFD-650/ D. Conner *MS/ 11/15/01*

BIOEQUIVALENCY - ACCEPTABLE Submission date: 8/31/01

- 1. WAIVER (WAI) Strengths: 6 mg/mL; 30 mg/vial
Outcome: AC
- 2. WAIVER (WAI) Strengths: 6 mg/mL; 100 mg/vial
Outcome: AC
- 3. WAIVER (WAI) Strengths: 6 mg/mL; 150 mg/vial
Outcome: AC
- 4. WAIVER (WAI) Strengths: 6 mg/mL; 300 mg/vial
Outcome: AC

Outcome Decisions: **AC** - Acceptable

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-233

**ADMINISTRATIVE
DOCUMENTS**

Verified slip request

**ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application: **ANDA 76233/000**
 Stamp: **05-SEP-2001** Regulatory Due:
 Applicant: **NAPRO**
6304 SPINE RD UNIV A
BOULDER, CO 80301

Priority:
 Action Goal:
 Brand Name:
 Established Name: **PACLITAXEL**
 Generic Name:
 Dosage Form: **INJ (INJECTION)**
 Strength: **30,100,150,300 MG/VIAL**

Org Code: **600**District Goal: **05-AUG-2002**

FDA Contacts: **M. DILLAHUNT (HFD-613)**
M. SMELA JR (HFD-625)

301-827-5848 , Project Manager
301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 10-MAY-2002 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 31-DEC-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1925262**
ABBOTT LABORATORIES
1776 NORTH CENTENNIAL DR
MCPHERSON, KS 67460

DMF No:
 AADA No:

Profile: **SVS** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **10-MAY-2002**
 Decision: **ACCEPTABLE**
 Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE
MANUFACTURER**

Establishment: **1722102**
NAPRO BIOTHERAPEUTICS, INC.
4880 STERLING DRIVE
BOULDER, CO 80301

DMF No: **15092**
 AADA No:

Profile: **CEX** OAI Status: **NONE**
 Last Milestone: **OC RECOMMENDATION**
 Milestone Date: **01-NOV-2001**
 Decision: **ACCEPTABLE**
 Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

Search results from the "Rx" table for query on "020262."

Active Ingredient:	PACLITAXEL
Dosage Form;Route:	Injectable; Injection
Proprietary Name	TAXOL
Applicant:	BRISTOL MYERS SQUIBB
Strength:	6MG/ML
Application Number:	020262
Product Number:	001
Approval Date:	DEC 29, 1992
Reference Listed Drug:	Yes
RX/OTC/DISCN:	RX
TE Code:	AP
Patent and Exclusivity Info for this product:	Click Here

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Proprietary Name Search Results from "Rx" table for query on "taxol."

Appi No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
075446	AT	No	BETAXOLOL HYDROCHLORIDE	Solution/Drops; Ophthalmic	EQ 0.5% BASE	BETAXOLOL	NOVEX
075386	AT	No	BETAXOLOL HYDROCHLORIDE	Solution/Drops; Ophthalmic	EQ 0.5% BASE	BETAXOLOL	AKORN
075630	AT	No	BETAXOLOL HYDROCHLORIDE	Solution/Drops; Ophthalmic	EQ 0.5% BASE	BETAXOLOL HCL	BAUSCH AND LOMB
075541	AB	No	BETAXOLOL HYDROCHLORIDE	Tablet; Oral	10MG	BETAXOLOL HCL	AMIDE PHARM
075541	AB	No	BETAXOLOL HYDROCHLORIDE	Tablet; Oral	20MG	BETAXOLOL HCL	AMIDE PHARM
020262	AP	Yes	PACLITAXEL	Injectable; Injection	6MG/ML	TAXOL	BRISTOL MYERS SQUIBB

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APPEARS THIS WAY
ON ORIGINAL

Paclitaxel inj.

76-233
NaPro

orig. strengths - 6mg/mL, 5mL, 16.7mL 25mL & 50mL vial
orig. cell.

- PIV for '398

- PIV for '537

PIV for '804

PIV for '803

PIV for '331

orig. exclusiv.

D-57 exp. 6/20/03

I-230 exp. 1/8/02

I-226 exp. 4/9/01

ODE exp. 8/4/04

I-270 exp. 10/25/02

I-202 exp. 8/4/00

} will carve out

ack. 9/5/01 w/ PIV

rr Vivo R certified US 12/19/01

rr BMS " " 1/3/02

rr DHHS " " 2/13/02

no suit w/in 45 days

received 7/1/02 Δ from PIV to MOU for '398

Redacted

2

pages of trade secret and/or

confidential

commercial

information

Patent and Exclusivity Search Results from query on 020262 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020262	001	5496804	MAR 09,2013	U-204
020262	001	5641803	AUG 03,2012	U-198
020262	001	5670537	AUG 03,2012	U-198
020262	001	6150398	MAY 08,2011	U-380

Use of Taxol in combination with G-CSF for treatment of patients with AIDS-related Kaposi's sarcoma.

Use of metastatic carcinoma of the ovary after first-line failure or subsequent chemotherapy, tx of breast cancer after failure of combination chemotherapy and second line tx of AIDS-related Kaposi's sarcoma.

Combinations of taxol + cisplatin which are suitable for the treatment of ovarian and non-small cell lung carcinomas.

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020262	001	D-57	JUN 20,2003
020262	001	I-270	OCT 25,2002
020262	001	I-230	JAN 08,2002
020262	001	ODE	AUG 04,2004

3 hour infusion of taxol given every 3 weeks followed by cisplatin for first line tx of advanced ovarian cancer.

tx of node positive breast cancer or administered sequentially carved out to doxorubicin-containing combination chemotherapy in combination with cisplatin - tx non-small cell lung CA

tx of AIDS-related Kaposi's sarcoma

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

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1st
8/10/02
IS

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

ANDA Number	76-233
Date of Submission	July 9, 2002, June 12, 2002 (NC) and April 5, 2002
Applicant	Napro
Drug Name	Paclitaxel Injection
Strength(s)	6 mg/ mL

FPL Approval Summary

Container Labels		Submitted
6 mg/mL	30 mg/ 5mL, 100 mg/ 16.7 mL, 150 mg/ 25 mL, 300 mg/ 50 mL -	April 5, 2002 vol 3.1 (FPL)
Carton labeling		
30 mg/ 5mL, 100 mg/ 16.7 mL, 150 mg/ 25 mL, 300 mg/ 50 mL	1's	April 5, 2002 vol 3.1 (FPL)
Package Insert Labeling	#RAO6452R3 REV 07/02	July 9, 2002 vol 3.1 (FPL)
Patient Leaflet.	#RAO6452R3 REV 07/02	July 9, 2002 vol 3.1 (FPL)

BASIS OF APPROVAL:

Patent Data for NDA 20-262

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6150398	May 08,2011	U-380	Combinations of paclitaxel and cisplatin which are suitable for the treatment of ovarian and non-small cell lung carcinomas	P-IV will change to a MOU <i>MOU in jacket</i>	CARVED OUT based on I-230 expiration of 1/8/02. Firm declined to add as requested. Gregg Davis consulted firm needs a MOU to exclude text .
5496804	Mar 09,2013	U-204	Use of taxol in combo with GCSF for treatment of patients with AIDS related kaposi's sarcoma	P - IV	CARVED OUT based on ODE expiration of 8/4/2004
6096331	Feb. 22, 2013	—	Method and compositions useful for administration of chemo agents Cremphor-Free form.	P - IV	NO IMPACT because generic uses cremphor.
5670537 & 5641803	Aug. 03, 2012	U-198	(1) Treatment of metastatic carcinoma of the ovary after 1 st line failure or subsequent chemotherapy	P - IV	Same As

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/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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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 1/2 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: The proposed formulation also uses a different species (taxus X media "Hicksii") the RLD uses "taxus baccata". JS/128/02

FOR THE RECORD:

- Review based on the labeling of taxol; BMS 20262/S-036, approved June 20, 2000. Review actually based on our first generic application ANDA 75-184/S-006, approved May 25, 2001 by Baker Norton. superseded by taxol S/037/S/038 approved March 4, 2002.
- Patent/ Exclusivities - See above chart. Review based on the labeling of taxol; BMS 20262/S-036, approved June 20, 2000.
- Patent/ Exclusivities - See above chart
- Storage Conditions:
NDA - store the vials in original cartons between 20-25C retain in original package to protect from light.
ANDA - same
USP -
- Dispensing Recommendations:
NDA - n/a
ANDA -
USP -
- Scoring: NA
NDA -
ANDA -
USP -
- Product Line:
The innovator markets their product in 6mg/mL (30 mg/5ml; 100 mg/16.7 ml; 300 mg/50mL MDV , 1/carton)
The applicant proposes to market their product in flint 1 glass vials - 30 mg/5ml; 100 mg/16.7 ml; 150 mg/25 ml, 300 mg/50mL MDV , 1/carton)
MDV , green color scheme.
- The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). N/A
- 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 109 vol 1.1 red. Purified Cremophor is not used in the generic. The generic used citric acid as a _____ and use Cremophor as the _____
- Manufactured by Abbott lab., 1776 N. centennial dr., Mcpherson, kansas.

10. Bio division found generic product to be equivalent to RLD.
11. GENERAL COMMENT - declined to revise. Referred to regulatory for possible change to MOU. Please note that you have filed a paragraph IV for patent number 6150398 that contains a U-380 code for the combination use of paclitaxel and cisplatin which are suitable for the treatment of ovarian and non small cell lung carcinomas. Associated with the use code are two exclusivities I - 230 expired 1/08/02 and I-226 expired on 4/09/2001. The text was curved out of your labeling. Now that the later exclusivity has expired and a PIV was filed, please revise your labeling to include text relating to the patent and exclusivities. We have enclosed a copy of the latest (Approved 3/4/02) labeling for guidance. Applicant spoke to Greg on today 7/1/02 and will be filing a MOU today.

Date of Review: July 15, 2002

Date of Submission: July 9, 2002, June 12, 2002 and April 5, 2002

cc: ANDA: 76-233
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmsnz/Napro/lets&rev/76233AP.Lab
Review

ISI
u
7/15/02
ISI
7/15/2002

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING#2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

(FAO)

ANDA Number: 76-233

Date of Submission: April 5, 2002

Applicant's Name: Napro

Established Name: Paclitaxel Injection 6 mg/ mL: 30 mg/ 5mL, 100 mg/ 16.7 mL, 150 mg/ 25 mL, 300 mg/ 50 mL vials

Labeling Deficiencies:

1. CONTAINER - 30 mg/ 5mL, 100 mg/ 16.7 mL, 150 mg/ 25 mL, 300 mg/ 50 mL - Satisfactory in final print.
2. CARTON - 30 mg/ 5mL, 100 mg/ 16.7 mL, 150 mg/ 25 mL, 300 mg/ 50 mL - Satisfactory in final print.
3. PROFESSIONAL INSERT

a. GENERAL COMMENT

Please note that you have filed a paragraph IV for patent number 6150398 that contains a U-380 code for the combination use of paclitaxel and cisplatin which are suitable for the treatment of ovarian and non small cell lung carcinomas. Associated with the use code are two exclusivities I - 230 expired 1/08/02 and I-226 expired on 4/09/2001. The text was curved out of your labeling. Now that the later exclusivity has expired and a PIV was filed, please revise your labeling to include text relating to the patent and exclusivities. We have enclosed a copy of the latest (Approved 3/4/02) labeling for guidance.

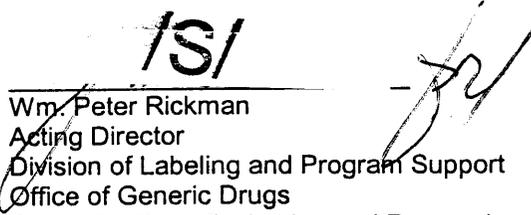
- b. ADVERSE REACTIONS section- We refer you to the enclosed copy of taxol for specific locations and text to be included in the two locations (Neurologic subsection, last paragraph and the Clinical Events subsection).

5. PATIENT LEAFLET – Satisfactory in final print.

Please revise your insert labeling, as instructed above, and submit 12 final printed insert labeling or draft labeling if you prefer.

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 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 No If no, list why:

Container Labels: 30 mg/ 5mL, 100 mg/ 16.7 mL, 150 mg/ 25 mL, 300 mg/ 50 mL - Satisfactory in final print vol. B3.1

Carton Labeling: 30 mg/ 5mL, 100 mg/ 16.7 mL, 150 mg/ 25 mL, 300 mg/ 50 mL - Satisfactory in final print vol. B3.1

Professional Package Insert Labeling:

Patient Package Insert Labeling:-

Revisions needed post-approval:

BASIS OF APPROVAL:

Patent Data for NDA 20-262

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6150398	May 08,2011	U-380	Combinations of paclitaxel and cisplatin which are suitable for the treatment of ovarian and non-small cell lung carcinomas	P-IV	CARVED OUT based on I-230 expiration of 1/8/02
5496804	Mar 09,2013	U-204	Use of taxol in combo with GCSF for treatment of patients with AIDS related kaposi's sarcoma	P - IV	CARVED OUT based on ODE expiration of 8/4/2004
6096331	Feb. 22, 2013	--	Method and compositions useful for administration of chemo agents Cremphor-Free form.	P - IV	NO IMPACT because generic uses cremphor.
5670537 & 5641803	Aug. 03, 2012	U-198	(1) Treatment of metastatic carcinoma of the ovary after 1 st line failure or subsequent chemotherapy	P - IV	Same As
5670537 & 5641803	Aug. 03, 2012	U-198	2) treatment of breast cancer after failure of combo chemotherapy for metastatic disease	P - IV	Sames As
5670537 & 5641803	Aug. 03, 2012	U-198	(3) second line treatment of AIDS related Kaposi's sarcoma	P - IV	CARVED OUT bases on ODE expiration of 8/4/2004

Exclusivity Data For NDA

Code/sup	Expiration	Description	Labeling impact
ODE	Aug.4, 2004	Treatment of AIDS related kaposi's	CARVED OUT
D-57/S-036	Jun. 20, 2003	3-hr infusion of taxol given every three weeks at a dose of 175 mg/ms followed by cisplatin dose of 75 mg/m2 for the firs-line treatment of advanced ovarian cancer.	CARVED OUT
I-270	Oct. 25, 2002	Adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combo chemotherapy.	CARVED OUT

I-230	Jan. 08, 2002	In combo 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	Previously CARVED OUT connected with U-380, now add
I-226	Apr.09, 2001	First line therapy for the treatment of advanced carcinoma of the ovary in combo with cisplatin	Previously CARVED OUT connected with U-380, now add
I-202	Aug. 04, 2000	Second line treatment of aids-related kaposi's scaroma	CARVED OUT based on ODE expiration of 8/4/2004

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Taxol

NDA Number: 20262

NDA Drug Name: Paclitaxel

NDA Firm: BMS

Date of Approval of NDA Insert and supplement #: S-036 app. June 20, 2000 superceded by S/037/S/038 approved March 4, 2002

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: sample in jacket

Basis of Approval for the Carton Labeling: sample in jacket

Other Comments: Review actually based on our first generic application ANDA 75-184/S-006, approved May 25, 2001 by Baker Norton. Must now add the combo use of paclitaxel with cisplatin.

Other Comments: Used the first generic Paclitaxel by baker Nortons as the model. Approved 5/2001. With the addition of a sentence in the boxed warning area regarding AIDS related kaposi sarcoma and changes to the ADERVSE REACTIONS, Neurologic subsection.

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/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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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 1/2 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: The proposed formulation also uses a different species (taxus X media "Hicksii") the RLD uses "taxus baccata".

FOR THE RECORD:

1. Review based on the labeling of taxol; BMS 20262/S-036, approved June 20, 2000. Review actually based on our first generic application ANDA 75-184/S-006, approved May 25, 2001 by Baker Norton. superceded by taxol S/037/S/038 approved March 4, 2002.
2. Patent/ Exclusivities - See above chart. Review based on the labeling of taxol; BMS 20262/S-036, approved June 20, 2000.
2. Patent/ Exclusivities - See above chart
3. Storage Conditions:
NDA – store the vials in original cartons between 20-25C retain in original package to protect from light.
ANDA – same
USP -
4. Dispensing Recommendations:

- NDA - n/a
ANDA -
USP -
5. Scoring: NA
NDA -
ANDA -
USP -
6. Product Line:
The innovator markets their product in 6mg/mL (30 mg/5ml; 100 mg/16.7 ml; 300 mg/50mL MDV ,
1/carton)
The applicant proposes to market their product in flint 1 glass vials - 30 mg/5ml; 100 mg/16.7 ml; 150 mg/25
ml, 300 mg/50mL MDV , 1/carton)
MDV , green color scheme.
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the
HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products
for Human Use; Final Rule, effective 9/13/95). N/A
8. 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 109 vol 1.1 red. Purified Cremophor is not used in the generic. The generic used citric
acid as a _____ and use Cremophor as the _____
9. Manufactured by Abbott lab., 1776 N. centennial dr., Mcpherson, kansas.
10. Bio division found generic product to be equivalent to RLD.

Date of Review: May 15, 2002

Date of Submission: April 5, 2002

cc: ANDA: 76-233
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmsnz/Napro/lets&rev/76233na2.L
Review'

ISI
5/20/02
7-11
ISI

5/20/2002

APPEARS THIS WAY
ON ORIGINAL

Ho, Sarah

From: Ho, Sarah
Sent: Wednesday, January 09, 2002 12:54 PM
To: Wiseman, Rosemarie*; Washington, Edward*; Green, Wayne*
Cc: Beers Block, Patricia M; Nashed, Nashed E; Fan, James M
Subject: ANDA 76-233

Hi Rose,

Could you please convert the 12/21/01 submission from "AA" to "AM".
The submission is in response to our CMC Minor deficiency.
I will bring the jacket down to you. Could you please return it to Nashed when done.
Thanks,
Sarah

**APPEARS THIS WAY
ON ORIGINAL**

o, Sarah

From: Ho, Sarah
Sent: Thursday, January 10, 2002 1:23 PM
To: Wiseman, Rosemarie*; Washington, Edward*; Green, Wayne*
Cc: Beers Block, Patricia M; Nashed, Nashed E; Fan, James M
Subject: RE: ANDA 76-233

Rose,

Let's keep it as AA. The chemist has been notified to review this submission with the first cycle review.
Thanks,
Sarah

-----Original Message-----

From: Wiseman, Rosemarie*
Sent: Wednesday, January 09, 2002 2:16 PM
To: Ho, Sarah; Washington, Edward*; Green, Wayne*
Cc: Beers Block, Patricia M; Nashed, Nashed E; Fan, James M
Subject: RE: ANDA 76-233

Sarah,

No deficiency letter went out on this appl, the system will not accept AM only AA or AC.
Please let me know your decision.

Thanks

Rose

-----Original Message-----

From: Ho, Sarah
Sent: Wednesday, January 09, 2002 12:54 PM
To: Wiseman, Rosemarie*; Washington, Edward*; Green, Wayne*
Cc: Beers Block, Patricia M; Nashed, Nashed E; Fan, James M
Subject: ANDA 76-233

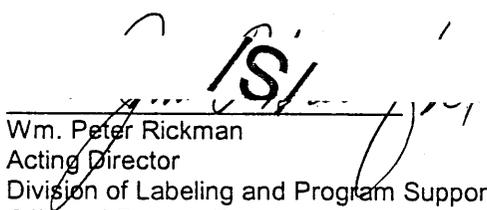
Hi Rose,

Could you please convert the 12/21/01 submission from "AA" to "AM".
The submission is in response to our CMC Minor deficiency.
I will bring the jacket down to you. Could you please return it to Nashed when done.
Thanks,
Sarah

Please revise your labels and labeling, as instructed above, and submit 12 final printed labels and labeling or draft labeling if you prefer.

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 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

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 76233/000**
Stamp: **05-SEP-2001** Regulatory Due:
Applicant: **NAPRO**
6304 SPINE RD UNIV A
BOULDER, CO 80301

Priority:
Action Goal:
Brand Name:
Established Name: **PACLITAXEL**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **30,100,150,300 MG/VIAL**

Org Code: **600**District Goal: **05-AUG-2002**

FDA Contacts: **M. DILLHUNT**
M. SMELA JR (HFD-625)

301-827-5848, Project Manager
301-827-5848, Team Leader

Overall Recommendation:

ACCEPTABLE on 31-DEC-2001 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1925262**
ABBOTT LABORATORIES
✓ **1776 NORTH CENTENNIAL DR**
MCPHERSON, KS 67460

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **INSPECTION PERFORMED**
Milestone Date: **04-FEB-2002**

Responsibilities: **FINISHED DOSAGE**
MANUFACTURER

Establishment: **1722102**
✓ **NAPRO BIOTHERAPEUTICS, INC.**
4880 STERLING DRIVE
BOULDER, CO 80301

DMF No: _____
AADA No:

Profile: **CEX** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-NOV-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE**
MANUFACTURER

**APPEARS THIS WAY
ON ORIGINAL**

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:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:-

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Patent Data For NDA 20-262

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
6150398	May 08, 2011	U-380	Combinations of paclitaxel and cisplatin which are suitable for the treatment of ovarian and non-small cell lung carcinomas	P-IV	CARVED OUT based on I-230 expiration of 1/8/02
5496804	Mar 09, 2013	U-204	Use of taxol in combo with GCSF for treatment of patients with AIDS related kaposi's sarcoma	P - IV	CARVED OUT based on ODE expiration of 8/4/2004
6096331	Feb. 22, 2013	—	Method and compositions useful for administration of chemo agents Cremphor-Free form.	P - IV	NO IMPACT because generic uses cremphor.
5670537 & 5641803	Aug. 03, 2012	U-198	(1) Treatment of metastatic carcinoma of the ovary after 1 st line failure or subsequent chemotherapy	P - IV	Same As
5670537 & 5641803	Aug. 03, 2012	U-198	2) treatment of breast cancer after failure of combo chemotherapy for metastatic disease	P - IV	Sames As
5670537 & 5641803	Aug. 03, 2012	U-198	(3) second line treatment of AIDS related Kaposi's sarcoma	P - IV	CARVED OUT bases on ODE expiration of 8/4/2004

Exclusivity Data For NDA

Code/sup	Expiration	Description	Labeling impact
ODE	Aug.4, 2004	Treatment of AIDS related kaposi's	CARVED OUT
D-57/S-036	Jun. 20, 2003	3-hr infusion of taxol given every three weeks at a dose of 175 mg/ms followed by cisplatin dose of 75 mg/m2 for the firs-line treatment of advanced ovarian cancer.	CARVED OUT
I-270	Oct. 25, 2002	Adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combo chemotherapy.	CARVED OUT

I-230	Jan. 08, 2002	In combo 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	CARVED OUT connected with U-380
I-226	Apr.09, 2001	First line therapy for the treatment of advanced carcinoma of the ovary in combo with cisplatin	CARVED OUT connected with U-380
I-202	Aug. 04, 2000	Second line treatment of aids-related kaposi's scaroma	CARVED OUT based on ODE expiration of 8/4/2004

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Taxol

NDA Number: 20262

NDA Drug Name: Paclitaxel

NDA Firm: BMS

Date of Approval of NDA Insert and supplement #: S-036 app. June 20, 2000

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: sample in jacket

Basis of Approval for the Carton Labeling: sample in jacket

Other Comments: Review actually based on our first generic application ANDA 75-184/S-006, approved May 25, 2001 by Baker Norton.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Other Comments: Used the first generic Paclitaxel by baker Nortons as the model. Approved 5/2001. With the addition of a sentence in the boxed warning area regarding AIDS related kaposi sarcoma and changes to the ADERVSE REACTIONS, Neurologic subsection.

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/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	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		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 1/2 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: The proposed formulation also uses a different species (taxus X media "Hicksii") the RLD uses "taxus baccata".

FOR THE RECORD:

- Review based on the labeling of taxol; BMS 20262/S-036, approved June 20, 2000. Review actually based on our first generic application ANDA 75-184/S-006, approved May 25, 2001 by Baker Norton.
- Patent/ Exclusivities - See above chart. Review based on the labeling of taxol; BMS 20262/S-036, approved June 20, 2000.
- Patent/ Exclusivities - See above chart
- Storage Conditions:
NDA – store the vials in original cartons between 20-25C retain in original package to protect from light.
ANDA – same
USP -
- Dispensing Recommendations:

- NDA - n/a
ANDA -
USP -
5. Scoring: NA
NDA -
ANDA -
USP -
6. Product Line:
The innovator markets their product in 6mg/mL (30 mg/5ml; 100 mg/16.7 ml; 300 mg/50mL MDV , 1/carton)
The applicant proposes to market their product in flint 1 glass vials - 30 mg/5ml; 100 mg/16.7 ml; 150 mg/25 ml, 300 mg/50mL MDV , 1/carton)
MDV , green color scheme.
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). N/A
8. 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 109 vol 1.1 red. Purified Cremophor is not used in the generic. The generic used citric acid as a _____ and use Cremophor as the _____
9. Manufactured by Abbott lab., 1776 N. centennial dr., Mcpherson, kansas.
10. Bio division found generic product to be equivalent to RLD.

Date of Review: January 7, 2002

Date of Submission: August 31, 2001

cc: ANDA: 76-233
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
V:firmsnz/Napro/lets&rev/76233na1.L
Review

|S| 01/08/02
|S| 1/9/2002

**APPEARS THIS WAY
ON ORIGINAL**

Shimer, Martin

From: Sager, Nancy B
Sent: Monday, October 15, 2001 9:15 AM
To: Shimer, Martin
Subject: RE: 76233 EA statement for Paclitaxel

The claim of categorical exclusion from the requirement to provide an EA is acceptable.

Nancy

-----Original Message-----

From: Shimer, Martin
Sent: Friday, October 12, 2001 8:56 AM
To: Sager, Nancy B
Subject: 76233 EA statement for Paclitaxel

Nancy,

Did the environmental assessment that I faxed over to you for this application appear complete?
If not what additional information is required?

Thanks,

Marty

APPEARS THIS WAY
ON ORIGINAL

Section XX. Environmental Impact Analysis Statement

Claim of Categorical Exclusions

The drug substance occurs naturally in the environment and its proposed use is not expected to significantly affect the quality of the human environment. There will be no significant alterations in its concentration or distribution as a result of the proposed action.

The Paclitaxel drug substance is not derived from Pacific yew trees nor does the drug product, Paclitaxel Injection, otherwise involve Pacific yew trees.

The biomass source used is identified as *Taxus X media 'Hicksii'* and is also identified as an ornamental yew. This biomass is plantation-grown and does not exist in the wild. It is commonly used as a landscape plant and requires no permits to harvest.

The primary growers for NaPro are:

These companies root, plant, cultivate and maintain NaPro-owned plants under contract arrangements. Likewise, other growers of the same ornamental yew may be used to a lesser extent depending on the availability of existing plants on their property and the need for additional biomass.

_____ is located in a _____
_____ is located in a largely government-owned undeveloped-forested area of _____ where the principal industries are logging and mining. _____ is located in a _____

Taxus X media 'Hicksii' is not determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened, entitled to a special protection under some other Federal law or international treaty to which the United States is a party, or the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to special protection under some other Federal law or international treaty to which the United States is a party.

Paclitaxel Injection
ANDA
Original Submission

ction XX. Environmental Impact Analysis Statement

Claim of Categorical Exclusions (Cont.)

For the above stated reasons, and to the applicant's knowledge, no extraordinary circumstances exist; this application qualifies for a categorical exclusion from the preparation of an EA or an EIS as permitted under 21 CFR 25.31(a):

"Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety."

In accordance with 21 CFR 25, attached is a certification letter issued by the drug product manufacturer, Abbott Laboratories, McPherson, Kansas facility.

APPEARS THIS WAY
ON ORIGINAL

Hospital Products Division

Abbott Laboratories
1700 Centennial Dr.
P.O. Box 1247
McPherson, KS 67460-1247

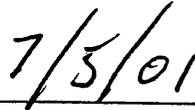
Tel: (316) 241-6200

ENVIRONMENTAL IMPACT ANALYSIS STATEMENT

This is to certify that the McPherson, Kansas facility of Abbott Laboratories/HPD meets all known
to us Federal, State, and Local environmental laws, with all permits current and reporting
requirements up-to-date.



L.O. Smith
Safety Supervisor



Date

**APPEARS THIS WAY
ON ORIGINAL**

Telecon Record

Date: October 12, 2001

ANDA: 76-233

Firm: NaPro Bio Therapeutics, Inc.

Drug: Paclitaxel Inj. 6mg/mL

FDA Participants: Martin Shimer

Industry Participants: Kip Vought (voice mail)

Phone #: (303) 516-8500

Agenda: Marty called Mr. Vought and asked that he submit the following documents:

1. Revised 356h that identifies the holder of the approved application as BMS
2. Revised patent certification to identify the correct date of patent #5641803 as August 3, 2012
3. Two additional separately bound copies of the methods validation, this is essentially section 16 of the submission
4. Revise page 278 to restate the maximum proposed scale-up commercial batch as the following(to be in compliance with 10X rule):
 - for the 5 mL and 50 mL fill sizes
 - for the 16.7 mL and 25 mL fill sizes

**APPEARS THIS WAY
ON ORIGINAL**

Active Ingredient Search Results from "Rx" table for query on "paclitaxel."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
075184	AP	No	PACLITAXEL	Injectable; Injection	6MG/ML	PACLITAXEL	BAKER NORTON
020262	AP	Yes	PACLITAXEL	Injectable; Injection	6MG/ML	TAXOL	BRISTOL MYERS SQUIBB
075297	AP	No	PACLITAXEL	Injectable; Injection	6MG/ML	PACLITAXEL	ZENITH GOLDLINE

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APPEARS THIS WAY
ON ORIGINAL

Search results from the "Rx" table for query on "020262."

Active Ingredient:	PACLITAXEL
Dosage Form;Route:	Injectable; Injection
Proprietary Name:	TAXOL
Applicant:	BRISTOL MYERS SQUIBB
Strength:	6MG/ML
Application Number:	020262
Product Number:	001
Approval Date:	Dec 29, 1992
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	AP
Patent and Exclusivity Info for this product:	Click Here

Thank you for searching the **Electronic Orange Book!**

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APPEARS THIS WAY
ON ORIGINAL

Patent and Exclusivity Search Results from query on 020262 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020262	001	5496804	MAR 09,2013	U-204
020262	001	5641803	AUG 03,2012	U-198
020262	001	5670537	AUG 03,2012	U-198
020262	001	6096331	FEB 22,2013	U-380
020262	001	6150398	MAY 08,2011	U-380

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020262	001	D-57	JUN 20,2003
020262	001	I-270	OCT 25,2002
020262	001	I-230	JAN 08,2002
020262	001	I-226	APR 09,2001
020262	001	ODE	AUG 04,2004

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

APPEARS THIS WAY
ON ORIGINAL

Application:	ANDA 76233/000	Action Goal:	
Stamp:	05-SEP-2001	District Goal:	05-AUG-2002
Regulatory Due:		Brand Name:	
Applicant:	NAPRO	Estab. Name:	PACLITAXEL
	6304 SPINE RD UNIV A	Generic Name:	
	BOULDER, CO 80301		
Priority:		Dosage Form:	(INJECTION)
Org Code:	600	Strength:	30,100,150,300 MG/VIAL
Application Comment:			
FDA Contacts:	M. DILLAHUNT (HFD-613)	301-827-5848	, Project Manager
	M. SMELA JR (HFD-625)	301-827-5848	, Team Leader

Overall Recommendation:

Establishment: 1925262

ABBOTT LABORATORIES
1776 NORTH CENTENNIAL DR
MCPHERSON, KS 67460

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SVS

OAI Status: NONE

Estab. Comment: THIS FACILITY IS RESPONSIBLE FOR THE MANUFACTURING PROCESS, TESTING, AND STABILITY TESTING OF THE FINISHED DOSAGE FORM (on 31-OCT-2001 by M. SHIMER II (HFD-615))

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-OCT-2001				SHIMERM

Establishment: 1722102

NAPRO BIOTHERAPEUTICS, INC.
4880 STERLING DRIVE
BOULDER, CO 80301

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CEX

OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-OCT-2001				SHIMERM

**APPEARS THIS WAY
ON ORIGINAL**

Attachment #1

FILE COPY *ce*

MEETING MINUTES

DATE: 6-10-98

OGD, MPN-II, Conference B

Subject: Cremophor EL as an ingredient in the following ANDAs:
#75278 Paclitaxel inj 6 mg/ml Mylan
#65004 Cyclosporine inj 50 mg/ml 5 ml vials Bedford labs
#75291 Paclitaxel inj 6 mg/ml Gensia Labs

Meeting Recorder: Nancy Chamberlin, Pharm.D.

/S/
6/15/98

FDA Participants:

- Dale Conner, Director, Division of Bioequivalence
- Shriniwas Nerurkar, Team leader, Division of Bioequivalence
- Yih Huang, Team leader, Division of Bioequivalence
- Barbara Davit, Team leader, Division of Bioequivalence
- Andre Jackson, Reviewer, Division of Bioequivalence
- Frank Holcombe, Director, Division of Chemistry II
- Mike Smela, Team Leader, Division of Chemistry I
- Vilayat Sayeed, Team Leader, Division of Chemistry I
- Nancy Chamberlin, Project Manager, Division of Bioequivalence
- Lizzie Sanchez, Project Manager, Division of Bioequivalence
- Cecelia Parise, Regulatory Counsel OGD
- Don Hare, Special Assistant to Director OGD

Meeting Objective: Discuss the use of Cremophor EL and _____

Discussions: Frank mentioned that Bristol buys cremophor EL and _____ methods used by _____ result in _____

_____ The viscosity does not meet NF as the ranges overlap. The range of the specifications are not changed.

After discussion chemistry concluded that cremophor EL and _____ are the same inactive ingredient, but different grade.

It could not be determined in the meeting if the different grades result in toxicity and/or efficacy issues.

Discussion was held on the use of citric acid as a _____ However, it was agreed that if inactive ingredients were used in other products in our referenced listings and the proposed quantity was less, that there should not be a safety or efficacy issue. When a firm exceeds the current highest accepted inactive ingredient usage or uses a new inactive ingredient it will be sent on pharmtox consult. Glycine still is an issue under review with Dr. Fanning. Mylan as proposed use of metabisulfite with what appears to be an _____

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APPEARS THIS WAY ON ORIGINAL

acceptable amount.

Conclusion:

Based on this meeting Bio reviews could be finalized due to chemistry's determination that cremophor EL and _____ are the same inactive ingredient, but different grades.

Drafted NC 6/10/98
Revised NC 6/15/98

x:\new\bio\issues\cremaphor

**APPEARS THIS WAY
ON ORIGINAL**

[

]

- 76-233
- 1.) Revised 356h with BMS identified as holder of approved application
 - 2.) Revised patent certification to identify correct date of patent # 5641803 as August 3 2012
 - 3.) Please provide 2 additional separately bound copies of methods validation essentially section 16 of this application New use product
 - 4.) Revise pg 278 to allow following max scale up commercial batch
 - for the 5ml fill
50ml fill
 - for the 16.7ml fill
25ml fill

Kip Vought (303) 516-8500

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76-233

CORRESPONDENCE



NaPro BioTherapeutics, Inc.

NEW CORRESP

NC

3.1
G. Buehler
ANDA 76-233
Page 1 of 1
July 25, 2002

July 25, 2002

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler
Director

Re: **ANDA 76-233 Paclitaxel Injection (6 mg/mL)**

PATENT AMENDMENT

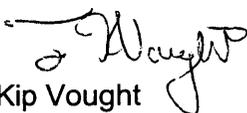
Reference is made to the original abbreviated new drug application submitted August 31, 2001 and amended.

NaPro BioTherapeutics, Inc. provided in this submission a Paragraph IV certification that patent no. 6096331 is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of paclitaxel injection for which this application is submitted.

Since this patent is no longer listed in the FDA Orange Book, NaPro hereby withdraws its Paragraph IV certification against patent 6096331.

Please contact me if you should have any additional questions or concerns in this matter.

Sincerely,


Kip Vought
Manager, Regulatory Affairs
NaPro BioTherapeutics, Inc.
Phone: (303) 516-8500
Fax: (303) 530-1296
Email: kvought@naprobio.com

RECEIVED
JUL 26 2002
OGD / CDER



NaPro BioTherapeutics, Inc.

G. Buehler
ANDA 76-233
Page 2 of 2
July 9, 2002

If you require any clarification or further information, please feel free to contact me.

Sincerely,

Kip Vought
Manager, Regulatory Affairs
NaPro BioTherapeutics, Inc.
Phone: (303) 516-8500
Fax: (303) 530-1296
Email: kvought@naprobio.com

**APPEARS THIS WAY
ON ORIGINAL**



NaPro BioTherapeutics, Inc.

6304 Spine Road, Unit A
Boulder, Colorado 80301
Tel: (303) 530-3891
Fax: (303) 530-1296

4.1

June 28, 2002

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler
Director

Re: **ANDA 76-233 Paclitaxel Injection (6 mg/mL)**

PATENT AMENDMENT

URGENT

NC

NAZ 7/10

-MOD for "6150398"

IS!

NaPro BioTherapeutics hereby amends ANDA 76-233 as allowed under 21 CFR 314.94(a)(12)(viii). We have reviewed the patent status of Paclitaxel Injection in anticipation of approval of our application, and determined that we should clarify our prior certification of U.S. Patent No. 6150398 contained in the original application, submitted August 31, 2001. A Patent Statement is attached. If you require any clarification or further information, please feel free to contact me.

Sincerely,

Kip Vought
Manager, Regulatory Affairs
NaPro BioTherapeutics, Inc.
Phone: (303) 516-8500
Fax: (303) 530-1296
Email: kvought@naprobio.com

RECEIVED

JUL 01 2002

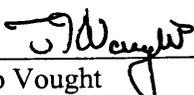
OGD / ODER

Patent Statement

NaPro BioTherapeutics amends Section III of the pending application with the following information:

Application No.	020262
Patent No.	6150398
Patent Expiration	May 8, 2011
Use Code	U-380 (COMBINATIONS OF TAXOL (PACLITAXEL) AND CISPLATIN WHICH ARE SUITABLE FOR THE TREATMENT OF OVARIAN AND NON-SMALL CELL LUNG CARCINOMAS)

NaPro BioTherapeutics hereby state that all claims of U.S. Patent No. 6150398 are directed to methods of using paclitaxel, and that U.S. Patent No. 6150398 does not claim any of the proposed indications for which NaPro BioTherapeutics is seeking approval.



Kip Vought
Manager, Regulatory Affairs

6/25/2002
Date

**APPEARS THIS WAY
ON ORIGINAL**



NAPro BioTHERAPEUTICS, INC.

6304 Spine Road, Unit A
Boulder, Colorado 80301
Tel: (303) 530-3891
Fax: (303) 530-1296

June 13, 2002

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

~~ORIG~~ AMENDMENT
N/A S

ATTENTION: Gary J. Buehler
Director

Re: **ANDA 76-233 Paclitaxel Injection (6 mg/mL)**

TELEPHONE AMENDMENT

Reference is made to the original abbreviated new drug application for the above-referenced subject drug product submitted August 31, 2001 and amended October 19, 2001, December 21, 2001, and April 5, 2002.

Reference is also made to a teleconference between Ms. Bonnie McNeal (FDA) and Mr. Kip Vought (NaPro) on June 4, 2002 and a follow-up teleconference on June 11, 2002 between representatives* of the Agency, NaPro BioTherapeutics and Abbott Laboratories.

*** FDA Representatives**

Bonnie McNeal	CSO, OGD
Nrapendra Nath, Ph.D.	Microbiology Reviewer

NaPro Representative

Kip Vought	Manager, Regulatory Affairs
Clara Yee	Associate Director, Regulatory Affairs

Abbott Representatives

Dan Proctor	Manager, Plant Quality Assurance
Tim Nicoll	Manager, Validation
Melissa Nguyen	Sr. Analyst, Regulatory Affairs
Valerie Welter	Manager, HPD Validation

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JUN 14 2002

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The Agency noted that the ANDA did not note the



NaPro BioTherapeutics, Inc.

G. Buehler
ANDA 76-233
Page 2 of 2
June 13, 2002

NaPro BioTherapeutics hereby certifies that we have sent a true copy of this submission to the Denver, Colorado, FDA District Office.

If you require any clarification or further information, please feel free to contact me.

Sincerely,

Kip Vought
Manager, Regulatory Affairs
NaPro BioTherapeutics, Inc.
Phone: (303) 516-8500
Fax: (303) 530-1296
Email: kvought@naprobio.com

APPEARS THIS WAY
ON ORIGINAL



NaPro BioTherapeutics, Inc.

6304 Spine Road, Unit A
Boulder, Colorado 80301
Tel: (303) 530-3891
Fax: (303) 530-1296

June 12, 2002

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

CORRESP
NC

ATTENTION: Gary J. Buehler
Director

Re: **ANDA 76-233 Paclitaxel Injection (6 mg/mL)**

LABELING AMENDMENT

Reference is made to the original abbreviated new drug application for the above-referenced subject drug product submitted August 31, 2001 and amended. We are responding to the Agency's action letter dated May 21, 2002.

The Agency's action letter requests responses to labeling deficiencies. The Agency's comments with NaPro's responses are as follows:

Labeling Deficiencies:

- 1. **CONTAINER-30 mg/5mL, 100 mg/16.7 mL, 150 mg/25 mL, 300 mg/50 mL – Satisfactory in final print.**
- 2. **CARTON-30 mg/5mL, 100 mg/16.7 mL, 150 mg/25 mL, 300 mg/50 mL – Satisfactory in final print.**
- 3. **PROFESSIONAL INSERT**
 - a. **GENERAL COMMENT**

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JUN 13 2002

OGD / CDEP

Please note that you have filed a paragraph IV for patent number 6150398 that contains a U-380 code for the combination use of paclitaxel and cisplatin which are suitable for the treatment of ovarian and non small cell lung carcinomas. Associated with the use code are two exclusivities I-230 expired 1/08/02 and I-226 expired on 4/09/2001. The text was curved out of your labeling. Now that the later exclusivity has expired and a PIV was filed, please revise your labeling to include text relating to the patent and exclusivities. We have enclosed a copy of the latest (Approved 3/4/02) labeling for guidance.

- b. **ADVERSE REACTIONS section – We refer you to the enclosed copy of taxol for specific locations and text to be included in the two locations (Neurologic subsection, last paragraph and the Clinical Events subsection).**



NaPro BioTherapeutics, Inc.

6304 Spine Road, Unit A
Boulder, Colorado 80301
Tel: (303) 530-3891
Fax: (303) 530-1296

5. PATIENT LEAFLET – Satisfactory in final print.

Please revise your labels and labeling, as instructed above, and submit 12 final printed labels and labeling or draft labeling if you prefer.

Response: We acknowledge that the periods of exclusivity for I-230 and I-226 have expired, however U.S. Patent 6150398 is still listed in the Orange Book and will not expire until May 8, 2011. Our counsel has advised NaPro not to revise the label as requested, as this could be considered as inducing others (a physician or pharmacist) to infringe on U.S. Patent 6150398 and could be actionable by the licensee of the patent (Bristol).

Therefore, NaPro BioTherapeutics respectfully declines the Agency's request.

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

Response: NaPro BioTherapeutics acknowledge that it may be necessary to further revise our labeling subsequent to approved changes for the reference listed drug.

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.

Response: Acknowledged. As no labeling revisions were made, side-by-side comparisons are not provided.

If you require any clarification or further information, please feel free to contact me.

Sincerely,

Kip Vought
Manager, Regulatory Affairs
NaPro BioTherapeutics, Inc.
Phone: (303) 516-8500
Fax: (303) 530-1296
Email: kvought@naprobio.com



NaPro BioTherapeutics, Inc.

6304 Spine Road, Unit A
Boulder, Colorado 80301
Tel: (303) 530-3891
Fax: (303) 530-1296

April 5, 2002

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**ELECTRONIC SUBMISSION
ENCLOSED**

ATTENTION: Gary J. Buehler
Director

**Re: ANDA 76-233 Paclitaxel Injection (6 mg/mL)
MINOR AMENDMENT**

Reference is made to the original abbreviated new drug application for the above-referenced subject drug product submitted August 31, 2001 and amended October 19 and December 21, 2001. We are responding to the Agency's action letter dated February 28, 2002.

The Agency's action letter requests responses to chemistry and labeling deficiencies. The Agency's comments with NaPro's responses are as follows:

Chemistry Deficiencies:

Comment 1: Please provide limits for _____
and tighten the limit for total related substance based on your
observed drug substance data."

Response 1: _____, are controlled
to a limit of NMT _____ as individual unknown impurities.
_____ are controlled to a limit of NMT
_____ as individual unspecified impurities. Unspecified impurities are
those that have been identified in NaPro drug substance, but not
individually listed on the specification since they are controlled to NMT

The total impurities limit has been tightened from "NMT _____ to
"NMT _____, which is supported by historical batch analysis data
provide in Table 1. Appended in Exhibit I is the revised specification
for the drug substance. DMF _____ will
also be updated with the new total impurity limit upon the next annual
update.

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APR 10 2002

OGD / CDER

Handwritten signature and date: 4/12/02



NAPRO BIOTHERAPEUTICS, INC.

G. Buehler
ANDA 76-233
Page 2 of 10
April 5, 2002

Additionally, we have also tightened the limit for _____ in the drug substance from NMT _____ to NMT _____. (Please refer to Exhibit I.)

Table 1: Historical Drug Substance Batch Analysis Data for Total Impurities

Lot Number	Total Impurities (% Area)
A-3120-96-0001	_____
A-3120-97-0001	_____
A-3120-97-0002	_____
A-3120-97-0003	_____
A-3120-97-0004	_____
A-3120-97-0005	_____
A-3120-97-0006	_____
A-3120-97-0007	_____
A-3120-97-0008	_____
A-3120-97-0008A	_____
A-3120-98-0001	_____
A-3120-98-0002	_____
A-3120-98-0003	_____
A-3120-98-0004	_____
A-3120-98-0005	_____
A-3120-98-0006	_____
A-3120-99-2001	_____
A-3200-99-4003	_____
A-3200-99-4009	_____

Comment 2:

“Please tighten the limit for _____ content for the drug substance based on your data.”

Response 2:

The _____ content in the drug substance has been tightened from “NMT _____” to “NMT _____”. This limit is supported by batch analysis data provided in Table 2. Appended in Exhibit I is the revised specification for the drug substance. DMF _____ will also be updated with the new _____ content limit upon the first annual update.



NAPRO BIOTHERAPEUTICS, INC.

G. Buehler
 ANDA 76-233
 Page 3 of 10
 April 5, 2002

Table 2: Historical Drug Substance Batch Analysis Data for Content

Lot Number	(%)
A-3120-96-0001	--
A-3120-97-0001	--
A-3120-97-0002	--
A-3120-97-0003	--
A-3120-97-0004	--
A-3120-97-0005	--
A-3120-97-0006	--
A-3120-97-0007	--
A-3120-97-0008	--
A-3120-97-0008A	--
A-3120-98-0001	--
A-3120-98-0002	--
A-3120-98-0003	--
A-3120-98-0004	--
A-3120-98-0005	--
A-3120-98-0006	--
A-3120-99-2001	--
A-3200-99-4003	--
A-3200-99-4009	--

Comment 3: "Please tighten the limits for paclitaxel assay and related compounds for the finished drug product release and stability."

Response 3: As requested, we have further tightened the limits for related compounds for the finished drug product based on the stability data generated on the exhibit lots. The specifications submitted in all previous submissions along with the current revised specifications are provided in the Table 3. For ease of review, the revisions from the original ANDA and amendments are in bold and shaded.

Table 3: Specifications for Related Compounds in the Drug Product

Name of Impurity	8/31/01 Original ANDA	12/21/01 Amendment	Current Proposed Specifications
Individual unknown (single largest)	NMT	NMT	NMT
	NMT	NMT	NMT
	NMT	NMT	NMT
	NMT	NMT	NMT
Total impurities	NMT	NMT	NMT

Redacted

4

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NAPRO BIOTHERAPEUTICS, INC.

G. Buehler
ANDA 76-233
Page 8 of 10
April 5, 2002

Labeling Deficiencies:

Comment 1: "CONTAINER – 30mg/5mL, 100mg/16.7mL, 150mg/25mL, 300mg/50mL

- a. Revise the storage statement to include "Retain in carton until contents are used. Protect..."
- b. Revise the Caution statement as follows: Caution: Dilution required prior to IV infusion." This statement should appear in red print as does the innovator."

Comment 2: "CARTON – 30mg/5mL, 100mg/16.7mL, 150mg/25mL, 300mg/50mL

- a. See comments under CONTAINER.
- b. Revise the statement of strength so that it appears as 30 mg/5 mL rather than _____. You may relocate 6 mg/mL so that it appears below the shaded box area. See the statement of strength on your container labels for guidance."

Comment 4: "PROFESSIONAL INSERT

- a. DESCRIPTION - ... molecular formula ... rather than ...
- b. INDICATIONS AND USAGE
 - i. Please note the revised section heading
 - ii. Paragraph 1, - ...is indicated after failure of first line or subsequent therapy for the treatment of advanced carcinoma of the ovary.
- c. PRECAUTIONS, Pregnancy-Revise subsection heading to read as follows: Pregnancy: Teratogenic Effects, Pregnancy Category D (See WARNINGS.)
- d. ADVERS REACTIONS, Neurologic – Revise paragraphs as follows:
 - i. Insert the following as the first paragraph:

The assessment of neurologic toxicity was conducted differently among the studies as evident from the data reported in each individual study (see tables __ - __). Moreover, the frequency and



NaPro BioTherapeutics, Inc.

G. Buehler
ANDA 76-233
Page 9 of 10
April 5, 2002

severity of neurologic manifestations were influenced by prior and/or concomitant therapy with neurotoxic agents.

ii. **Replace the current first paragraph with the following:**

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent paclitaxel. 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 34-51% 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. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy."

Comment 5: "PATIENT LEAFLET – Please include "injection" as part of the product name in the following sections headings: "What is Paclitaxel Injection?" and "How is Paclitaxel Injection Given?" (added injection)."

Please revise your labels and labeling, as instructed above, and submit 12 final printed labels and labeling or draft labeling if you prefer.

Response: The labels and labeling have been revised as requested. Twelve copies final printed labels and labeling are provided as Exhibit VIII.

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

Response: NaPro BioTherapeutics acknowledge that it may be necessary to further revise our labeling subsequent to approved changes for the reference listed drug.

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.

Response: A side-by-side comparisons of our proposed labeling with our last submission, with all differences annotated and explained, is provided as Exhibit IX.



NAPro BioTHERAPEUTICS, INC.

G. Buehler
ANDA 76-233
Page 10 of 10
April 5, 2002

We have also enclosed two diskettes (in duplicate and write protected) containing our electronic submission as part of the Office of Generic Drugs (OGD) electronic submission program using Entry Validation Application (EVA). A one-page print out of the EVA log file is attached. The information included in the electronic submission is the same as the hardcopy paper submission.

NaPro BioTherapeutics hereby certifies that we have sent a true copy of this submission to the Denver, Colorado, FDA District Office.

If you require any clarification or further information, please feel free to contact me.

Sincerely,

Kip Vought
Manager, Regulatory Affairs
NaPro BioTherapeutics, Inc.
Phone: (303) 516-8500
Fax: (303) 530-1296
Email: kvought@naprobio.com

**APPEARS THIS WAY
ON ORIGINAL**



NaPro BioTherapeutics, Inc.

6304 Spine Road, Unit A
Boulder, Colorado 80301
Tel: (303) 530-3891
Fax: (303) 530-1296

TSI
4-11-02

PATENT AMENDMENT

April 4, 2002

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

NEW CORRESP
NC

Attention: Gary Buehler
Acting Director

Re: ANDA 76-233 Paclitaxel Injection, 30 mg/vial, 100 mg/vial, 150 mg/vial and 300 mg/vial

Patent Amendment

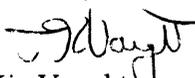
Pursuant to 21 CFR 314.95(b) and 21 CFR 314.95(e), NaPro BioTherapeutics, Inc. hereby submits a patent amendment to pending ANDA 76-233.

NaPro provided notice on March 11, 2002 that it has complied with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of the patent or their representatives, and to the holder of the approved application for the drug product that is claimed by the patent or a use of which is claimed by the patent and with the requirements under 21 CFR 314.95(c) with respect to the content of the notice.

As requested in FDA's October 31, 2001 ANDA receipt letter, NaPro BioTherapeutics, Inc. is submitting notice that no lawsuit has commenced within 45 days of a patent holder's receipt of notification. Also, NaPro BioTherapeutics, Inc. and Abbott Laboratories announced on November 29, 2001, that they have entered into a non-exclusive cross license agreement with Bristol-Myers Squibb (BMS) relating to paclitaxel. The agreement grants NaPro a license under BMS patents to market paclitaxel injection, pursuant to an ANDA approval. NaPro has the right under the agreement to sublicense to its distributor, Abbott Laboratories.

I trust that this submission is complete. Please contact me at (303) 516-8548 if you should have any additional questions or comments.

Sincerely,


Kip Vought
Manager, Regulatory Affairs

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APR 05 2002
OGD / CDER



NaPro BioTherapeutics, Inc.

*Acknowledged
NA TSI
3/14/02*

6304 Spine Road, Unit A
Boulder, Colorado 80301
Tel: (303) 530-3891
Fax: (303) 530-1296

PATENT AMENDMENT

March 11, 2002

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

*NC
NA TSI
3/14/02*

Attention: Gary Buehler
Acting Director

Re: **ANDA 76-233 Paclitaxel Injection, 30 mg/vial, 100 mg/vial, 150 mg/vial and 300 mg/vial**

Patent Amendment

Pursuant to 21 CFR 314.95(b) and 21 CFR 314.95(e), NaPro BioTherapeutics, Inc. hereby submits a patent amendment to pending ANDA 76-233.

NaPro has complied with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of the patent or their representatives, and to the holder of the approved application for the drug product that is claimed by the patent or a use of which is claimed by the patent and with the requirements under 21 CFR 314.95(c) with respect to the content of the notice. Copies of the certification statement and return receipts are attached.

As requested in FDA's October 31, 2001 ANDA receipt letter, NaPro BioTherapeutics Inc., will submit amendment(s) to this application to document litigation and/or any settlement outcome. If no lawsuit is commenced against NaPro BioTherapeutics, Inc. by a party provided notice within the statutory 45-day period, we will provide the Agency a letter to that effect.

I trust that this submission is complete. Please contact me at (303) 516-8548 if you should have any additional questions or comments.

Sincerely,

Kip Vought
Manager, Regulatory Affairs

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MAR 12 2002
OGD / CDER

*DW
3/14/02*



NaPro BioTherapeutics, Inc.

131 151

6304 Spine Road, Unit A
Boulder, Colorado 80301
Tel: (303) 530-3891
Fax: (301) 530-1296

December 21, 2001

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA
ORIG AMENDMENT

ELECTRONIC SUBMISSION
ENCLOSED

ATTENTION: Gary J. Buehler
Director

Re: **ANDA 76-233 Paclitaxel Injection (6 mg/mL)**

AMENDMENT

Reference is made to the original abbreviated new drug application for the above-referenced subject drug product submitted August 31, 2001 and amended October 19, 2001.

Reference is also made to Abbott Laboratories' pending ANDA 76-131 for Paclitaxel Injection, submitted March 2, 2001. Abbott received a minor chemistry/labeling deficiency letter on August 29, 2001 for their Paclitaxel Injection ANDA. Additionally, Abbott has provided NaPro BioTherapeutics copies of this deficiency letter and Abbott's October 10, 2001 amendment containing their responses. For your convenience, a copy of the August 29, 2001 FDA review letter is included in Exhibit I.

NaPro BioTherapeutics is the active pharmaceutical ingredient _____ for both _____ ANDA 76-131 and NaPro's ANDA 76-233; and _____ is the finished dosage form _____ for NaPro's ANDA 76-233.

NaPro BioTherapeutics, Inc hereby due diligently amends the current pending ANDA 76-233 to address all of the chemistry deficiencies commented by FDA on August 29, 2001 for _____ ANDA 76-131 in conjunction with this application. The following is the amended information in comment/response format.

Chemistry Deficiencies:

Comment 1: The DMF's for the extract and drug substance were found inadequate. Deficiencies have been forwarded to the DMFs holder. The application may not be approved until all deficiencies are addressed satisfactorily.



Redacted

9

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information



NaPro BioTherapeutics, Inc.

G. Buehler
ANDA 76-233
Page 11 of 11
December 21, 2001

We have also enclosed two diskettes (in duplicate and write protected) containing our electronic submission as part of the Office of Generic Drugs (OGD) electronic submission program using Entry Validation Application (EVA). A one-page print out of the EVA log file is attached. The information included in the electronic submission is the same as the hardcopy paper submission.

NaPro BioTherapeutics hereby certifies that we have sent a true copy of this submission to the Denver, Colorado, FDA District Office.

If you require any clarification or further information, please feel free to contact me.

Sincerely,

Kip Vought
Manager, Regulatory Affairs
NaPro BioTherapeutics, Inc.
Phone: (303) 516-8500
Fax: (303) 530-1296
Email: kvought@naprobio.com

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-233

OCT 31 2001

NaPro BioTherapeutics, Inc.
Attention: Kip Vought
6304 Spine Road, Unit A
Boulder, CO 80301
|||||

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.

Reference is made to the telephone conversation dated October 12, 2001 and your correspondence dated October 19, 2001.

NAME OF DRUG: Paclitaxel Injection, 6 mg/mL, 5 mL, 16.7 mL, 25 mL and 50 mL vials

DATE OF APPLICATION: August 31, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: September 5, 2001

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:
 - 1) Each owner of the patent or the representative designated by the owner to receive the notice;
 - 2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.
 - 3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.
- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.
- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.
- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301)827-5862.

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:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,



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



NaPro BioTherapeutics, Inc.

6304 Spine Road, Unit A
Boulder, Colorado 80301
Tel: (303) 530-3891
Fax: (303) 530-1296

October 19, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

ATTENTION: Gary J. Buehler
Acting Director

Re: **ANDA 76-233 Paclitaxel Injection (6 mg/mL)**
AMENDMENT



NaPro BioTherapeutics, Inc. hereby amends the above-referenced original abbreviated new drug application for the subject drug product submitted August 31, 2001. We are responding to telephone calls between Mr. Martin Shimer (FDA) and Mr. Kip Vought (NaPro BioTherapeutics, Inc.) on October 12 and 16, 2001. The Agency made the following four requests:

REQUEST: 1. **The 356h form needs to be revised to state Bristol-Myers Squibb as the holder of the approved application – the box was left blank.**

RESPONSE: Page one of the 356h form dated 8/31/01 has been revised as requested and is provided as Exhibit I.

REQUEST: 2. **Patent certification for 5641803 needs to have its date revised to August 3, 2012 versus August 3, 2013.**

RESPONSE: Exhibit II contains the revised patent certification letter as requested.

REQUEST: 3. **Need two additional separately bound copies of the analytical methods validation section (Section XVI).**

RESPONSE: Two additional separately bound copies of Section XVI (Original Application, dated 8/31/01) are enclosed with this amendment. Please note that these additional copies are not also included in the archive, review and field copies of this amendment.



NaPro BioTherapeutics, Inc.

G. Buehler
ANDA 76-233
October 19, 2001
Page 2 of 2

REQUEST: 4. On page 278, revise the proposed batch sizes to read as follows:

- ~~_____~~ 16.7 mL fill in 20 mL Vial
25 mL fill in 25 mL Vial
- ~~_____~~ 5 mL fill in 5 mL Vial
50 mL fill in 50 mL Vial

NaPro may be approved for the ~~_____~~ proposed batch sizes upon review; however, the batch sizes need to be revised to agree with the actual batch sizes used to manufacture the demonstration batches in order to be accepted for filing.

RESPONSE: To allow the ANDA to be accepted for filing, NaPro BioTherapeutics agrees to make the requested change. Exhibit III contains revised page 278. During review of the application, we do request that our original proposed maximum commercial batch sizes of ~~_____~~ and ~~_____~~ be reconsidered as acceptable based upon the ANDA exhibit batch sizes.

NaPro BioTherapeutics hereby certifies that we have sent a true copy of this submission to the Denver, Colorado, FDA District Office.

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

Kip Vought
Manager, Regulatory Affairs
NaPro BioTherapeutics, Inc.
Phone: (303) 516- 8500
Fax: (303) 530-1296
Email: kvought@naprobio.com



NaPRO BIOTHERAPEUTICS, INC.

August 31, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD 600
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Gary J. Buehler
Acting Director

Re: **Paclitaxel Injection (6 mg/mL)**
Original Abbreviated New Drug Application

In accordance with Section 505(j) of the Federal Food, Drug, and Cosmetic Act, NaPro BioTherapeutics, Inc. hereby submits an Abbreviated New Drug Application for Paclitaxel Injection, 6 mg/mL, 5 mL fill in 5 mL vial (30 mg/vial), 16.7 mL fill in 20 mL vial (100 mg/vial), 25 mL fill in 25 mL vial (150 mg/vial), and 50 mL fill in 50 mL vial (300 mg/vial). The data supporting this application is provided in three volumes.

The subject drug is a prescription drug and not an over-the-counter drug. The dosage form and manufacturing site may be described as follows:

List Number	Strength (Total Product Content)	Fill Volume	Container	Dosage Form	Manufacturing Facility
5088-01	30 mg/vial	5 mL	5 mL vial	Injection	Abbott Laboratories Hospital Products Div. 1776 N. Centennial Dr. McPherson, KS 67460
5088-02	100 mg/vial	16.7 mL	20 mL vial		
5088-03	150 mg/vial	25 mL	25 mL vial		
5088-04	300 mg/vial	50 mL	50 mL vial		

Paclitaxel Injection is listed in "Approved Drug Products with Therapeutic Equivalence Evaluations", 20th Edition, page 3-261. A copy appears in Section II.

The active ingredient, route of administration, and dosage form for Paclitaxel Injection are the same as those of the innovator's product, TAXOL[®], sponsored by Bristol-Meyers Squibb. The indications are the same except those for which the referenced listed drug is entitled to periods of marketing exclusivity. The strengths are the same except for the addition of a new strength, namely 150 mg/vial, based on the suitability petition granted to Fujisawa USA, Inc. on June 10, 1997 (Docket No. 97P-0058/CP1). Comparative information is contained in Section IV.

The labeling is the same in content as that of the referenced listed drug, TAXOL[®]. Side-by-side labeling comparisons are provided in Section V.

Handwritten notes: 505(j)(2)(A) OK, ISI, 31-OCT-2001, ISI

6304 Spine Road, Unit A
Boulder, Colorado 80301
Tel: (303) 530-3891
Fax: (303) 530-1296



**STERILITY ASSURANCE AND
ELECTRONIC SUBMISSION
ENCLOSED**



NaPro BioTherapeutics, Inc.

G. Buehler
Page 2 of 3
August 31, 2001

The first three production batches of Paclitaxel Injection, 6 mg/mL, 5 mL fill in 5 mL vial (30 mg/vial), 16.7 mL fill in 20 mL vial (100 mg/vial), 25 mL fill in 25 mL vial (150 mg/vial), and 50 mL fill in 50 mL vial (300 mg/vial), will be placed into our stability program and reported at regular intervals for as long as necessary to support the proposed 24-month expiration date. Our complete stability protocol and post-approval commitments are contained in Section XVII.

For the convenience of the Agency, documentation for Sterilization Process Validation is contained in a separate volume with a dedicated table of contents.

We have also enclosed two diskettes (in duplicate and write protected) containing our electronic submission as part of the Office of Generic Drugs (OGD) electronic submission program using Entry Validation Application (EVA). A one-page print out of the EVA log file is attached. The information included in the electronic submission is the same as the hardcopy paper submission.

NaPro's DMF No. _____ and No. _____ referenced in this ANDA have already been reviewed in conjunction with Abbott Laboratories' Paclitaxel Injection ANDA 76-131, submitted March 2, 2001. In addition, a successful pre-approval inspection of our API manufacturing facility was concluded in August 2001.

NaPro BioTherapeutics' Paclitaxel Injection (30 mg, 100 mg, 150 mg and 300 mg MDV), when approved, will be marketed and distributed exclusively by Abbott Laboratories.

The Field Copy Certification Statement is provided on the following page.

We trust that this submission is complete. If you require any clarification or further information, please feel free to contact me.

Sincerely,

Kip Vought
Manager, Regulatory Affairs
NaPro BioTherapeutics, Inc.
Phone: (303) 516- 8500
Fax: (303) 530-1296
Email: kvought@naprobio.com



NaPRO BIOTHERAPEUTICS, INC.

G. Buehler
Page 3 of 3
August 31, 2001

FIELD COPY CERTIFICATION

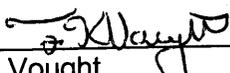
Paclitaxel Injection

<u>List Number</u>	<u>Container</u>	<u>Product Dosage Form</u>	<u>Strength</u>
5088	Multiple-dose Vial	Paclitaxel Injection	30 mg/vial
5088	Multiple-dose Vial	Paclitaxel Injection	100 mg/vial
5088	Multiple-dose Vial	Paclitaxel Injection	150 mg/vial
5088	Multiple-dose Vial	Paclitaxel Injection	300 mg/vial

Per Section 314.94 (d) (5) of the Final Rule, published in the Federal Register, September 8, 1993,

"The applicant shall submit a field copy of the abbreviated application...and a certification that the field copy is a true copy of the technical section contained in the archival and review copies of the abbreviated application."

We certify that the field copy is a "true" copy of the technical section contained in the archival and review copies of the above-referenced application, and this copy has been submitted to the Denver FDA District Office, which is the applicant's home district office.



Kip Vought
Manager, Regulatory Affairs
NaPro BioTherapeutics, Inc.
Phone: (303) 516- 8500
Fax: (303) 530-1296
Email: kvought@naprobio.com

8/31/2001
Date

