CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75491

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA # 75-491

DRUG PRODUCT: Bupropion Hydrochloride Tablets 75 mg and 100 mg

FIRM: Mylan Pharmaceuticals Inc.

DOSAGE FORM: Tablets

STRENGTHS: 75 mg and 100 mg

CGMP STATEMENT/EIR UPDATE STATUS:
An acceptable EER was issued on 10/06/99.

Facilities included:

Mylan pharmceuticals Inc.
781 Chestnut Ridge Road
Morgantown, WV 26505

Function: Manufacturing, Packaging, Labeling, Quality Control Testing of Components, Testing of Finished Dosage Form, Storage and Stability Testing.

cGMP certification - provided on page 2576.

Function: Contract testing facility for the elemental analysis of Bupropion Hydrochloride House Standard.

cGMP certification - provided on page 2581.

Function: Mylan may employ as a contract manufacturing facility for the Microcrystalline Cellulose used in the manufacture of Bupropion Hydrochloride Tablets, 75 & 100 mg.

cGMP certification - provided on page 2582.

Function: Drug substance manufacturer.

BIO STUDY:
Satisfactory per CS Chaurasia on 03/09/00.

VALIDATION:
The method validation by the Philadelphia District Laboratory was completed on December 16, 1999 and found acceptable

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Post-approval Protocol and Commitment:
First three commercial lots of the smallest and the largest size of each container/closure system to be marketed would be placed on stability at 250C + 20C/60% R.H + 5% R.H, tested at 0, 3, 6, 9, 12, 18, 24, 30 and 36 months. Minimum of one lot packaged in the largest and smallest size of each marketed container/closure system will be added to the long term stability program, data submitted to FDA in the periodic reports, lots that fail will be withdrawn from market.

Expiration Date:
24 months tentative based on 3 months accelerated stability data at 400C + 20C/75% RH + 5% RH.

LABELING:
Satisfactory per A. Vezza on 08/30/99

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
Exhibit batch: lot #2E001B (75 mg tablets). tablets.
Exhibit batch: lot #2E002B (100 mg tablets), tablets.

DMF has been reviewed and found satisfactory by S. Basaran on September 1999.

SIZE OF STABILITY BATCHES:
Same as bio batch.

PROPOSED PRODUCTION BATCH:

Exhibit Batch Size
Production Batch Size
Ratio

Bupropion HCl Tablets 75 mg
Tabs
Tabs

Bupropion HCl Tablets 100 mg
Tabs
Tabs

CHEMIST: Bita Mirzai-Azarm DATE: 03/29/00

SUPERVISOR: Ubrani Venkataram, Ph.D. DATE: 04/03/00

/S/ 4/6/2000

DV

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 1

2. **ANDA #** 75-491

3. **NAME AND ADDRESS OF APPLICANT**
Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. **LEGAL BASIS FOR SUBMISSION**
The firm includes a patent certification statement on page 10. The firm amends the patent certification statement on November 23, 1998 (page 5). A basis for ANDA submission is on page 8. The reference listed drug for this ANDA is Wellbutrin® (Bupropion Hydrochloride) Tablets, 75 and 100 mg manufactured by Glaxo Wellcome.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Bupropion Hydrochloride Tablets

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

9. **AMENDMENTS AND OTHER DATES:**
Firm:
October 30, 1998 - Original Submission
November 23, 1998 - Patent Amendment

FDA:
December 9, 1998 - Acknowledgement letter

10. **PHARMACOLOGICAL CATEGORY**
Anti-depressant

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
See review element #37

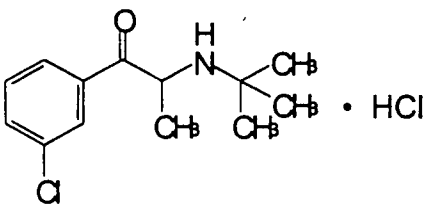
13. **DOSAGE FORM**
Oral tablets

14. **POTENCIES**
75 and 100 mg

15. **CHEMICAL NAME AND STRUCTURE**
Chemical name:
1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (±)-

Chemical Formula	Molecular weight	Cas Number
$C_{13}H_{18}ClNO \cdot HCl$	276.2	31677-93-7

Structure:



16. **RECORDS AND REPORTS**

17. **COMMENTS**
This application has the following CMC deficiencies:
- DMF
- Raw material controls
- Manufacturing and processing
- Container Closure
- Laboratory Controls
- Stability

Labeling review status: Unsatisfactory, A. Vezza, on 03/05/99

Bioequivalence status: Unsatisfactory, CS Chaurasia, on 01/26/99

EER: Pending

MV: Need MV since non-U.S.P. drug substance and drug product.

18. **CONCLUSIONS AND RECOMMENDATIONS**

This application is not approvable at this time.

19. **REVIEWER:** Bita Mirzai-Azarm **DATE COMPLETED:** 05/26/99

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Chem-Review #1

JUN 28 1999

Chemistry Comments to be Provided to the Applicant

ANDA: 75-491 APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Bupropion Hydrochloride Tablets 75 and 100 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. It is recommended that you include a test for Bulk Density and Tapped Density in your drug substance testing specifications.

2. Certificate of Analysis for Bupropion Hydrochloride drug substance (page 2453) showed either very small amounts of the known related compounds or none detected. It is recommended that you tighten these specifications.

3. Please include the testing specification for 3'- which appears on your COA on page 2453 to the testing specifications for Bupropion Hydrochloride for future commercial production batches (page 2450).

4. Please provide COA for the Microcrystalline Cellulose (supplier lot #9806491).

5. The mixing time on page 2837 is reported as minutes for Part I-A Solution Manufacture Instructions whereas for Part II-A (page 2841) and Part III-A (page 2845) is reported as minutes and minutes respectively. Please clarify the difference in mixing times.

6. Please provide more information on poly-liners, used for storage of intermediate.

7. Please provide bottle manufacturer's testing data and specifications for container resins.

8. Please provide closure manufacturer's testing data and specifications for closure resins.

9. It is recommended that you include the as an in-process control in the master production records. Please revise and resubmit appropriate documents, include sampling and specifications. It is recommended that samples be drawn either from the blender or drums (more than six samples) and the sample size should not be more than 1-3 dosage units. acceptance criteria of ( ) (mean of individual test results) with relative standard deviation (RSD) of NMT % is recommended.

10. On page 3035 and page 3036 you have included test results for the bulk final blend samples for each strength. The results actually do fall in the recommended acceptance criteria above. Please provide the actual sample size which was used for

11. Please set a target for tablet hardness and tablet thickness.

12. The proposed weight gain range for Coated Tablet Specifications are wide. Please tighten these limits.

13. Accelerated stability studies on pages 3467 - 3479 showed either very small amounts of the known related compounds or none detected. It is recommended that you further tighten these specifications for the final product specifications at release and stability.

14. Please include identification tests in your Microcrystalline Cellulose specifications.

15. It is recommended that you stress the Bupropion Hydrochloride Tablets under strong acid, strong base and oxidation conditions to investigate the stability-indicating properties of the Assay and Related Compounds procedures.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The referenced DMF is deficient and the deficiency has been communicated to the DMF holder.

2. The Establishment Evaluation Request (EER) is pending.

3. Your Method Validation package is being sent to our Philadelphia District Laboratory.

Sincerely yours,

/S/

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.** 2

2. **ANDA #** 75-491

3. **NAME AND ADDRESS OF APPLICANT**
Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. **LEGAL BASIS FOR SUBMISSION**
The firm includes a patent certification statement on page 10. The firm amends the patent certification statement on November 23, 1998 (page 5). A basis for ANDA submission is on page 8. The reference listed drug for this ANDA is Wellbutrin® (Bupropion Hydrochloride) Tablets, 75 and 100 mg manufactured by Glaxo Wellcome.

5. **SUPPLEMENT(s)**
N/A

6. **PROPRIETARY NAME**
N/A

7. **NONPROPRIETARY NAME**
Bupropion Hydrochloride Tablets

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

9. **AMENDMENTS AND OTHER DATES:**
Firm:
October 30, 1998 - Original Submission
November 23, 1998 - Patent Amendment
August 16, 1999 - Major amendment

FDA:
December 9, 1998 - Acknowledgement letter
June 28, 1999 - Deficiency letter (Major)

10. **PHARMACOLOGICAL CATEGORY**
Anti-depressant

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
See review element #37

13. **DOSAGE FORM**
Oral tablets

14. **POTENCIES**
75 and 100 mg

15. **CHEMICAL NAME AND STRUCTURE**
Chemical name:
1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (±)-

Chemical Formula	Molecular weight	Cas Number
$C_{13}H_{18}ClNO \cdot HCl$	276.2	31677-93-7

~~Structure:~~

16. **RECORDS AND REPORTS**

17. **COMMENTS**
The applicant needs to perform forced degradation study on samples of the drug product.

18. **CONCLUSIONS AND RECOMMENDATIONS**
This application is not approvable at this time.

19. **REVIEWER:** Bita Mirzai-Azarm

DATE COMPLETED: 02/08/00

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Chem Review #2

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-491

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
The firm includes a patent certification statement on page 10. The firm amends the patent certification statement on November 23, 1998 (page 5). A basis for ANDA submission is on page 8. The reference listed drug for this ANDA is Wellbutrin® (Bupropion Hydrochloride) Tablets, 75 and 100 mg manufactured by Glaxo Wellcome.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Bupropion Hydrochloride Tablets

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

9. AMENDMENTS AND OTHER DATES:
Firm:
October 30, 1998 - Original Submission
November 23, 1998 - Patent Amendment
August 16, 1999 - Major amendment
March 21, 2000 - Facsimile amendment

FDA:
December 9, 1998 - Acknowledgement letter
June 28, 1999 - Deficiency letter (Major)
February 25, 2000 - Deficiency letter (Minor)
March 20, 2000 - Telephone conversation

10. **PHARMACOLOGICAL CATEGORY**
Anti-depressant

11. **Rx or OTC**
Rx

12. **RELATED IND/NDA/DMF(s)**
See review element #37

13. **DOSAGE FORM**
Oral tablets

14. **POTENCIES**
75 and 100 mg

15. **CHEMICAL NAME AND STRUCTURE**
Chemical name:
1-Propanone, 1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-, hydrochloride (±)-

Chemical Formula	Molecular weight	Cas Number
$C_{13}H_{18}ClNO \bullet HCl$	276.2	31677-93-7

16. **RECORDS AND REPORTS**

17. **COMMENTS**
CMC, Bio-review, Labeling, MV and EER are satisfactory.

18. **CONCLUSIONS AND RECOMMENDATIONS**
This application is approvable.

19. **REVIEWER:** Bita Mirzai-Azarm

DATE COMPLETED: 03/27/00

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Chem Review #3