APPLICATION NUMBER:
75417

CHEMISTRY REVIEW(S)
## ANDA APPROVAL SUMMARY

<table>
<thead>
<tr>
<th>ANDA:</th>
<th>CHEMIST:</th>
<th>DATE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>75-417</td>
<td>Neeru B. Takiar</td>
<td>April 19, 1999</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DRUG PRODUCT:</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Clozapine</td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>FIRM:</th>
<th>STRENGTH:</th>
<th></th>
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<tbody>
<tr>
<td>Mylan Pharmaceuticals Inc.</td>
<td>25 mg and 100 mg</td>
<td></td>
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<table>
<thead>
<tr>
<th>DOSAGE FORM:</th>
<th>cGMP:</th>
<th></th>
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<tbody>
<tr>
<td>Tablets</td>
<td>EER was found acceptable on October 02, 1998.</td>
<td></td>
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<thead>
<tr>
<th>BIO:</th>
<th>VALIDATION:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Bio study was acceptable by C.Kim on February 23, 1999.</td>
<td>The DS and DP are not covered by monographs in the USP. Method verifications performed by the FDA District Laboratory were satisfactory.</td>
<td></td>
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<thead>
<tr>
<th>STABILITY:</th>
<th>LABELING:</th>
<th></th>
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<tbody>
<tr>
<td>The firm has provided satisfactory 3 months accelerated and 24 months room temperature stability data for both strengths (25 mg and 100 mg tablets). The stability data support an expiration period of 24 months.</td>
<td>Labeling was found acceptable by L. Golson on March 24, 1999.</td>
<td></td>
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</tbody>
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<thead>
<tr>
<th>STERILIZATION VALIDATION (If applicable):</th>
<th>SIZE OF BIO BATCH (Firm’s source of NDS ok?):</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>Size of the bio batch for 25 mg and 100 mg is tablets. The drug substance was manufactured by and found acceptable by NBT on April 19, 1999.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIZE OF STABILITY BATCHES (If different from bio batch, were they Manufactured via the same process?):</th>
</tr>
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<tbody>
<tr>
<td>Size of stability batch is same as that of the bio batch.</td>
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<thead>
<tr>
<th>PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:</th>
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<tbody>
<tr>
<td>Size of the proposed production batch size for 25 mg and 100 mg is Tablets. The manufacturing process is identical to the exhibit batch.</td>
</tr>
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<thead>
<tr>
<th>Signature of chemist:</th>
<th>Signature of supervisor:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neeru B. Takiar</td>
<td>Paul Schwartz, Ph.D.</td>
</tr>
</tbody>
</table>

\[\text{Signature with dates: N/A 5/13/99 and Paul Schwartz, Ph.D. 5/19/99}\]
OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMISTRY REVIEW NO. #  2

2. ANDA #  75-417

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:
Reference listed drug:
Clozaril® Tablets, 25 mg & 100 mg
NDA Nos: N19758 001 and 002 (Sep 26, 1989)
Manufacturer: Novartis Pharmaceuticals Corporation.
The firm certifies that, in its opinion and to best of its
knowledge, Clozaril® is not covered by any patents or exclusivity
provisions.

5. SUPPLEMENT(s):  N/A

6. PROPRIETARY NAME:  N/A

7. NONPROPRIETARY NAME:  Clozapine

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

9. AMENDMENTS AND OTHER DATES:
Applicant:
07-16-1998  Date of application
02-12-1999  Response to Fax deficiency letter dated 1/19/99
04-06-1999  Response to telecon - submitted information
FDA:
07-17-1998  Acceptable for filling
08-11-1998  ANDA Acceptance letter
01-19-1999  Deficiency letter - Facsimile
04-06-1999  Telecon

10. PHARMACOLOGICAL CATEGORY:  For management of severely ill
    schizophrenic patients.

11. Rx or OTC:  Rx
12. RELATED IND/NDA/DMF(s):
   DMF# Type   Product               DMF holder
   Clozapine
   Stear-O-Wet M
   75 cc Bottles
   Resin
   200 cc Bottles
   Resin
   CR Closure
   Closure
   Polypropylene
   Petrothene®
   Cotton
   Cotton

13. DOSAGE FORM: Tablet

14. POTENCY: 25 mg and 100 mg

15. CHEMICAL NAME AND STRUCTURE:
   Clozapine. 5H-Dibenzo[b,e][1,4]diazepine, 8-chloro-11-(4-methyl-
   1-piperazinyl)-. C₁₈H₁₉ClN₄. 326.83. 5786-21-0. Sedative.
   USAN 1993, page 164.

16. RECORDS AND REPORTS: N/A

17. COMMENTS: N/A

18. CONCLUSIONS AND RECOMMENDATIONS: The application is approvable.

19. REVIEWER: Neeru B. Takiar
    Endorsed by P. Schwartz, Ph.D.
    DATE COMPLETED: 04/19/99
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secret and/or

confidential

commercial

information

Chem. Review # 2
38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-417          APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Clozapine Tablets, 25 mg and 100 mg

The deficiencies presented below represent Facsimile deficiencies.

A. Deficiencies:

Raw Material Controls - Active Ingredient:

1. Please perform identification test A (melting point), heavy metals, tapped bulk density, and testing as listed on the manufacturer's certificate of analysis. Establish the limits and provide them on your revised COA for the drug substance, clozapine. Also, revise your specification for assay per manufacturer's COA % and include a complete name for CDD.

Manufacturing and Processing:

2. Please clarify the size and number of samples that will be collected for blend uniformity testing. Also include the percent RSD value in your specification for the blend samples of clozapine tablets, 25 mg and 100 mg.

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

1. The FDA district laboratory will be performing methods validation on the new drug substance and the finished dosage form.

Sincerely yours,

[Signature]

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMISTRY REVIEW NO.#  1

2. ANDA #  75-417

3. NAME AND ADDRESS OF APPLICANT:
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781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

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knowledge, Clozaril® is not covered by any patents or exclusivity
provisions.

5. SUPPLEMENT(s): N/A

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7. NONPROPRIETARY NAME: Clozapine

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9. AMENDMENTS AND OTHER DATES:
Applicant:
07-16-1998 Date of application

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08-11-1998 ANDA Acceptance letter

10. PHARMACOLOGICAL CATEGORY: For management of severely ill
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11. Rx or OTC: Rx

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    Stear-O-Wet M
    75 cc Bottles
Resin
200 cc Bottles
Resin
CR Closure
Closure
Polypropylene
Petrothene®
Cotton
Cotton

13. **DOSAGE FORM:** Tablet

14. **POTENCY:** 25 mg and 100 mg

15. **CHEMICAL NAME AND STRUCTURE:**
Clozapine. 5H-Dibenzo[b,e][1,4]diazepine, 8-chloro-11-(4-methyl-1-piperazinyl)-. C_{18}H_{19}ClN_{4}. 326.83. 5786-21-0. Sedative. USAN 1993, page 164.

![Chemical Structure](image)

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
The following sections are **NOT SATISFACTORY:**
23. Raw material - active ingredient
26. Manufacturing and Processing
The following Section is **PENDING:**
32. Labeling

18. **CONCLUSIONS AND RECOMMENDATIONS:**
The application is not approvable. A Fax NA will issue.

19. **REVIEWER:** Neeru B. Takiar
   **DATE COMPLETED:** 11/30/98
   Endorsed by P. Schwartz, Ph.D.
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pages of trade secret and/or confidential commercial information

Chem Review #1