

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75184

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 75-184

DRUG PRODUCT: Paclitaxel Injection

FIRM: Baker Norton Pharmaceuticals, Inc.

DOSAGE FORM: Injection

STRENGTH: 30 mg/5mL, 150 mg/25mL, 300 mg/50mL

CGMP: Statement/EIR Update Status:

EER is acceptable (OC recommendation, 8/21/00)

BIO: A waiver for the bioequivalent study was granted by the Division of Bioequivalence. (Bioequivalence reviewer Z. Wahba, 7/9/99).

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

The FDA Southeast Regional Laboratory has completed the method validation of the Paclitaxel drug substance and Paclitaxel Injections.

The methods tested have been found to be suitable for regulatory purposes.

STABILITY: (Are containers used in study identical to those in container section?)

The containers used in the stability study are identical to those described in the container section.

LABELING:

Container, carton and insert labeling have been found satisfactory (Labeling approval summary 8/18/00, reviewed by T. Watkins)

STERILIZATION VALIDATION (IF APPLICABLE):

Satisfactory (microbiology reviewer N. Nrapendra, 7/11/00)

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

The L of the exhibit batches of the Paclitaxel Injections 30 mg/5mL, 150 mg/25mL, 300 mg/50mL were manufactured respectively.

DMF the Paclitaxel drug substance was found adequate (6/5/00, reviewed by Liang-Lii Huang)

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

The exhibit batches of the Paclitaxel Injections, 30 mg/5mL (lot #8016858), 150 mg/25mL (lot #8026859), and 300 mg/50mL (lot #8016861) were the stability batches.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

The proposed production batches are L of the Paclitaxel Injections, 30 mg/5mL, 150 mg/25mL, and 300 mg/50mL respectively. The manufacturing process will be the same as that was used for the exhibit batches.

CHEMIST: Liang-Lii Huang, Ph.D.

DATE: September 8, 2000

SUPERVISOR: Paul Schwartz, Ph.D.

DATE: September 8, 2000

PS 9/8/00

Addendum

Review of Chemistry, Manufacture, and Controls

ANDA # 75-184

Paclitaxel Injection, 6mg/mL
(30 mg/5 mL vial, 150 mg/25 mL vial, 300 mg/50 mL vial)

NAME AND ADDRESS OF APPLICANT

Baker Norton Pharmaceuticals, Inc.
Attention: Steven M Viti
4400 Biscayne Boulevard
Miami, FL 33137

Telephone amendment of August 24, 2000

Included in the amendment are the 18-month stability data for the sterility test and particulate matter for the exhibit batches of 150 mg/25mL (lot# 8026859) and 300 mg/50mL (lot# 8016861) of the Paclitaxel Injections respectively. Results are evaluated to be satisfactory.

Baker Norton Pharmaceuticals also commits to conducting post-approval stability studies with the packaged products stored upright and vertical positions.

Furthermore, BPN commits to using the qualified source and grade of excipient, polyoxyl 35 castor oil, NF, manufactured by

Should it be necessary to change the source and grade of this substance, a prior approval supplement will be requested.

COMMENTS

This application is approvable.

CONCLUSIONS AND RECOMMENDATIONS

This application is approvable.

REVIEWER:

Liang-Lii Huang, Ph.D.

DATE COMPLETED:

August 25, 2000

Endorsed by Paul Schwartz, Ph.D./August 25, 2000

cc:

ANDA 75184
ANDA DUP 75184
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627/Liang-Lii Huang, Ph.D./8/25/00
HFD-627/Paul Schwartz, Ph.D./8/25/00

JSI , *8/25/00* *8/25/00*

August 25, 2000

Chemistry review - approvable - tentatively

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-184

3. NAME AND ADDRESS OF APPLICANT

Immunex Corporation
Attention; Nancy Kercher
51 University Street
Seattle, WA 98101-2936

4. LEGAL BASIS FOR SUBMISSION

The listed drug referred to in this application is Taxol® Injection, 6mg/mL, held by Bristol-Myers Squibb. The marketing exclusivity of the referenced listed drug expired December 29, 1997. Immunex corporation submitted the Paragraph IV certification to certify that US patent No. 5,504,102 and 5,641,803 are invalid and will not be infringed by the manufacture, use or sale of paclitaxel for which this application is submitted (page 12A and 12B).

November 26, 1997 Immunex corporation submitted the Paragraph IV certification

Immunex Corporation certifies that US patent No. 5,670,537 is invalid and will not be infringed by the manufacture, use or sale of paclitaxel for which this application is submitted.

On January 8, 1998 Bristol-Myers Squibb Company (BMS) filed a lawsuit against Immunex in federal district court in Newark, New Jersey, alleging infringement of United States Patents No. 5,641,803 and 5,670,537.

5. SUPPLEMENT(s)

None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Paclitaxel Injection, 6mg/mL

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

None

9. AMENDMENTS AND OTHER DATES:

Date of submission - Jul 30, 1997

Amendment - October 7, 1997

10. PHARMACOLOGICAL CATEGORY

Treatment of breast cancer

11. Rx or OTC

RX

12. RELATED IND/NDA/DMF(s)

Listed referenced drug Taxol® (Paclitaxel Injection, 6mg/mL)

NDA 20262

NDA sponsor: Bristol Myers Squibb

Date of approval: Dec 29, 1992

DMF ✓

DMF

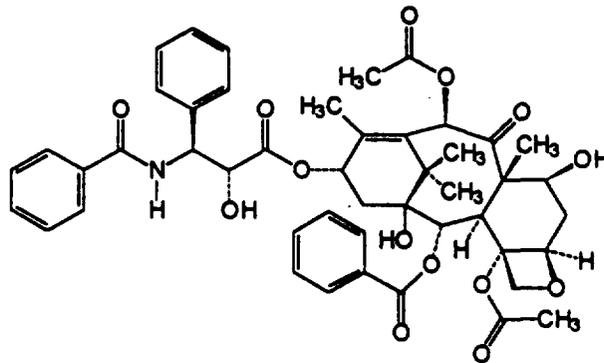
LOA: page 156

13. DOSAGE FORM
Injection

14. POTENCY
6 mg/mL (30 mg/5mL)

15. CHEMICAL NAME AND STRUCTURE

Paclitaxel. Benzenepropanoic acid, β -(benzoylamino)- α -hydroxy-, 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR-[2a α ,4 β ,4a β ,6 β ,9 α (α R*, β S*),11 α ,12 α ,12a α ,12b α]]-. C₄₇H₅₁NO₁₄. 853.93. 33069-62-4. Antineoplastic. USAN 1995, page 499.



16. RECORDS AND REPORTS
None

17. COMMENTS
This application is not approvable.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is not approvable.

19. REVIEWER: Liang-Lii Huang, Ph.D. DATE COMPLETED: February 3, 1998

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Chem #1

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-184

3. NAME AND ADDRESS OF APPLICANT

Baker Norton Pharmaceuticals, Inc.
Attention: Steven M Viti
4400 Biscayne Boulevard
Miami, FL 33137

4. LEGAL BASIS FOR SUBMISSION

The listed drug referred to in this application is Taxol® Injection, 6mg/mL, held by Bristol-Myers Squibb. The marketing exclusivity of the referenced listed drug expired December 29, 1997. Immunex corporation submitted the Paragraph IV certification to certify that US patent No. 5,504,102 and 5,641,803 are invalid and will not be infringed by the manufacture, use or sale of paclitaxel for which this application is submitted (page 12A and 12B).

November 26, 1997 Immunex corporation submitted the Paragraph IV certification

Immunex Corporation certifies that US patent No. 5,670,537 is invalid and will not be infringed by the manufacture, use or sale of paclitaxel for which this application is submitted.

On January 8, 1998 Bristol-Myers Squibb Company (BMS) filed a lawsuit against Immunex in federal district court in Newark, New Jersey, alleging infringement of United States Patents No. 5,641,803 and 5,670,537.

Patent certification (Amendment of June 30, 1999)

Paclitaxel injection 30mg/5mL, 150mg/25mL, and 300mg/50mL

U.S. Patent 5,496,804 expiry date: March 9, 2013

U.S. Patent 5,496,804 Paragraph viii certification

Baker Norton Pharmaceuticals certifies that this method of use patent does not claim any of the proposed indications for which the applicant is seeking approval.

Exclusivity statement

Paclitaxel injection 30mg/5mL, 150mg/25mL, and 300mg/50mL

Baker Norton Pharmaceuticals does not seek marketing approval for any of the indications covered under the exclusivities as described by codes ODE, I-202, I-226, and I-230.

5. SUPPLEMENT(s)

None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Paclitaxel Injection, 6mg/mL -

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

None

9. AMENDMENTS AND OTHER DATES:

Date of submission - Jul 30, 1997

Amendment - October 7, 1997

Notification of the ownership transfer: August 20, 1998

Major amendment: April 2, 1999

New amendment: June 15 and June 30, 1999 (two additional sizes)

10. PHARMACOLOGICAL CATEGORY
Treatment of breast cancer

11. Rx or OTC
RX

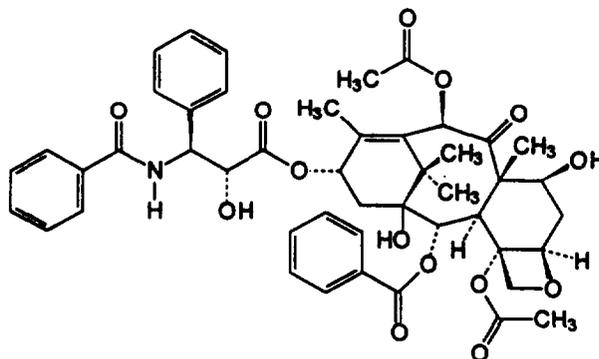
12. RELATED IND/NDA/DMF(s)
Listed referenced drug Taxol® (Paclitaxel Injection, 6mg/mL)
NDA 20262
NDA sponsor: Bristol Myers Squibb
Date of approval: Dec 29, 1992

DMF [
DMF
LOA: page 156]

13. DOSAGE FORM
Injection

14. POTENCY
6 mg/mL (30 mg/5mL, 150mg/25mL, 300mg/50mL)

15. CHEMICAL NAME AND STRUCTURE
Paclitaxel. Benzenepropanoic acid, β -(benzoylamino)- α -hydroxy-, 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR-[2a α ,4 β ,4a β ,6 β ,9 α (α R*, β S*),11 α ,12 α ,12a α ,12b α]]-. C₄₇H₅₁NO₁₄. 853.93. 33069-62-4. Antineoplastic. USAN 1995, page 499.



16. RECORDS AND REPORTS

None

17. COMMENTS

Baker Norton Pharmaceuticals notified the Agency that Immunex had transferred ownership and all rights to ANDA 75-184, and that Immunex had submitted to this ANDA a letter of transfer of

ownership, August 20, 1998.

Immunex notify FDA of the transfer of ownership of ANDA 75-184 for Paclitaxel, 6 mg/mL in 5 mL (30mg) from Immunex Corporation to Baker Norton Pharmaceuticals, Inc., effective August 21, 1998.

Amendment of June 15 and June 30, 1999 to provide for two additional vial sizes i.e. 150mg/25mL and 300mg/30mL

This application is not approvable.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable.

19. REVIEWER: DATE COMPLETED:
Liang-Lii Huang, Ph.D. October 19, 1999
Endorsed by Paul Schwartz, Ph.D. /10/19/99

cc: ANDA 75-184
ANDA 75-184 DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):
HFD-627/Liang-Lii Huang, Ph.D./9/28/99; 10/19/99
HFD-627/Paul Schwartz; Ph.D./9/28/99; 10/19/99
HFD-617/Joseph Buccine/9/28/99; 10/19/99

Date: October 19, 1999
CHEMISTRY REVIEW - NOT APPROVABLE -MAJOR

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Chem #2

1. CHEMISTRY REVIEW NO. 32. ANDA # 75-1843. NAME AND ADDRESS OF APPLICANT

Baker Norton Pharmaceuticals, Inc.
Attention: Steven M Viti
4400 Biscayne Boulevard
Miami, FL 33137

4. LEGAL BASIS FOR SUBMISSION

The listed drug referred to in this application is Taxol® Injection, 6mg/mL, held by Bristol-Myers Squibb. The marketing exclusivity of the referenced listed drug expired December 29, 1997. Immunex corporation submitted the Paragraph IV certification to certify that US patent No. 5,504,102 and 5,641,803 are invalid and will not be infringed by the manufacture, use or sale of paclitaxel for which this application is submitted (page 12A and 12B).
November 26, 1997 Immunex corporation submitted the Paragraph IV certification

Immunex Corporation certifies that US patent No. 5,670,537 is invalid and will not be infringed by the manufacture, use or sale of paclitaxel for which this application is submitted.

On January 8, 1998 Bristol-Myers Squibb Company (BMS) filed a lawsuit against Immunex in federal district court in Newark, New Jersey, alleging infringement of United States Patents No. 5,641,803 and 5,670,537.

Patent certification (Amendment of June 30, 1999)

Paclitaxel injection 30mg/5mL, 150mg/25mL, and 300mg/50mL

U.S. Patent 5,496,804 expiry date: March 9, 2013

U.S. Patent 5,496,804 Paragraph viii certification

Baker Norton Pharmaceuticals certifies that this method of use patent does not claim any of the proposed indications for which the applicant is seeking approval.

Exclusivity statement

Paclitaxel injection 30mg/5mL, 150mg/25mL, and 300mg/50mL

Baker Norton Pharmaceuticals does not seek marketing approval for any of the indications covered under the exclusivities as described by codes ODE, I-202, I-226, and I-230.

5. SUPPLEMENT (s)

None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Paclitaxel Injection, 6mg/mL

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

None

9. AMENDMENTS AND OTHER DATES:

Date of submission - Jul 30, 1997

Amendment - October 7, 1997

Notification of the ownership transfer: August 20, 1998

Major amendment: April 2, 1999

New amendment: June 15 and June 30, 1999 (two additional sizes)

Major amendment: December 8, 1999

Additional info: March 8, 2000

10. PHARMACOLOGICAL CATEGORY

Treatment of breast cancer

11. Rx or OTC

RX

12. RELATED IND/NDA/DMF(s)

Listed referenced drug Taxol® (Paclitaxel Injection, 6mg/mL)

NDA 20262

NDA sponsor: Bristol Myers Squibb

Date of approval: Dec 29, 1992

DMF/

DMF

LOA: page 156

13. DOSAGE FORM

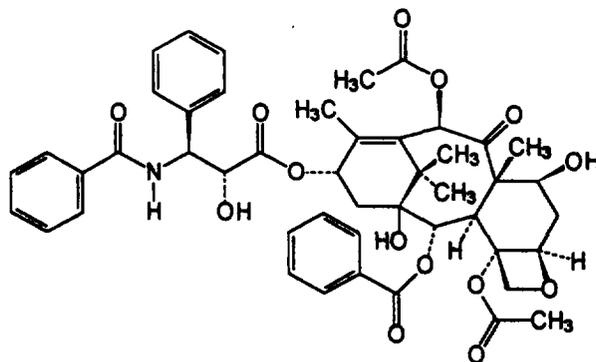
Injection

14. POTENCY

6 mg/mL (30 mg/5mL, 150mg/25mL, 300mg/50mL)

15. CHEMICAL NAME AND STRUCTURE

Paclitaxel. Benzenepropanoic acid, β -(benzoylamino)- α -hydroxy-, 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR-[2 α ,4 β ,4a β ,6 β ,9 α (α R*, β S*),11 α ,12 α ,12a α ,12b α]]-. C₄₇H₅₁NO₁₄. 853.93. 33069-62-4. Antineoplastic. USAN 1995, page 499.

16. RECORDS AND REPORTS

None

17. COMMENTS

Baker Norton Pharmaceuticals notified the Agency that Immunex had transferred ownership and all rights to ANDA 75-184, and that Immunex had submitted to this ANDA a letter of transfer of ownership, August 20, 1998.

Immunex notify FDA of the transfer of ownership of ANDA 75-184 for Paclitaxel, 6 mg/mL in 5 mL (30mg) from Immunex Corporation to Baker Norton Pharmaceuticals, Inc., effective August 21, 1998.

Amendment of June 15 and June 30, 1999 to provide for two additional vial sizes i.e. 150mg/25mL and 300mg/50mL

This application is not approvable.

18. CONCLUSIONS AND RECOMMENDATIONS

This application is not approvable.

19. REVIEWER: DATE COMPLETED:
Liang-Lii Huang, Ph.D. April 4, 2000
Endorsed by Paul Schwartz, Ph.D. /April 4, 2000

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Chem # 3

1. CHEMISTRY REVIEW NO. 4 (four)

2. ANDA # 75-184

3. NAME AND ADDRESS OF APPLICANT

Baker Norton Pharmaceuticals, Inc.
Attention: Steven M Viti
4400 Biscayne Boulevard
Miami, FL 33137

4. LEGAL BASIS FOR SUBMISSION

The listed drug referred to in this application is Taxol® Injection, 6mg/mL, held by Bristol-Myers Squibb. The marketing exclusivity of the referenced listed drug expired December 29, 1997. Immunex corporation submitted the Paragraph IV certification to certify that US patent No. 5,504,102 and 5,641,803 are invalid and will not be infringed by the manufacture, use or sale of paclitaxel for which this application is submitted (page 12A and 12B).
November 26, 1997 Immunex corporation submitted the Paragraph IV certification

Immunex Corporation certifies that US patent No. 5,670,537 is invalid and will not be infringed by the manufacture, use or sale of paclitaxel for which this application is submitted.

On January 8, 1998 Bristol-Myers Squibb Company (BMS) filed a lawsuit against Immunex in federal district court in Newark, New Jersey, alleging infringement of United States Patents No. 5,641,803 and 5,670,537.

Patent certification (Amendment of June 30, 1999)

Paclitaxel injection 30mg/5mL, 150mg/25mL, and 300mg/50mL

U.S. Patent 5,496,804 expiry date: March 9, 2013

U.S. Patent 5,496,804 Paragraph viii certification

Baker Norton Pharmaceuticals certifies that this method of use patent does not claim any of the proposed indications for which the applicant is seeking approval.

Exclusivity statement

Paclitaxel injection 30mg/5mL, 150mg/25mL, and 300mg/50mL

Baker Norton Pharmaceuticals does not seek marketing approval for any of the indications covered under the exclusivities as described by codes ODE, I-202, I-226, and I-230.

5. SUPPLEMENT (s)

None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Paclitaxel Injection, 6mg/mL

(30 mg/5 mL vial, 150 mg/25 mL vial, 300 mg/50 mL vial)

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

None

9. AMENDMENTS AND OTHER DATES:

Date of submission - Jul 30, 1997

Amendment - October 7, 1997

Notification of the ownership transfer: August 20, 1998

Major amendment: April 2, 1999

New amendment: June 15 and June 30, 1999 (two additional sizes)

Major amendment: December 8, 1999

Additional info: March 8, 2000

Minor amendment: April 21, 2000

Telephone conference: June 2, 2000 (OGD and Baker Norton)
Telephone amendment: June 5, 2000

10. PHARMACOLOGICAL CATEGORY

Treatment of breast cancer

11. Rx or OTC

RX

12. RELATED IND/NDA/DMF(s)

Listed referenced drug Taxol® (Paclitaxel Injection, 6mg/mL)
NDA 20262

NDA sponsor: Bristol Myers Squibb

Date of approval: Dec 29, 1992

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DMF

LOA: page 156

13. DOSAGE FORM

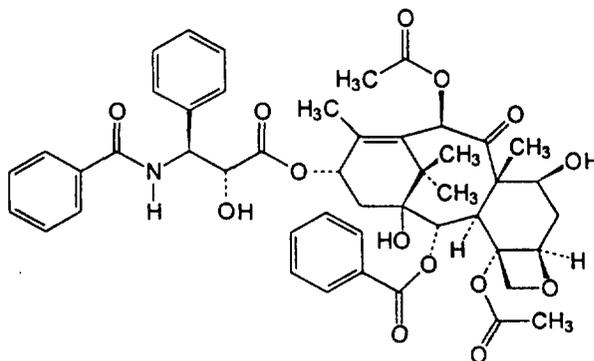
Injection

14. POTENCY

6 mg/mL (30 mg/5mL, 150mg/25mL, 300mg/50mL)

15. CHEMICAL NAME AND STRUCTURE

Paclitaxel. Benzenepropanoic acid, β -(benzoylamino)- α -hydroxy-, 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR-[2a α ,4 β ,4a β ,6 β ,9 α (α R*, β S*),11 α ,12 α ,12a α ,12b α]]-. C₄₇H₅₁NO₁₄. 853.93. 33069-62-4. Antineoplastic. USAN 1995, page 499.



16. RECORDS AND REPORTS

None

17. COMMENTS

Baker Norton Pharmaceuticals notified the Agency that Immunex had transferred ownership and all rights to ANDA 75-184, and that Immunex had submitted to this ANDA a letter of transfer of ownership, August 20, 1998. Immunex notify FDA of the transfer of ownership of ANDA 75-184 for Paclitaxel, 6 mg/mL in 5 mL (30mg) from Immunex Corporation to Baker Norton

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Chem #4

1. CHEMISTRY REVIEW NO. 5 (five)

2. ANDA # 75-184

3. NAME AND ADDRESS OF APPLICANT

Baker Norton Pharmaceuticals, Inc.
Attention: Steven M Viti
4400 Biscayne Boulevard
Miami, FL 33137

4. LEGAL BASIS FOR SUBMISSION

The listed drug referred to in this application is Taxol® Injection, 6mg/mL, held by Bristol-Myers Squibb. The marketing exclusivity of the referenced listed drug expired December 29, 1997. Immunex corporation submitted the Paragraph IV certification to certify that US patent No. 5,504,102 and 5,641,803 are invalid and will not infringe by the manufacture, use or sale of paclitaxel for which this application is submitted (page 12A and 12B).
November 26, 1997 Immunex corporation submitted the Paragraph IV certification

Immunex Corporation certify that US patent No. 5,670,537 is invalid and will not infringe by the manufacture, use or sale of paclitaxel for which this application is submitted.

On January 8, 1998 Bristol-Myers Squibb Company (BMS) filed a lawsuit against Immunex in federal district court in Newark, New Jersey, alleging infringement of United States Patents No. 5,641,803 and 5,670,537.

Patent certification (Amendment of June 30, 1999)

Paclitaxel injection 30mg/5mL, 150mg/25mL, and 300mg/50mL

U.S. Patent 5,496,804 expiry date: March 9, 2013

U.S. Patent 5,496,804 Paragraph viii certification

Baker Norton Pharmaceuticals certifies that this method of use patent does not claim any of the proposed indications for which the applicant is seeking approval.

Exclusivity statement

Paclitaxel injection 30mg/5mL, 150mg/25mL, and 300mg/50mL

Baker Norton Pharmaceuticals does not seek marketing approval for any of the indications covered under the exclusivities as described by codes ODE, I-202, I-226, and I-230.

Paragraph IV Patent certification (revised) August 14, 2000

U.S. Patent 6,096,331 - Paragraph IV Patent certification

Baker Norton Pharmaceuticals, Inc. certifies that this patent will not be infringed by the manufacture, use or sale of paclitaxel injection, 30 mg/5mL, 150 mg/25 mL and 300 mg/50 mL for which this application is submitted. Baker Norton Pharmaceuticals, Inc. will comply with the notification requirements defined in Section 505(j)(2)(B)(i), paragraphs I and II of the Federal Food, Drug and Cosmetic Act, (Codified at 21 CFR 314.95(a)). The content of the notice will conform to the requirements defined in 505(j)(2)(B)(ii) (codified at 21 CFR 314.95(c)).

5. SUPPLEMENT(s)

None

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Paclitaxel Injection, 6mg/mL

(30 mg/5 mL vial, 150 mg/25 mL vial, 300 mg/50 mL vial)

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

None

9. AMENDMENTS AND OTHER DATES:

Date of submission - Jul 30, 1997

Amendment - October 7, 1997

Notification of the ownership transfer: August 20, 1998

Major amendment: April 2, 1999

New amendment: June 15 and June 30, 1999 (two additional sizes)

Major amendment: December 8, 1999

Additional info: March 8, 2000

Minor amendment: April 21, 2000

Telephone conference: June 2, 2000 (OGD and Baker Norton)

Telephone amendment: June 5, 2000

Minor amendment: June 23, 2000

Telephone amendment: July 25, 2000

Telephone amendment: August 7, 2000

Paragraph IV certification for patent #6,096,331: August 14, 2000

Telephone amendment: August 22 and 23, 2000

10. PHARMACOLOGICAL CATEGORY

Treatment of breast cancer

11. Rx or OTC

RX

12. RELATED IND/NDA/DMF(s)

Listed referenced drug Taxol® (Paclitaxel Injection, 6mg/mL)

NDA 20262

NDA sponsor: Bristol Myers Squibb

Date of approval: Dec 29, 1992

DMF ✓

DMF

LOA: page 156

13. DOSAGE FORM

Injection

14. POTENCY

6 mg/mL (30 mg/5mL, 150mg/25mL, 300mg/50mL)

15. CHEMICAL NAME AND STRUCTUREPaclitaxel. Benzenepropanoic acid, β -(benzoylamino)- α -hydroxy-,
6,12b-bis(acetyloxy)-12-(benzoyloxy)-

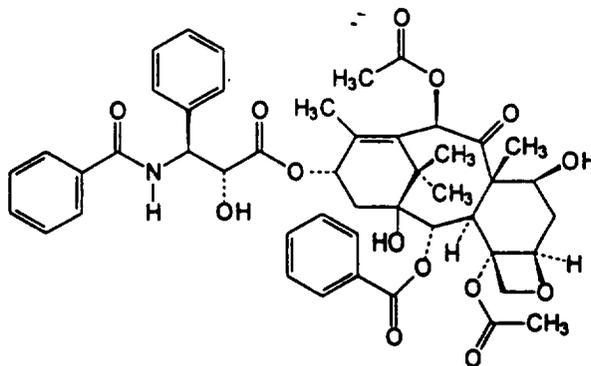
2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-

4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-

cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester, [2aR-

[2 α ,4 β ,4a β ,6 β ,9 α (α R*, β S*),11 α ,12 α ,12a α ,12b α]]-. C₄₇H₅₁NO₁₄.

853.93. 33069-62-4. Antineoplastic. USAN 1995, page 499.



16. RECORDS AND REPORTS

None

17. COMMENTS

Baker Norton Pharmaceuticals notified the Agency that Immunex had transferred ownership and all rights to ANDA 75-184, and that Immunex had submitted to this ANDA a letter of transfer of ownership, August 20, 1998. Immunex notify FDA of the transfer of ownership of ANDA 75-184 for Paclitaxel, 6 mg/mL in 5 mL (30mg) from Immunex Corporation to Baker Norton Pharmaceuticals, Inc., effective August 21, 1998.

Amendment of June 15 and June 30, 1999 to provide for two additional vial sizes i.e. 150mg/25mL and 300mg/50mL.

This application is approvable (tentatively).

18. CONCLUSIONS AND RECOMMENDATIONS

This application is approvable (tentatively).

19. REVIEWER:

DATE COMPLETED:

Liang-Lii Huang, Ph.D. August 23, 2000
 Endorsed by Paul Schwartz, Ph.D. /August 23, 2000

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Chem # 5

**REVIEW
OF
ENVIRONMENTAL ASSESSMENT
FOR**

ANDA 75-184

Paclitaxel Injection

**OFFICE OF GENERIC DRUGS (HFD-600)
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE COMPLETED: June 13, 2000

SUMMARY

A FONSI is recommended.

A *Federal Register* notice, Paclitaxel Drug Products; Environmental Information Needed in New Drug Applications, Abbreviated New Drug Applications, and Investigational New Drug Applications, published on November 18, 1996, [61 FR 58694]. This notice was issued to clarify the environmental information that must be submitted to CDER for drug products containing paclitaxel derived from Pacific Yew trees (*Taxus brevifolia*). Although action on ANDAs are not considered to increase use and are categorically excluded under 25.31(a), the ANDA applicant's paclitaxel drug substance is derived from an inventory of previously harvested Pacific Yew tree bark and therefore an EA has been provided.

The applicant intends to use paclitaxel derived from the bark of Pacific Yew (*Taxus brevifolia*) trees from a reserve inventory of bark that was collected prior to November 18, 1996 from both public and private lands. No further Pacific Yew harvesting will occur for this product.

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

The discussion included in the EA regarding the controls used during harvesting (e.g., harvesting packet and oversight by Hauser, system to trace origin of bark), government oversight, compliance with laws and regulations, and mitigation measures support the conclusion that a finding of no significant impact is appropriate.

The applicant is still investigating the alternatives that they will use when their supply of Pacific Yew tree derived material is exhausted. They have confirmed that they will notify FDA and provide additional environmental information, as required, to support the use of the new source.

ENVIRONMENTAL ASSESSMENT

1. Date:

EA dated: 12/09/1996
Review #1: 02/12/1998
EA dated: 03/1999
Review #2: 04/05/2000
EA dated: 04/27/2000 (superseded 4/21/2000 EA)
T-con: 05/25/2000
EA dated: 05/26/2000
Review #3: 06/13/2000

OGD Contact: Harvey Greenberg

2. Name of applicant/petitioner:

Baker Norton Pharmaceuticals, Inc.

Adequate

3. Address:

4400 Biscayne Blvd.
Miami, FL 33137

Adequate

The following are the responses to the deficiencies (italicized) identified in review #2:

- Section 4.a: The application indicated that you would be submitting additional vial sizes. If this has occurred or will occur before approval of ANDA 75-184, you should update the executive summary and section 4.a of the EA.*

RESPONSE: The additional vial sizes have been submitted and the EA has been updated appropriately.

Adequate

- Section 6.2.a/Use of Resources: Please provide the last date of harvesting from state lands.*

RESPONSE: All harvesting on state lands was done before September 1996.

Adequate

3. *Section 6.2.a/Permitting Authorities:*

- *In the discussion under permitting authorities for private and state lands, harvesting from state land in Washington and Montana is discussed. Appendix A implies that these are the only two states where harvesting occurred from state lands but it is identified as a partial list. Please specifically identify the states where harvesting from state lands occurred. If harvesting from state land occurred in other states, provide additional information similar to what is provided for Washington and Montana.*

RESPONSE: The EA has been revised to include a statement that "Of the states mentioned, harvesting from state lands only occurred in Washington and Montana."

Adequate

- *Confirmation should be included that harvesting from private, state and federal land was conducted in accordance with all applicable federal, state, and local laws, regulations, and guidances.*

RESPONSE: An affirmative statement has been added to the guidance.

Adequate

4. *Section 6.2.a/Endangered Species and Yew: Information on any federal, state or local regulations and guidances that were intended to provide protection to endangered or threatened species under circumstances that would have included harvesting of Pacific Yew Trees should be provided. Also, information on whether these regulations or guidances were followed should be provided.*

RESPONSE: A discussion of the federal, state, and local laws, regulation and guidances that were intended to provide protection to endangered or threatened species under circumstances that would have included harvesting of Pacific Yew has been provided. Idaho and Montana use the Federal Endangered Species Act. California, Oregon, and Washington have specific state laws pertaining to protection of species. An affirmative statement that the harvesting complied with all state, local, and federal regulations and guidances that were intended to provide protection to endangered and threatened species under circumstances that

would have included harvesting of Pacific Yew was included.

Additional clarification needed:

The applicant should identify the state laws in California, Oregon, and Washington.

The last version of the EA included a statement that "The Pacific yew is not listed under the Federal Endangered Species Act (ESA), or under the Convention on International Trade in Endangered Species (CITES) as endangered or threatened." This statement was not included in this version of the EA. It should be put back in.

RESPONSE: In the amendment dated May 26, 2000, the applicant has identified the state laws in California, Oregon, and Washington and included the statement about Pacific Yew not being listed under the ESA or CITES.

Adequate

5. *Section 7: Please confirm that you accomplished the mitigation measures required by the federal, state, and local governmental authorities.*

RESPONSE: A discussion has been included that confirms that required mitigation measures were accomplished.

Adequate

6. *Section 8:*

- *For each alternative, a discussion should be included of any environmental factors that were considered in deciding whether or not to use the alternative.*

RESPONSE: The last version of the EA indicated that the applicant would be using cultivated *Taxus media* once their stockpiled Pacific Yew ran out. This version deletes this information and states that "...future supplies of paclitaxel will either come from non-endangered wild species or cultivated yew. At this time we have not selected a future source." More detailed information about the alternatives they are investigating should be provided.

The applicant has included some discussion of the environmental factors for the synthetic process.

Additional clarification needed:

The use of non-endangered wild species (other than Pacific Yew) and cultivated yew need to be listed as separate alternatives. The specific species that are being investigated, the status of your investigation, the factors, including environmental that will be considered in deciding whether or not to use the alternative should be discussed.

The second sentence in section 8 says that they "propose" that no further Pacific Yew will be collected. This should be changed to state that they "confirm" this.

RESPONSE: In the amendment dated May 26, 2000, the applicant has clarified that no more Pacific Yew will be collected and has listed the harvesting of wild and cultivated yew species as alternatives. The alternatives discussion includes the environmental and business factors that the applicant will consider when deciding on a new source.

Adequate

- The EA indicates that you will be switching to a cultivated biomass source and will continue to investigate alternative sources. This should be clarified to state that when you switch biomass sources, FDA will be notified in accordance with 21 CFR 314.96 or 314.70 and additional EA information will be provided to FDA if required.

RESPONSE: The suggested statement has been added.

Adequate

**T-con Record
ANDA 75-184**

On May 25, 2000 I contacted Steve Viti (305-575-6336), briefly discussed the issues listed below, and asked him to provide a revised EA. I asked that the official copies be submitted to the ANDA and a desk copy FEDexed to me.

Section 6.2.a-Endangered Species and Yew

Please identify the specific state laws in California, Oregon, and Washington for protecting endangered or threatened species.

The last version of the EA included a statement that "The Pacific yew is not listed under the Federal Endangered Species Act (ESA), or under the Convention on International Trade in Endangered Species (CITES) as endangered or threatened." This statement was not included in this version of the EA. It should be put back in.

Section 8-Alternatives

The use of non-endangered wild species (other than Pacific Yew) and cultivated yew need to be listed as separate alternatives. The specific species that are being investigated, the status of your investigation, and the factors, including environmental that will be considered in deciding whether or not to use the alternative should be discussed.

The second sentence in section 8 says that they "propose" that no further Pacific Yew will be collected. This should be clarified to state that there will not be any further harvesting.

Note: The applicant sent in an amendment dated May 26, 2000 to address these issues.

Endorsements:

HFD-357/NBSager *NBSager 6/13/00*

HFD-600/GBuehler *Tom Buehler 6/15/00*

CC: Original to ANDA 75-184/through HGreenberg/HFD-615
EA File 75-184

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**ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR**

Paclitaxel Injection

ANDA 75-184

**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)**

FINDING OF NO SIGNIFICANT IMPACT

ANDA 75-184

Paclitaxel Injection

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

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

In support of its abbreviated new drug application for **paclitaxel injection, Baker Norton Pharmaceuticals, Inc.** has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the harvesting of a wild plant species from which paclitaxel is derived. Paclitaxel injection is used for the treatment of metastatic carcinoma of the ovary or breast after failure of standard therapy.

The applicant intends to use paclitaxel derived from the bark of Pacific Yew (*Taxus brevifolia*) trees from a reserve inventory of bark that was collected prior to November 18, 1996. The bark was collected from both public and private land. No further Pacific Yew harvesting will occur for this product.

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

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

At U.S. hospitals, clinics, and pharmacies, empty or partially empty packages will be disposed of in accordance to the facility's procedures. Empty or partially empty containers from homes of patients will typically be disposed of by a community's solid waste management system which could include landfills, incineration and/or recycling. Minimal quantities of unused drug could

be disposed of in sewer systems.

No adverse effects are anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places. The Center for Drug Evaluation and Research has concluded that no adverse environmental effects are expected from the use and disposal from use of the product.

6/13/00
DATE

Nancy B. Sager

PREPARED BY
Nancy B. Sager
Environmental Officer
Center for Drug Evaluation and Research

6/15/00
DATE

Gary Buehler

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

Attachment: Environmental Assessment

SECTION XX

ENVIRONMENTAL ASSESSMENT

PACLITAXEL INJECTION

30 mg/5 mL (6 mg/mL)

150 mg/25 mL (6 mg/mL)

300 mg/50 mL (6 mg/mL)

ANDA #75-184

**Baker Norton Pharmaceuticals, Inc.
Miami, FL 33137**

**April, 1999
(Revised May 26, 2000)**

010006

**ENVIRONMENTAL ASSESSMENT FOR
PACLITAXEL INJECTION, 30 mg/5 mL (6 mg/mL),
150 mg/25 mL (6 mg/mL) and 300 mg/50 mL (6 mg/mL)**

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EXECUTIVE SUMMARY

Baker Norton Pharmaceuticals Inc. is submitting an Abbreviated New Drug Application for Paclitaxel Injection, 30 mg/5 mL (6 mg/mL), 150 mg/25 mL (6 mg/mL) and 300 mg/50 mL (6 mg/mL) strength. It is not envisioned that approval of this application will increase the use of paclitaxel, the active moiety or that the estimated concentration of the substance at the point of entry into the aquatic environment will be 1 ppb or greater. In this case, an Environmental Assessment is not generally required for Abbreviated New drug Applications as per the *Guidance for Industry Environment Assessment of Human Drug and Biologics Applications* dated July 1998. However as the active moiety represented by this application is paclitaxel, derived from or otherwise involving the Pacific Yew tree, an Environmental Assessment is required as per the *Federal Register Notice (61 FR 58694)*. It is the intention of Baker Norton to focus this Environmental Assessment on information regarding the source of the biomass, mitigation measures and the alternatives.

This Environmental Assessment is part of the Abbreviated New Drug Application (ANDA) for the Paclitaxel Injection Concentrate. Paclitaxel Injection is indicated for the treatment of metastatic carcinoma of the ovary or breast cancer as a chemotherapeutic agent. The proposed action will provide a new therapeutic choice for the treatment of ovarian cancer and breast cancer after failure of standard therapy.

ENVIRONMENTAL ASSESSMENT

1. DATE

May 26, 2000. The original submission was dated December 9, 1996; amendments were submitted on April 21, 2000 and April 27, 2000.

March, 1999,
NS 6/13/00

2. NAME OF APPLICANT/PETITIONER

Baker Norton Pharmaceuticals, Inc.

3. ADDRESS

4400 Biscayne Boulevard.
Miami, Florida 33137

4. DESCRIPTION OF PROPOSED ACTION

4.a Requested Approval

Baker Norton Pharmaceuticals Inc. is requesting approval for the manufacture, marketing and use of Paclitaxel Injection, 30 mg/5 mL (6 mg/mL), 150 mg/25 mL (6mg/mL) and 300 mg/50 mL (6 mg/mL).

This Environmental Assessment (EA) report is a part of the Abbreviated New Drug Application (ANDA #75-184) for Paclitaxel Injection. This document format is arranged as specified in the Center for Drug Evaluation and Research's (CDER) *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July 1998) and the *Notice for Paclitaxel Drug Products; Environmental Information Needed in New Drug Applications, Abbreviated New Drug Applications, and Investigational New Drug Applications* (Federal Register, November 18, 1996) by the Department of Health and Human Services, Food and Drug Administration. The product concerned represents an antineoplastic agent for the treatment of metastatic carcinoma of the ovary or breast after failure of standard therapy.

Paclitaxel Injection, 30 mg/5 mL (6 mg/mL), 100 gm/16.67 mL (6mg/mL) and 300 mg/50 mL (6 mg/mL) sizes have been manufactured and marketed by Bristol-Myers Squibb Company under the trade name of Taxol[®] for Injection Concentrate. Under the proposed action, the drug product will not be administered at higher dosage levels nor for longer duration than were previously

010010

in effect. It is not expected that approval of this application will increase the overall usage of paclitaxel, nor will it result in an increase in the amount of paclitaxel getting into the environment.

4.b Need for Action

Paclitaxel Injection is indicated for the treatment of metastatic carcinoma of the ovary or breast cancer after failure of standard therapy.

4.c Location of Use

As a prescribed therapy for ovarian and breast cancer after failure of standard therapy, this drug will be distributed and used in the United States. Locations of use include hospitals, clinics and/or patients in their homes as well as in private practices.

4.d Disposal Sites

All used vials that contain residues of the drug product should be secured and disposed of in accordance with established procedures for anticancer/antineoplastic drugs. Hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures. In the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system that may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

5. IDENTIFICATION OF SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION.

5.a Nomenclature

i. Established Name (U.S. Adopted Name-USAN)

Paclitaxel

ii. Brand/Propriety Name/Tradename

Paxene®

010011

iii. Chemical Name

Chemical Abstracts (CA) Index Name (inverted form):

2aR-[2a α , 4 β , 4a β , 6 β , 9a(aR*, β S*),11 α ,12 α , 12a α , 12b α]}- β -(Benzoylamino)- α -hydroxybenzenepropanoic acid, 6, 12-bis(acetyloxy)-12-(benzoyloxy)-2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12 a, 12b-dodecahydro-4, 11-dihydroxy-4a, 8, 13, 13-(tetramethyl-5-oxo-7, 11-methano-1H-cyclodeca[3, 4]benz[1, 2-b]oxet-9-yl ester

(Chemical Abstracts Service (CAS) Name)

Systematic Chemical Name (uninverted form)

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

5.b Chemical Abstracts Service (CAS) Registration Number

33069-62-4

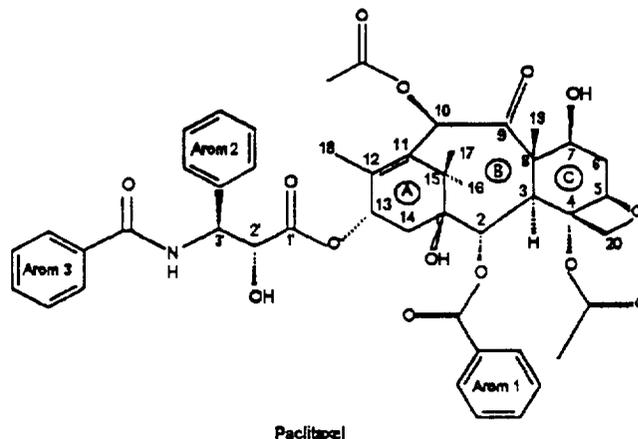
5.c Molecular Formula

C₄₇H₅₁NO₁₄

5.d Molecular Weight

854

5.e Structural Formula



010012.

6. ENVIRONMENTAL ISSUES

This Environmental Assessment is being prepared in accordance with the *Federal Register Notice (61 FR 58694)* which requires an EA for applications which involve paclitaxel derived from Pacific Yew trees (*Taxus brevifolia*).

In accordance with the *Guidance for Industry Environment Assessment of Human Drug and Biologics Applications* dated July 1998 all environmental issues specific to this application will be addressed. The environmental issues associated with this application are primarily related to "Use of Flora or Fauna" and are presented in section 6.2 below. It is the intention of Baker Norton to focus this Environmental Assessment on information regarding the source of the biomass, mitigation measures and the alternatives.

6.1 ASSESSING TOXICITY TO ENVIRONMENTAL ORGANISMS

This EA is being prepared in accordance with the *Guidance for Industry Environment Assessment of Human Drug and Biologics Applications* dated July 1998. This section on Assessing Toxicity To Environmental Organisms is not relevant to this application because approval of the ANDA will not increase the use of paclitaxel, the active moiety; and also the estimated concentration of the substance at the point of entry into the aquatic environment will not be more than 1 part per billion. See **Confidential Appendix 1** for Expected Introduction Concentration Calculation (EIC).

6.2 USE OF FLORA OR FAUNA

This section of the Environmental Assessment will focus on information regarding the source of the biomass, mitigation measures and the alternatives to the Pacific Yew tree.

6.2.a Use of Resources

Paclitaxel is a natural product that is extracted, isolated and purified from biomass (bark) obtained from the wild Pacific Yew tree (*Taxus brevifolia*). The bark obtained from the Pacific Yew is not a renewable resource. See **Confidential Appendix 2** for information on the quantity of bark in reserve, the approximate bulk weight needed to yield a kilogram of active moiety, and the amount of bark that has been harvested to date to support the proposed Agency action for the product. Information regarding the amount of biomass needed to produce the active moiety can be found in **Confidential Appendix 3**.

The raw materials from which paclitaxel is extracted are contained in a reserve inventory of Pacific Yew bark that was collected prior to November 18, 1996, by or on behalf of Hauser, in accordance with the requirements of the Pacific Yew Act, 16 U.S.C. §§ 4801-4807, the Pacific Yew Final Environmental Impact Statement (FEIS) published in August 1993 by the U.S. Department of Agriculture (USDA) Forest Service and under permits validly issued by the U.S. Forest Service or Bureau of Land Management (BLM), as applicable. In the course of such bark collection activities, all of the mitigation measures specified in the FEIS and in "An Interim Guide to the Conservation and Management of