

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-954

CHEMISTRY REVIEW(S)

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

NDA #: 20-954

CHEM. REVIEW#: 5

REVIEW DATE: Feb. 1, 1999

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	Aug. 3, 1998	Aug. 4, 1998	Aug. 7, 1998
BC	Oct. 20, 1998	Oct. 21, 1998	Oct. 26, 1998
BC	Dec. 8, 1998	Dec. 9, 1998	Dec. 11, 1998
BC	Jan. 15, 1999	Jan. 15, 1999	Jan. 15, 1999
BC	Jan. 25, 1999	Jan. 25, 1999	Jan. 25, 1999
Fax Amendment	Jan. 28, 1999	Jan. 28, 1999	Jan. 28, 1999

NAME AND ADDRESS OF APPLICANT:

Orphan Medical, Inc.
13911 Ridgedale drive, Suite 475
Minnetonka, MN 55305

DRUG PRODUCT NAMES:

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

Busulfex™ Injection
Busulfan
CAS 55-98-1
3-P

PHARMACOL. CATEGORY/INDICATION:

Use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation...

DOSAGE FORM/STRENGTHS:

10mL (6mg/mL)

ROUTE OF ADMINISTRATION:

Intravenous

MANUFACTURER:

A. Drug Substance

Ash Stevens, Inc.
5861 John C. Lodge Freeway
Detroit, MI 48202

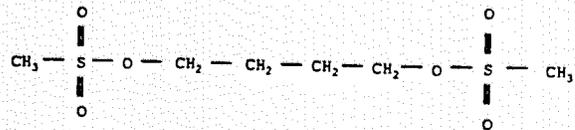
B. Drug Product

Ben Venue Laboratories, Inc.
270 Northfield road
P.O. Box 46568
Bedford, OH 44146-0568

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

1,4 -butanediol-dimethanesulfonate esters

C₆H₁₄O₆S₂, MW = 246.31



SUPPORTING DOCUMENTS:

DMF

Acceptable

DMF

acceptable

DMF

Acceptable

DMF

10/19/98
 rev
 acceptable.

DMF

Acceptable
 1/1/99

DMF

acceptable.

DMF

na:

IND

acceptable.

CONSULTS:**Consult**
EER**Status**
Complete**Comments**Acceptable recommended by
the Office of Compliance
on 10/19/98

Methods Validation

Pending

Will be submitted after
the NDA approval

Trademark

Complete

Acceptable
Refer to Dr. Dan Boring's
email dated 1/21/99

Pharma/Tox

Complete

Acceptable
Reviewed by Dr. McGuinn
on 2/1/99

Microbiology

Complete

Acceptable
Reviewed by Dr. Brenda
Uratani on 1/13/99

Environmental Assessment.

Categorical
exclusion

Acceptable

REMARK/COMMENTS:

The drug substance and the drug product deficiencies have been addressed in the fax amendment dated Jan. 29, 1999. There are a number of Phase IV commitment that the applicant has furnished.

CONCLUSIONS AND RECOMMENDATIONS:

This NDA is recommended for approval.

ISI

1/28/99

Xiao Hong Chen, Ph.D., Review Chemist

ISI

1/29/99

Nallaperumal Chidambaram, Ph.D.
Review Chemist

ISI

1/29/99

Liang Zhou, Ph.D.
Chemistry Team Leader

- CC:
- Orig. NDA 20-954
- HFD-150 Division File
- HFD-150/XChen
- HFD-150/NChidambaram
- HFD-150/LZhou
- HFD-150/PGuinn
- HFD-810/Directors

DMF

acceptable.

DMF

Acceptable

DMF

acceptable.

DMF

IND

acceptable.

CONSULTS:

Consult
EER

Status
Complete

Comments
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the Office of Compliance
on 10/19/98

Methods Validation

Pending

Will be submitted after
the deficiencies have been
addressed by the applicant

Trademark

Complete

Acceptable
Refer to Dr. Dan Boring's
email dated 1/21/99

Pharma/Tox

Pending

Submitted on 9/21/98

Microbiology

Complete

Acceptable
Reviewed by Dr. Brenda
Uratani on 1/13/99

Environmental Assessment.

Categorical
exclusion

Acceptable

REMARK/COMMENTS:

There are a number of deficiencies related to the drug substance and the drug product. The deficiencies were conveyed to the applicant before and during three teleconferences that were held on Jan. 22 and 27, 1999 to discuss the CMC comments and deficiencies. The applicant has agreed to our concerns and deficiencies, they will submit their responses to the Agency.

CONCLUSIONS AND RECOMMENDATIONS:

This NDA cannot be approved until their responses are received and reviewed.

ISI 1/28/99
Xiao Hong Chen, Ph.D., Review Chemist

ISI 1 01/29/99
Nallaperumal Chidambaram, Ph.D.
Review Chemist

ISI 1/29/99
Liang Zhou, Ph.D.
Chemistry Team Leader

CC:
Orig. NDA 20-954
HFD-150 Division File
HFD-150/XChen
HFD-150/NChidambaram
HFD-150/LZhou
HFD-150/PGuinn
HFD-810/Directors

DMF

acceptable.

Acceptable

DMF

acceptable.

DMF

IND

CONSULTS:**Consult**

EER

Status

Complete

Comments

Acceptable recommended by the Office of Compliance on 10/19/98

Methods Validation

Pending

Will be submitted after the deficiencies have been addressed by the applicant

Trademark

Pending

Submitted on 1/7/97

Statistics

Pending

Submitted on 9/10/98

Pharma/Tox

Pending

Submitted on 9/21/98

Microbiology

Complete

Acceptable
Reviewed by Dr. Brenda Uratani on 1/13/99

Environmental Assessment.

Categorical
exclusion

Acceptable

REMARK/COMMENTS:

Drug Substance: There are a number of deficiencies related to the drug substance. The deficiencies are conveyed to the applicant and they should be addressed before this NDA can be approved.

Drug Product: There are quite a few deficiencies related to drug product section. They need to be addressed before approval is recommended.

CONCLUSIONS AND RECOMMENDATIONS:

This NDA cannot be approved until all the CMC deficiencies are satisfactorily addressed and pending consults are completed.

/S/

1/20/99

Xiao Hong Chen, Ph.D., Review Chemist

/S/

1/20/99

Nallaperumal Chidambaram, Ph.D.
Review Chemist

/S/

1/21/99

Liang Zhou, Ph.D.
Chemistry Team Leader

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- HFD-150/LZhou
- HFD-150/PGuinn
- HFD-810/Directors

acceptable.

DMF

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acceptable.

DMF

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CONSULTS:

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EER	Complete	Acceptable recommended by the Office of Compliance on 10/19/98
Methods Validation	Pending	Will be submitted after the deficiencies have been addressed by the applicant
Trademark	Pending	Submitted on 1/7/97
Statistics	Pending	Submitted on 9/10/98
Pharma/Tox	Pending	Submitted on 9/21/98
Microbiology	Pending	Submitted on 8/18/98
Environmental Assessment.	Categorical exclusion	Acceptable

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CONCLUSIONS AND RECOMMENDATIONS:

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151

1/8/99

Xiao Hong Chen, Ph.D., Review Chemist

/S/

1/8/98

Mallaperumal Chidambaram, Ph.D.
Review Chemist

/S/

1/8/99

Liang Zhou, Ph.D.
Chemistry Team Leader

CC:
Orig. NDA 20-954
HFD-150 Division File
HFD-150/XChen
HFD-150/NChidambaram
HFD-150/LZhou
HFD-150/PGuinn
HFD-810/Directors

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acceptable.

DMF

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EER

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Comments

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Methods Validation

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Submitted on 1/7/97

Statistics

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Submitted on 9/10/98

Pharma/Tox

Pending

Submitted on 9/21/98

Microbiology

Pending

Submitted on 8/18/98

Environmental Assessment.

Categorical exclusion

Acceptable

REMARK/COMMENTS:

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CONCLUSIONS AND RECOMMENDATIONS:

This NDA cannot be approved until all the CMC deficiencies are satisfactorily addressed and pending consults are completed.

151

11/30/95

Xiao Hong Chen, Ph.D., Review Chemist

151

11/30/98

Nallaperumal Chidambaram, Ph.D.
Review Chemist

/S/

12/1/98

Liang Zhou, Ph.D.
Chemistry Team Leader

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HFD-150/XChen
HFD-150/NChidambaram
HFD-150/LZhou
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