

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21174

CHEMISTRY REVIEW(S)

APR 28 2000

Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 21-174

CHEM. REVIEW#: 1

REVIEW DATE: Apr.28,2000

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	Oct. 29, 1999	Oct. 29, 1999	Nov. 4, 1999
BC	Mar. 15, 2000	Mar. 16, 2000	Mar. 16, 2000
AC	Apr. 13, 2000	Apr. 14, 2000	Apr. 14, 2000

NAME AND ADDRESS OF APPLICANT:

Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101-8299

DRUG PRODUCT NAMES:

Proprietary:
Nonproprietary/USAN:
Code Name/#:
Chem. Type/Ther. Class

Mylotarg™ for Injection
gemtuzumab ozogamicin
N/A
1-P

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

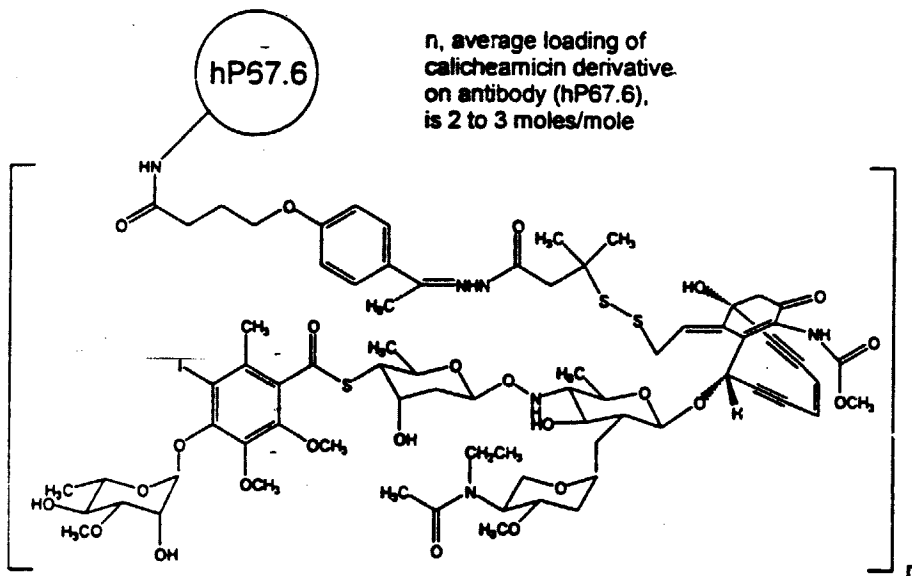
Wyeth-Ayerst Pharmaceuticals
Lederle Parenterals, Inc.
Division of American Cyanamid Company
Km 9.7 65th Infantry Ave.
Carolina, Puerto Rico, 00987

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

P67.6-Nac-gamma calicheamicin DMH AcBut conjugate

hP67.6-C₇₃H₉₆O₂₅N₅S₃I

Average Molecular Mass: 154 kDa



SUPPORTING DOCUMENTS:

DMF	N-Ac-calicheamicin Type II	Reviewed by C. Liang Deficiency letter sent.
DMF	N-Ac-calicheamicin Type II derivative	Reviewed by C. Liang and found adequate.
DMF	P67.6 Antibody	Type II Reviewed by M. Shapiro and found adequate.
DMF	Vial	Type III Reviewed by Dr. Paul Dietze (HFD-150) on 1/27/95 and R. Harapanhalli on 7/24/98 and is found to be acceptable.
DMF	Rubber Closure	Type III Reviewed by M. Bennett on 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:

<u>Consult</u>	<u>Status</u>	<u>Comments</u>
EER	Acceptable	Submitted on 11/10/99 and 12/3/99. are found to be acceptable.
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	Acceptable	Submitted on 11/10/99
Environmental Assessment.	Categorical exclusion	Acceptable

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.

ISI 4/28/00

Xiao Hong Chen, Ph.D., Review Chemist

ISI 4/28/00

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

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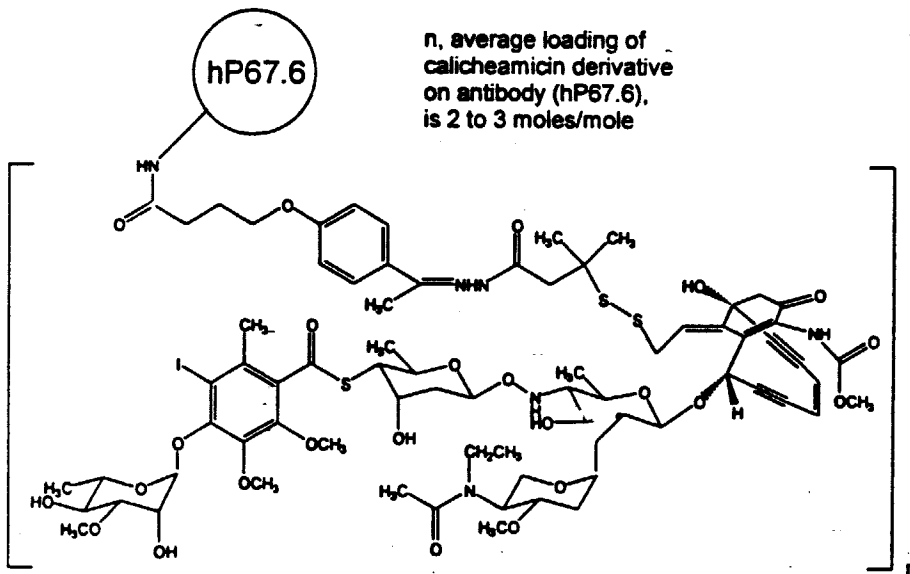
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Status
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Comments

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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.

ISI 4/26/00

Xiao Hong Chen, Ph.D. / Review Chemist.

ISI 4/26/00

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

APR 6 2000

Division of Oncology Drug Products
Review of Chemistry, Manufacturing and Controls

NDA #: 21-174

CHEM. REVIEW#: 1

REVIEW DATE: Apr. 4, 2000

SUBMISSION TYPE

Original

DOCUMENT DATE

Oct. 29, 1999

CDER DATE

Oct. 29, 1999

ASSIGNED DATE

Nov. 4, 1999

NAME AND ADDRESS OF APPLICANT:

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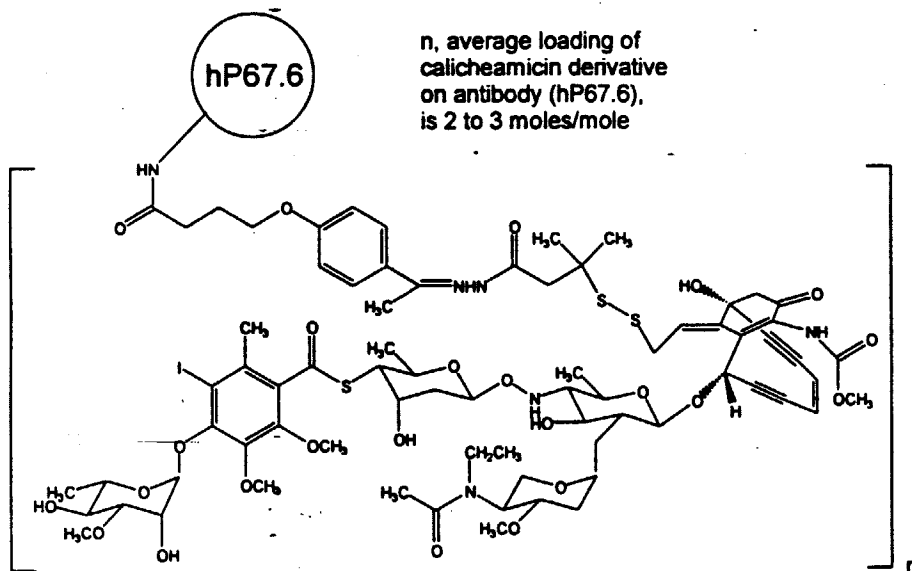
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	BioProcess Container	Type III Review pending at CBER

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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.

IS/ 4/6/00
Xiao Hong Chen, Ph.D., Review Chemist

IS/ 4/6/00
Eric Duffy, Ph.D.
Chemistry Team Leader

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HFD-150/EDuffy
HFD-150/SBradley
HFD-810/Directors

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**Please See Chemistry
Review
for Environmental
Assessment Review**