

**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

75-278

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-278

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Paclitaxel

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

N/A

9. AMENDMENTS AND OTHER DATES:

December 19, 1997 original submission

January 21, 1998 amendment (revised patent certification;
draft vial/carton labeling annotated
against labeling of referenced listed
drug)

March 23, 1998 New Correspondence (re: Paragraph IV
patent certification)

April 29, 1998 New Correspondence (Bristol-Myers Squibb
notified FDA that they are suing Mylan
regarding infringement of Bristol-Myers
Squibb's patents for Taxol)

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

NDA 20-262 Bristol Myers Squibb

DMF _____

DMF _____

DMF _____

13. DOSAGE FORM

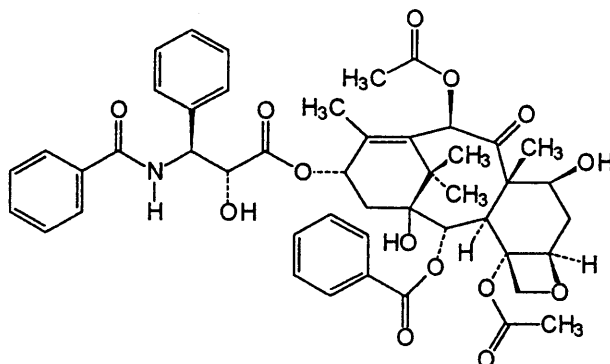
Injectable

14. POTENCY

30 mg/5 mL (6 mg/mL)

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

N/A

17. COMMENTS

COMPONENTS AND COMPOSITION

[]

The cover letter dated December 19, 1997 states that

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[]
DMF CHECKLIST

DMF _____

18. CONCLUSIONS AND RECOMMENDATIONS

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

19. REVIEWER:

DATE COMPLETED:

Shirley S. Brown

July 17, 1998

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1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-278

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT (s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Paclitaxel

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

N/A

9. AMENDMENTS AND OTHER DATES:

December 19, 1997 Original submission

January 21, 1998 Amendment (revised patent certification;
draft vial/carton labeling annotated against
labeling of referenced listed drug)

March 23, 1998 New Correspondence (re: Paragraph IV patent
certification)

April 29, 1998 New Correspondence (Bristol-Myers Squibb
notified FDA that they are suing Mylan regarding
infringement of Bristol-Myers Squibb's patents
for Taxol)

* January 18, 1999 Amendment (responding to chemistry deficiencies
per review #1)

April 23, 1999 Amendment (sterility assurance information)

May 18, 1999 New Correspondence (authorization to confer with
Dr. Erwin Peters of Mattson Jack Technical
Services re: Environmental Assessment)

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

NDA 20-262 Bristol Myers Squibb

DMF _____

DMF _____

DMF _____

13. DOSAGE FORM

Injectable

14. POTENCY

30 mg/5 mL (6 mg/mL)

15. CHEMICAL NAME AND STRUCTURE

See Review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

See item #38 of review.

18. CONCLUSIONS AND RECOMMENDATIONS

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

19. REVIEWER:

Shirley S. Brown

DATE COMPLETED:

June 30, 1999

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1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-278

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT (s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Paclitaxel

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

N/A

9. AMENDMENTS AND OTHER DATES:

December 19, 1997	Original submission
January 21, 1998	Amendment (revised patent certification; draft vial/carton labeling annotated against labeling of referenced listed drug)
March 23, 1998	New Correspondence (re: Paragraph IV patent certification)
April 29, 1998	New Correspondence (Bristol-Myers Squibb notified FDA that they are suing Mylan regarding infringement of Bristol-Myers Squibb's patents for Taxol)
January 18, 1999	Amendment (responding to chemistry deficiencies per review #1)
April 23, 1999	Amendment (sterility assurance information)
May 18, 1999	New Correspondence (authorization to confer with Dr. Erwin Peters of Mattson Jack Technical Services re: Environmental Assessment)
August 18, 1999	Amendment (response to EA issues)

B. Review of Environmental Assessment amendment of August 18, 1999.

19. REVIEWER:

DATE COMPLETED:

Shirley S. Brown

January 27, 2000

March 23, 2000 (revised to incorporate MV report)

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Chemistry Closed

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-278

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT (s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Paclitaxel

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

N/A

9. AMENDMENTS AND OTHER DATES:

December 19, 1997	Original submission
January 21, 1998	Amendment (revised patent certification; draft vial/carton labeling annotated against labeling of referenced listed drug)
March 23, 1998	New Correspondence (re: Paragraph IV patent certification)
April 29, 1998	New Correspondence (Bristol-Myers Squibb notified FDA that they are suing Mylan regarding infringement of Bristol-Myers Squibb's patents for Taxol)
January 18, 1999	Amendment (responding to chemistry deficiencies per review #1)
April 23, 1999	Amendment (sterility assurance information)
May 18, 1999	New Correspondence (authorization to confer with Dr. Erwin Peters of Mattson Jack Technical Services re: Environmental Assessment)
August 18, 1999	Amendment (response to EA issues)

November 9, 1999 Amendment (re: Patent Exclusivity)

January 13, 2000 Amendment (responding to microbiological deficiencies)

January 13, 2000 Amendment (responding to chemistry deficiencies per review #2)

*March 24, 2000 Telephone Amendment which was converted to a New Correspondence on 3/31/00 (responding to February 2, 2000 telecon)

*May 5, 2000 Amendment (responding to chemistry deficiencies per review #3)

May 12, 2000 Amendment (Revised Environmental Assessment)

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

NDA 20-262 Bristol Myers Squibb

DMF _____

DMF _____

DMF _____

13. DOSAGE FORM

Injectable

14. POTENCY

30 mg/5 mL (6 mg/mL)

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Note and acknowledge comments per the March 28, 2000 deficiencies.

1. Microbiologist review for the January 13, 2000 sterility assurance amendment is pending.

2. Review of the Environmental Assessment amendment of August 18, 1999 is pending.
3. The test failure in Item 3.a. above is considered a significant issue. Please contact the Philadelphia District Laboratory, if needed, to resolve this problem.

Response:

1. Mylan acknowledges that the Microbiologist review for the January 13, 2000 sterility assurance amendment is pending.
2. The review of the Environmental Assessment amendment of August 18, 1999 has been completed and comments from the Agency in a letter dated April 11, 2000 were received. The response to the April 11, 2000 comments will be forwarded to the Agency in a separate amendment.
3. Based on a statement with Ms. Michelle Dillahunt of FDA, no further action is required.

18. CONCLUSIONS AND RECOMMENDATIONS

Chemistry is closed.

Pending: Review of Environmental Assessment amendment dated May 12, 2000.

19. REVIEWER:

SS!
Shirley S. Brown

DATE COMPLETED:

5/26/00
May 23, 2000

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1. CHEMISTRY REVIEW NO. 5

2. ANDA # 75-278

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT (s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Paclitaxel

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

N/A

9. AMENDMENTS AND OTHER DATES:

December 19, 1997 Original submission

September 19, 2000 Tentative Approval (5 ml)

*September 29, 2000 Amendment (providing for additional package sizes)

*December 29, 2000 Amendment (provides for use of *Taxus yunnanensis* species of the yew tree in manufacture of the drug substance) including an EA.

*subject of this review

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF (s)

NDA 20-262 Bristol Myers Squibb

DMF _____

DMF _____

DMF

13. DOSAGE FORM

Injectable

14. POTENCY

6 mg/mL: 30 mg/5 mL vial
100 mg/16.7 mL vial
300 mg/50 mL vial

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

The ANDA was tentatively approved September 19, 2000.

18. CONCLUSIONS AND RECOMMENDATIONS

Chemistry deficiency. See item 38.

Environmental Deficiencies per the December 29, 2001 amendment were faxed on 4/17/01.

Pending: (A) Microbiology review for September 29, 2000 amendment.
(B) EER Update.

19. REVIEWER:

DATE COMPLETED:

Shirley S. Brown

April 30, 2001

Shirley S. Brown

May 2, 2001

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Chemistry Closed

1. CHEMISTRY REVIEW NO. 6

2. ANDA # 75-278

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Paclitaxel

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

N/A

9. AMENDMENTS AND OTHER DATES:

December 19, 1997 Original submission

September 19, 2000 Tentative Approval (5 ml)

September 29, 2000 Amendment (providing for additional package sizes)

December 29, 2000 Amendment (provides for use of *Taxus yunnanensis* species of the yew tree in manufacture of the drug substance) including an EA.

*May 11, 2001 Amendment (response to May 10, 2001 deficiencies)

*subject of this review

10. PHARMACOLOGICAL CATEGORY

Antineoplastic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

NDA 20-262 Bristol Myers Squibb

DMF _____

DMF _____

DMF _____

13. DOSAGE FORM

Injectable

14. POTENCY

6 mg/mL: 30 mg/5 mL vial
100 mg/16.7 mL vial
300 mg/50 mL vial

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

The applicant was asked to note and acknowledge the following.

1. Microbiology review for the September 29, 2000 amendment is pending.
2. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

Response:

1. Acknowledged. Per discussions with the Agency, the review for the September 29, 2000 amendment will be initiated within the next two weeks. Based on the classification of the CMC correspondence as a FAX Amendment, a request will be made to Microbiology Review branch to prioritize the review.
2. Acknowledged.

Note: The ANDA was tentatively approved September 19, 2000 for the 30 mg/5 mL vial size.

18. CONCLUSIONS AND RECOMMENDATIONS

Chemistry Closed.

Pending: (A) Microbiology review for September 29, 2000 amendment.
(B) EER Update.

(C) Satisfactory response to the Environmental Deficiencies that were faxed on 4/17/01.

19. REVIEWER: |

Shirley S. Brown

DATE COMPLETED:

May 14, 2001

May 14, 2001

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5/14/01

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1. ADDENDUM TO CHEMISTRY REVIEW NO. 6

2. ANDA # 75-278

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. NONPROPRIETARY NAME

Paclitaxel

5. DOSAGE FORM

Injectable

6. POTENCY

6 mg/mL: 30 mg/5 mL vial
100 mg/16.7 mL (20 mL vial)
300 mg/50 mL (50 mL vial)

7. AMENDMENTS Since CR#6 (CMC Satisfactory)

May 11, 2001 Labeling and Patents
May 14, 2001 Environmental Assessment
May 22, 2001 Amendment (provides for response to May 18, 2001 deficiencies regarding Environmental Assessment)
May 23, 2001 Amendment (provides for response to May 23, 2001 deficiencies regarding Environmental Assessment)
May 30, 2001 Amendment (provides for response to May 24, 2001 Microbiology deficiency)
June 12, 2001 Environmental Assessment
June 14, 2001 Amendment (provides for response to June 14, 2001 deficiencies regarding Environmental Assessment)

8. MANUFACTURING AND PROCESSING

The submission was recommended for approval on the basis of sterility assurance per the microbiology May 31, 2001 review of

Satisfactory

9. LABELING

Reference May 25, 2001 approval summary of Angela Payne.

Satisfactory

10. ESTABLISHMENT INSPECTION

The EER was Acceptable as of October 2, 1998.

Update - Acceptable as of June 29, 2001.

Satisfactory

11. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Conclusion per the June 15, 2001 review of Nancy Sager. A Finding of No Significant Impact is appropriate.

Satisfactory

12. CONCLUSIONS AND RECOMMENDATIONS

The ANDA is approvable.

13. REVIEWER:

Shirley S. Brown
Shirley S. Brown

DATE COMPLETED:

July 19 2001
July 2, 2001

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14. DMF CHECKLIST FOR ANDA # 75-278 ADDENDUM TO REVIEW # 6

<u>DMF #</u>	<u>DMF TYPE/SUBJECT/HOLDER</u>	<u>ACTION CODE</u>	<u>RESULT OF REVIEW</u>	<u>DATE REVIEW COMPLETED</u>
II/		3	Adequate	5/1/2001
Comments:				
III/		4		
Comments:				
III/		4		
Comments:				

ACTION CODES:

(1) DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;

(3) Reviewed previously and no revision since last review;

(4) Sufficient information in application

(5) Authority to reference not granted

(6) DMF not available

(7) Other (explain under "Comments").

Page 1 of 1.

Shirley S. Brown

Reviewer

/S/

Signature

July 19, 2001

Date

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15. Chemistry Comments to be Provided to the Applicant

N/A

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