CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21174

CHEMISTRY REVIEW(S)
Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 21-174  CHEM. REVIEW#: 1  REVIEW DATE: Apr.28, 2000

SUBMISSION TYPE
Original
BC
AC

DOCUMENT DATE
Oct. 29, 1999
Mar. 15, 2000
Apr. 13, 2000

CDER DATE
Oct. 29, 1999
Mar. 16, 2000
Apr. 14, 2000

ASSIGNED DATE
Nov. 4, 1999
Mar. 16, 2000
Apr. 14, 2000

NAME AND ADDRESS OF APPLICANT:
Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

DRUG PRODUCT NAMES:
Proprietary: Mylotarg™ for Injection
gemtuzumab ozogamicin

Nonproprietary/USAN: N/A

Code Name/#: 1-P

Chem. Type/Ther. Class

PHARMACOL. CATEGORY/INDICATION:
Treatment of relapsed acute myeloid leukemia (AML)

DOSAGE FORM/STRENGTHS:
Sterile powder for injection 5 mg/vial

ROUTE OF ADMINISTRATION:
Intravenous

MANUFACTURER:
A. Drug Substance
Wyeth-Ayerst Pharmaceuticals
Lederle Pharmaceuticals Division
401 N, Middletown Rd.
Pearl River, NY 10965-1299

B. Drug Product
Wyeth-Ayerst Pharmaceuticals
Lederle Parenterals, Inc.
Division of American Cyanamid Company
Km 9.7 65th Infantry Ave.
Carolina, Puerto Rico, 00987

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:
P67.6-Nac-gamma calicheamicin DMH AcBut conjugate
hP67.6-C11H40O23N2S3I

Average Molecular Mass: 154 kDa

n, average loading of calicheamicin derivative on antibody (hP67.6), is 2 to 3 moles/mole
## SUPPORTING DOCUMENTS:

<table>
<thead>
<tr>
<th>Document Type</th>
<th>Description</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF</td>
<td>N-Ac-calicheamicin</td>
<td>Type II</td>
<td>Reviewed by C. Liang, deficiency letter sent.</td>
</tr>
<tr>
<td>DMF</td>
<td>N-Ac-calicheamicin derivative</td>
<td>Type II</td>
<td>Reviewed by C. Liang, found adequate.</td>
</tr>
<tr>
<td>DMF</td>
<td>P67.6 Antibody</td>
<td>Type II</td>
<td>Reviewed by M. Shapiro, found adequate.</td>
</tr>
<tr>
<td>DMF</td>
<td>Vial</td>
<td>Type III</td>
<td>Reviewed by Dr. Paul Dietze (HFD-150) on 1/27/95 and R. Harapanhalli on 7/24/98 and is found to be acceptable.</td>
</tr>
<tr>
<td>DMF</td>
<td>Rubber Closure</td>
<td>Type III</td>
<td>Reviewed by M. Bennett on 7/19/96 and is found to be acceptable.</td>
</tr>
<tr>
<td>DMF</td>
<td>BioProcess Container</td>
<td>Type III</td>
<td>Reviewed by Stephanie Simek from CBER on 2/7/2000 and found acceptable.</td>
</tr>
</tbody>
</table>

## CONSULTS:

<table>
<thead>
<tr>
<th>Consult</th>
<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EER</td>
<td>Acceptable</td>
<td>Submitted on 11/10/99 and 12/3/99, found to be acceptable.</td>
</tr>
</tbody>
</table>

## METHODS VALIDATION

<table>
<thead>
<tr>
<th>Type</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Trademark (OPDRA)</td>
<td>Acceptable</td>
<td>Submitted on 1/6/2000</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Acceptable</td>
<td>Submitted on 11/4/99</td>
</tr>
<tr>
<td>CBER</td>
<td>Acceptable</td>
<td>Submitted on 11/10/99</td>
</tr>
<tr>
<td>Environmental Assessment</td>
<td>Categorical exclusion</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>

## REMARK/COMMENTS:

After reviewing the applicant's responses to our questions, the remaining outstanding issues were discussed in the teleconference held on 4/26/00. These issues were resolved based on the discussion occurred in the teleconference as...
well as the Phase 4 commitments that the applicant was willing to make. Please refer to the 4/26/00 meeting minutes. The overall acceptable recommendation for EES inspection for this NDA was received on 4/27/00. DMF [ ] is found adequate based on CBER reviewer's recommendation.

CONCLUSIONS AND RECOMMENDATIONS:
The NDA is recommended for approval from the CMC perspective.

Xiao Hong Chen, Ph.D., Review Chemist

Eric Duffy, Ph.D., Chemistry Team Leader

CC:
Orig. NDA 21-174
HFD-150 Division File
HFD-150/Xchen
HFD-150/CLiang
HFD-150/EDuffy
HFD-150/SBradley
HFD-810/Directors
Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 21-174  CHEM. REVIEW#: 1  REVIEW DATE: Apr. 25, 2000

SUBMISSION TYPE  DOCUMENT DATE  CDER DATE  ASSIGNED DATE

NAME AND ADDRESS OF APPLICANT:
Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

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1-P
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Reviewed by C. Liang
Deficiency letter sent.

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Rubber Closure Type III
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7/19/96 and is found to be
acceptable.

BioProcess Container Type III
Reviewed by Stephanie Simek
from CBER on 2/7/2000 and
found acceptable.

CONSULTS:

Consult Status Comments
EER Pending Submitted on 11/10/99 and
are

Methods Validation Pending Will be submitted after
the deficiencies have been
addressed by the applicant

Trademark (OPDRA) Acceptable Submitted on 1/6/2000

Microbiology Acceptable Submitted on 11/4/99

CBER Pending Submitted on 11/10/99

Environmental Assessment. Categorical
exclusion Acceptable

REMARK/COMMENTS:
The applicant has responded to our comments. Most of their responses are
satisfactory. However, there are still a few outstanding issues need to be
resolved before this application can be recommended for approval. In addition,
the overall recommendation for EES inspection is still pending. OC recommended withholding approval based on the testing site used by Eric and I spoke with the investigator, Thomas Arista on 4/25/00 regarding this facility. It seems that the firm is willing to take corrective action on 483 citation. In addition, CBER consult review for response to the deficiency letter regarding DMF.

CONCLUSIONS AND RECOMMENDATIONS:
The NDA is approvable provided that CMC deficiencies are addressed satisfactorily and consultative reviews are completed.

Xiao Hong Chen, Ph.D. Review Chemist

Eric Duffy, Ph.D.
Chemistry Team Leader

CC: Orig. NDA 21-174
HFD-150 Division File
HFD-150/Xchen
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Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

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SUBMISSION TYPE  DOCUMENT DATE  CDER DATE  ASSIGNED DATE

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BioProcess Container Type III
Review pending at CBER

CONSULTS:

Consult Status Comments
EER Pending Submitted on 11/10/99 and
are found to be acceptable.

Methods Validation Pending Will be submitted after
the deficiencies have been addressed by the applicant

Trademark (OPDRA) Pending Submitted on 1/6/2000

Microbiology Pending Submitted on 11/4/99

CBER Pending Submitted on 11/10/99

Environmental Assessment Categorical Acceptable

REMARK/COMMENTS:

For Drug Substance and Drug Product: There are a number of deficiencies related
to the drug substance as well as the pivotal intermediates described in the three
DMFs. The deficiencies will be conveyed to the applicant and the DMF holder.
These deficiencies should be addressed before this NDA can be approved. Total of
seven facilities were requested for inspection. Four of them are recommended as
acceptable. The other three are still pending. The microbiology, CBER and
trademark consults are still pending.
CONCLUSIONS AND RECOMMENDATIONS:
The NDA is approvable provided that CMC deficiencies are addressed satisfactorily and consultative reviews are completed.

\[1st\] 4/6/00
Xiao Hong Chen, Ph.D., Review Chemist

[Signature] 4/6/00
Eric Duffy, Ph.D.
Chemistry Team Leader

CC:
Orig. NDA 21-174
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HFD-810/Directors
Please See Chemistry Review for Environmental Assessment Review