PUVA therapy

- This therapy is not proven effective for children with acute GHVD. May be considered for refractory disease, especially if it is chronic skin GVHD.
- Patients receive 0.6 mg/kg of Psoralen 2 hours prior to exposure to UVA light. Usual frequency is 3 - 4 times per week for several weeks.

Plaquenil

- Plaquenil is a 4-aminoquinolone antimalarial drug used to treat autoimmune disorders. It is being studied in phase I/II trials in the treatment of progressive acute and chronic GVHD. It acts by reducing the secretion of IL-1, IL-6 and TNF.
- Starting dose for chronic GVHD is 800 mg/day po for adults and 12 mg/kg/day for children less than 50 kg. The dose may be divided bid. Max dose for adults is 1000mg/day. The acute GVHD protocol is being revised.
- Side effects include: ocular toxicity with prolonged use, nausea, diarrhea, rash and photosensitivity.
- Plaquenil levels are drawn as per protocol, usually at. A therapeutic level is between 5 - 15 µml. It takes up to four weeks to get a therapeutic level.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont Office Complex - Two
1451 Rockville Pike, Rockville, MD 20852

To:	Carol Curme	**From:**	Sean Bradley
Fax:	952-541-9209	**Fax:**	301-827-4590
Phone:	952-513-6974	**Phone:**	301-594-5750
Pages, including cover sheet:	1	**Date:**	April 25, 2002
Re:	NDA 20-954/S-004 Clinical Info Request #9		APR 29 2002

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Carol –

Following are two clinical requests:

1. Please provide results of the skin biopsies obtained in the following patients with GVHD: 03501; 09502; 10502

2. The modified Seattle criteria for GVHD listed in the protocol define grade for each organ but not overall grading for an individual patient. Dataset GVHD includes a column listing overall grade. Please clarify how the assessment of overall GVHD grade was made.

3. The approach (or approaches) used in the prophylaxis and treatment of acute GVHD is not apparent. If this information is provided in the submission, please specify its location. If not, please provide the information. We recognize that different approaches may have been used at different institutions.

Please provide your response to this request via fax followed by a hard-copy submission to the NDA.

Thank you for your prompt attention to our request. If you have any questions regarding this transmission, please contact me at 301-594-5750.

Sean Bradley, R. Ph.
/S/
Regulatory Project Manager

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Dianne Spillman
Fax:	(952) 541-9209	**Fax:**	(301) 594-0499
Phone:	(952) 513-6974	**Phone:**	(301) 594-5746
Pages (including cover):	1	**Date:**	April 23, 2002
Re:	NDA 20-954 / S-004 – Clinical Info Request #8		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Carol – Following is a clinical request.

Regarding your table 12.2 describing adverse events occurring in > or = 15% of patients in OMC-BUS-5, FDA analysis of COSTART events as listed in the AEALL dataset results in numbers of patients which are different than those you listed for the following COSTART terms:

Term	OMI number	FDA number
tachycardia	13	14
anorexia	23	24
anemia	22	23
hypokalemia	15	16
lung disease	6	7
pneumonia	4	5
graft vs hostd	6	5
rectal dis	10	11

Please clarify these apparent discrepancies by providing a response to this request via fax, followed by a hard-copy submission to the NDA. Thank you.

Regards,

Dianne Spillman
Project Manager, Oncology Drugs

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Dianne Spillman
Fax:	(952) 541-9209	**Fax:**	(301) 594-0499
Phone:	(952) 513-6974	**Phone:**	(301) 594-5746
Pages (including cover):	1	**Date:**	April 22, 2002
Re:	NDA 20-954 / S-004 – Clinical Info Request #7		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Carol –

Following are two clinical requests.

1. We received your April 16, 2002 e-mail response to our clinical information request #5 dated April 9, 2002.

   Please provide results of the liver biopsy and doppler ultrasound studies for patient #23-501. These were not provided in the original submission and are not a part of the case report form you sent via e-mail although the form indicates that a liver biopsy was done.

2. Although the study report states that 22 of 24 patients were infused with cells from 6/6 HLA matched sibling donors, one with cells from a 5/6 matched sibling, and one from a 6/6 matched first cousin, the source of cells (sibling or other) and degree of match (5,6 or other) is not provided in appendix 16.2.21 nor in the BMT dataset for a number of patients. Please provide this information for the following patients : 01501, 03501, 08501, 08502, 09501, 09503, 10501, 10502.

Please provide a response to this request via fax, followed by a hard-copy submission to the NDA. Thank you.

Regards,

/S/

Dianne Spillman
Project Manager, Oncology Drugs

☑ Checked in DFS 4-22-02... NDA 20-954 / SE2-004
cc: R.Dagher/D.Griebel
c:\...\20954\S-004\faxes\020422m-fax-ir7-fu#5&new.doc

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/s/

Dianne Spillman
4/22/02 05:41:59 PM
CSO

DUPLICATE

ORPHAN MEDICAL

NDA SUPP AMEND
SE2-004
PU

April 22, 2002

Richard Pazdur, M.D.
Division of Oncology Drug Products [HFD-150]
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II
1451 Rockville Pike
Rockville, MD 20852
Ph: (301) 827-1537

Subject: **Busulfex® (busulfan) Injection; NDA #20-954/S-004**
Response to FDA's Facsimiles dated April 9 and 10, 2002
Regarding the Supplement of Pediatric Information;
User Fee #3,396, Orphan Designation #94-830

Dear Dr. Pazdur:

Orphan Medical, Inc. submits this response to the FDA's question related to the supplement of pediatric information that was presented in the facsimile from the FDA, dated April 9 and 10, 2002. Copies of these facsimiles are included in Attachment 1. Orphan Medical's response to the FDA's question is presented on the following page.

Sincerely,

Carol S. Curme, J.D., RAC
Senior Manager of Regulatory Affairs
(952) 513-6974

cc: Dayton Reardan, Ph.D., RAC, Vice-President of Regulatory Affairs

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Dianne Spillman
Fax:	(952) 541-9209	**Fax:**	(301) 594-0499
Phone:	(952) 513-6974	**Phone:**	(301) 594-5746
Pages (including cover):	1	**Date:**	April 10, 2002
Re:	NDA 20-954 / S-004 – Clinical Info Request #6		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Carol –

Following is a clinical request.

> Please clarify why chimersim data is not available for patients 10503 and 08501. Was no data collected or was data collected and deemed uninterpretable?'

Please provide a response to this request via fax, followed by a hard-copy submission to the NDA. Thank you.

Regards,

/S/

Dianne Spillman
Project Manager, Oncology Drugs

☑ Checked in DFS 4-10-02... NDA 20-954 / SE2-004
cc: R.Dagher/D.Griebel
c:\...\20954\S-004\faxes\020410m-fax-ir6.doc

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/s/

Dianne Spillman
4/10/02 05:43:39 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Dianne Spillman
Fax:	(952) 541-9209	**Fax:**	(301) 594-0499
Phone:	(952) 513-6974	**Phone:**	(301) 594-5746
Pages (including cover):	1	**Date:**	April 9, 2002
Re:	NDA 20-954 / S-004 – Clinical Info Request #5		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Carol –

Following is a clinical request.

Please provide a hard copy of the case report form for patient 23-501.

Please provide a response to this request via fax, followed by a hard-copy submission to the NDA. Thank you.

Regards,

Dianne Spillman
Project Manager, Oncology Drugs

☑ Checked in DFS 4-9-02... NDA 20-954 / SE2-004
cc: R.Dagher/D.Griebel
c:\...\20954\S-004\faxes\020409m-fax-ir5.doc

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/s/

Dianne Spillman
4/9/02 05:04:57 PM
CSO

RECORD OF TELEPHONE CONVERSATION

NDA #: 20-954/SE2-004

DATE: March 13, 2002

PRODUCT NAME: Busulfex (busulfan) injection

APPLICANT: Orphan Medical, Inc.

TELEPHONE #: (952) 513-6974

Conversation Held With: Carol Curme, J.D., RAC
Sr. Mgr., Reg. Affairs

SUBJECT: Pediatric Exclusivity

I called Ms. Curme and informed her that the Pediatric Exclusivity Board determined that they would grant pediatric exclusivity to Busulfex. This exclusivity will attach to any existing exclusivities and patents that Orphan Medical currently has, including the dosage formulation exclusivity which expired on Feb 4, 2002. They will receive no other notification regarding granting the pediatric exclusivity. However, this information will be available on the Pediatric Web page in a few days and the next monthly update of the Orange Book.

Ms. Curme was happy to hear the news and thanked me for the information.

{See appended signature page}

Dianne Spillman, Project Manager

☑ Checked in DFS 3-13-02...NDA 20-954/SE2-004
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/s/

Dianne Spillman
3/13/02 09:33:18 AM
CSO

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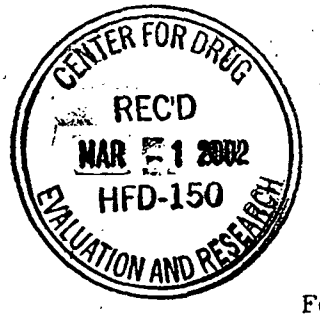
ORPHAN MEDICAL



SE2-004
BZ

February 25, 2002

Richard Pazdur, M.D.
Division of Oncology Drug Products [HFD-150]
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II
1451 Rockville Pike
Rockville, MD 20852
Ph: (301) 827-1537

Subject: Busulfex® (busulfan) Injection; NDA #20-954/S-004
Response to FDA's Facsimile dated February 21, 2002
Regarding the Supplement of Pediatric Information;
Categorical Exclusion from Requirement of an
Environmental Assessment;
User Fee #3,396, Orphan Designation #94-830

Dear Dr. Pazdur:

Orphan Medical, Inc. submits this response to the FDA's question related to the supplement of pediatric information as presented in the facsimile from the FDA, dated February 21. A copy of this facsimile is included in Attachment 1. Orphan Medical's response to the FDA's question is presented on the following page.

Also included in this response is the request for categorical exclusion from the requirement to prepare an environmental assessment. The request for categorical exclusion is included in Attachment 2.

Sincerely,

Carol S. Curme

Carol S. Curme, J.D., RAC
Senior Manager of Regulatory Affairs
(952) 513-6974

cc: Dayton Reardan, Ph.D., RAC, Vice-President of Regulatory Affairs

R:\Busulfan\Pediatric Supp\postsupp\BUSPED41 OF 2

RESPONSE TO THE FDA'S QUESTION

Facsimile dated February 21, 2002
FDA's Request: Please clarify what is meant by 'N' under column 'infused' in clinical dataset BMT for patients 04502 and 14501, especially since all 24 patients appear to have received busulfan/cytoxan and stem cell infusions.

RESPONSE:

The meaning of the entry "infused" in the clinical dataset BMT refers to whether the marrow was infused without a filter. Both patients 04502 and 14501 had stem cell infusions with a filter, and therefore, the response 'N' was provided under this entry. This information can be readily found by accessing the corresponding page of the Case Report Form for the entry "infused" per the following file path: n11CRT/datasets/OMC-BUS-5/define.pdf. In the first table titled "Datasets for Study OMC-BUS-5," click on hyperlink for "BMT" under the column heading "Dataset."

ORPHAN MEDICAL

February 25, 2002

Richard Pazdur, M.D.
Division of Oncology Drug Products [HFD-150]
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II
1451 Rockville Pike
Rockville, MD 20852
Ph: (301) 827-1537

SUBJECT: Busulfex® (busulfan) Injection, NDA #20-954
Efficacy Supplement S-004
Request for Categorical Exclusion from Requirement of an Environmental Assessment

Dear Dr. Pazdur:

The requested action, approval of the efficacy supplement to Busulfex® (busulfan) Injection (NDA 20-954/S-004), qualifies for a categorical exclusion from the requirement of preparing and filing an environmental assessment under 21 CFR 25.31(b).

The subject of the proposed action will not significantly affect the quality of the human environment and meets the requirements for a categorical exclusion from submitting and environmental assessment per 21 CFR 25.31(b). This action may increase the use of the active moiety, but estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. To Orphan Medical's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

Sincerely,

Carol S. Curme

Carol S. Curme, J.D., RAC
Senior Manager of Regulatory Affairs
Phone: (952) 513-6974

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Dianne Spillman
Fax:	(952) 541-9209	**Fax:**	(301) 594-0499
Phone:	(952) 513-6974	**Phone:**	(301) 594-5746
Pages (including cover):	1	**Date:**	February 21, 2002
Re:	NDA 20-954 / S-004 – Clinical Info Request #4		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Carol –

Following is a clinical request.

> Please clarify what is meant by 'N' under column 'infused' in clinical dataset BMT for patients 04502 and 14501, especially since all 24 patients appear to have received busulfan/cytoxan and stem cell infusions.

Please provide a response to this request via fax, followed by a hard-copy submission to the NDA. Thank you.

Regards,

Dianne Spillman
Project Manager, Oncology Drugs

☑ Checked in DFS 2-21-02... NDA 20-954 / SE2-004
cc: R.Dagher/D.Griebel
c:\...\20954\S-004\faxes\020221m-fax-ir4.doc

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/s/

Dianne Spillman
2/21/02 04:23:07 PM
CSO

ORPHAN MEDICAL

DUPLICATE

NDA SUPPLEMENT
SE2-004
BM

February 15, 2002

Richard Pazdur, M.D.
Division of Oncology Drug Products [HFD-150]
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II
1451 Rockville Pike
Rockville, MD 20852
Ph: (301) 827-1537

Subject: Busulfex® (busulfan) Injection; NDA #20-954/S-004
Response to FDA's Facsimile dated February 15, 2002 regarding the supplement of pediatric information
User Fee #3,396, Orphan Designation #94-830

Dear Dr. Pazdur:

Orphan Medical, Inc. submits this response to the FDA's question, in a facsimile dated February 15, 2002, related to the supplemental New Drug Application to provide pediatric information and request revisions to current labeling. A copy of this facsimile is included in Attachment 1.

The response to the FDA's question is presented on the following page.

Sincerely,

Carol S. Curme

Carol S. Curme, J.D., RAC
Senior Manager of Regulatory Affairs
(952) 513-6974

cc: Dayton Reardan, Ph.D., RAC, Vice-President of Regulatory Affairs

RESPONSE TO THE FDA'S QUESTION

Facsimile dated February 15, 2002

FDA's Request: Clarification on the apparent discrepancies between the distribution of hematologic diseases listed in PASTDIAGN and Appendix 16.2.5, and that described in the study report synopsis in Section 8.5.3.

RESPONSE: The distribution of diseases described in Appendix 16.2.5 (PASTDIAGN) and Section 8.5.3 are different because they list diagnoses made during two different points in time. Both of these points in time are captured in the Appendices 16.2.5 and 16.2.6 (see below), representing prior medical disease history (past diagnosis) and current disease/diagnosis at enrollment.

16.2.5: Pretreatment Evaluation: Past Diagnosis (corresponding to dataset "Pastdiag")

16.2.6: Pretreatment Evaluation: Current Disease Status (cross reference in-text Table 11.1 and dataset "Ptcurr")

In three patients, a change in diagnosis from past history versus diagnosis at enrollment occurred (#09-501, #09-503, #15-501). In two of these patients, a secondary malignancy developed (#09-501, #09-503). These changes in diagnoses are presented in detail in Table 1.

Table 1 Diagnoses from past history versus enrollment

Patient No.	Past Diagnosis Appendix 16.2.5	Current Diagnosis Appendix 16.2.6*	In-text Table 11.1*
09-501	Wilm's tumor	MDS	MDS (RAEBT); secondary malignancy; previously treated for Wilm's tumor
09-503	ALL, T-cell	MDS	New disease; secondary malignancy; previously treated for ALL and T-cell leukemia
15-501	MDS	AML	AML; disease progression from MDS

* Current diagnosis was confirmed prior to study enrollment.

Therefore, no discrepancy exists between the synopsis and the data listings.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Dianne Spillman
Fax:	(952) 541-9209	**Fax:**	(301) 594-0499
Phone:	(952) 513-6974	**Phone:**	(301) 594-5746
Pages (including cover):	1	**Date:**	February 15, 2002
Re:	NDA 20-954 / S-004 – Clinical Info Request #3		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Carol –

Following is a clinical request.

In addition to the information provided in your fax of 2/14/02, dataset PASTDIAGN and appendix 16.2.5 indicate the following distribution of hematologic diagnoses :

AML 7, ALL 3, MDS 1,CML 1, JCML 2, one additional patient with a malignant condition had wilms tumor.

However, the study report synopsis section 8.5.3 Patient characteristics describes 8 patients with AML, 2 with ALL, 2 with MDS, 2 with JCML, and 1 with CML. There is no mention of the patient with wilms tumor.

Please clarify these apparent discrepancies.

Please provide a response to this request via fax, followed by a hard-copy submission to the NDA. Thank you.

Regards,

Dianne Spillman
Project Manager, Oncology Drugs

☑ Checked in DFS 2-15-02... NDA 20-954 / SE2-004
cc: R.Dagher/D.Griebel
c:\...\20954\S-004\faxes\020215m-fax-ir3.doc

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/s/

Dianne Spillman
2/15/02 01:44:08 PM
CSO

ORPHAN MEDICAL

DUPLICATE

NDA SUPP AMEND
SE2-004
BZ

February 14, 2002

Richard Pazdur, M.D.
Division of Oncology Drug Products [HFD-150]
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II
1451 Rockville Pike
Rockville, MD 20852
Ph: (301) 827-1537

Subject: Busulfex® (busulfan) Injection; NDA #20-954/S-004
Response to FDA's Facsimiles dated February 8 & 13, 2002 regarding the supplement of pediatric information
User Fee #3,396, Orphan Designation #94-830

Dear Dr. Pazdur:

Orphan Medical, Inc. submits this response to the FDA's questions related to the supplement of pediatric information, that were included in 3 facsimiles from the FDA, dated February 8 and 13. Copies of these facsimiles are included in Attachment 1.

Responses to the FDA's questions are presented on the following page.

Sincerely,

Carol S. Curme

Carol S. Curme, J.D., RAC
Senior Manager of Regulatory Affairs
(952) 513-6974

cc: Dayton Reardan, Ph.D., RAC, Vice-President of Regulatory Affairs

RESPONSES TO THE FDA'S QUESTIONS

Facsimile dated February 8, 2002
FDA's Request: The study report mentions that the study was conducted in 10 centers. However, appendix 16.1.3 lists only 8 investigators and their addresses. Please clarify this apparent discrepancy.

RESPONSE: Appendix 16.1.3, on pages 1867-1869 of the study report, lists 10 centers and their addresses. The sites listed include: 01, 02, 03, 04, 08, 09, 10, 14, 15 and 23. Therefore, a discrepancy does not exist between the text in the study report and Appendix 16.1.3.

Facsimile #1 dated February 13, 2002
FDA's Request:

RESPONSE:

Facsimile #2 dated February 13, 2002
FDA's Request: Please provide specific diagnoses for patient #14501 (row 11 of PASTDIAG. dataset) and #15501 (row 22 of PASTDIAG. Dataset) as these are not provided in the aforementioned dataset.

RESPONSE: Please excuse the omission of the specific diagnoses of these two patients. The past diagnoses for these two patients are:

Patient 14-501: chronic myelogenous leukemia
Patient 15-501: myelodysplastic syndrome

This information can also be found in Appendix 16.2.5 (Listing of Pre-Treatment Evaluation: Past Diagnosis) of the clinical study report for OMC-BUS-5. The diagnosis for Patient 15-501 changed to acute myelogenous leukemia just prior to treatment. The diagnosis for Patient 14-501 remained the same (i.e., CML).

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Dianne Spillman
Fax:	(952) 541-9209	**Fax:**	(301) 594-0499
Phone:	(952) 513-6974	**Phone:**	(301) 594-5746
Pages (including cover):	1	**Date:**	February 13, 2002
Re:	NDA 20-954 / S-004 – Clinical Info Request #2		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Carol –

Following is a clinical request.

> Please provide specific diagnoses for patient #14501 (row 11 of PASTDIAG. dataset) and #15501 (row 22 of PASTDIAG. dataset) as these are not provided in the aforementioned dataset.

Please provide a response to this request via fax, followed by a hard-copy submission to the NDA. Thank you.

Regards,

Dianne Spillman
Project Manager, Oncology Drugs

☑ Checked in DFS 2-13-02... NDA 20-954 / SE2-004
cc: R.Dagher/D.Griebel
c:\...\20954\S-004\faxes\020213m-fax-ir2.doc

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/s/

Dianne Spillman
2/13/02 04:17:11 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Dianne Spillman
Fax:	(952) 541-9209	**Fax:**	(301) 594-0499
Phone:	(952) 513-6974	**Phone:**	(301) 594-5746
Pages (including cover):	1	**Date:**	February 13, 2002
Re:	NDA 20-954 / S-004 – Clinical Pharmacology and Biopharmaceutic Info Request #2		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

- **Comments:**

Carol –

Please refer to our February 11, 2002 fax providing a list of requests from the clinical pharmacology and biopharmaceutic team. We also refer to your February 11, 2002 e-mail, sent at 6:47 p.m., providing instructions for accessing the Population Pharmacokinetics Report submitted in the sNDA.

Your e-mail addresses issues 1-4 and 6 of our February 11, 2002 fax; however, we ask that you clarify one additional point with regard to issue #5 in that fax. Glancing over the file, you seem to indicate that this is

Please clarify which s the final one you chose to analyze the data.

Please provide a response to this request via fax, followed by a hard-copy submission to the NDA. Thank you.

Regards,

Dianne Spillman
Project Manager, Oncology Drugs

☑ Checked in DFS 2-13-02... NDA 20-954 / SE2-004
cc: B.Booth/A.Rahman
c:\...\20954\S-004\faxes\020213b-fax-ir2.doc

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/s/

Dianne Spillman
2/13/02 01:08:31 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Dianne Spillman
Fax:	(952) 541-9209	**Fax:**	(301) 594-0499
Phone:	(952) 513-6974	**Phone:**	(301) 594-5746
Pages (including cover):	2	**Date:**	February 11, 2002
Re:	NDA 20-954 / S-004 – Clinical Pharmacology and Biopharmaceutic Info Request #1		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Carol –

The following page is a list of information requested by the clinical pharmacology and biopharmaceutic team.

Please provide a response to this request via fax, as appropriate, followed by a hard-copy submission to the NDA and/or a submission to the electronic document room. We would appreciate a response to this request before February 22, 2002. Thank you.

Regards,

Dianne Spillman
Project Manager, Oncology Drugs

☑ Checked in DFS 2-11-02... NDA 20-954 / SE2-004
cc: B.Booth/A.Rahman
c:\...\20954\S-004\faxes\020211b-fax-ir1.doc

INFORMATION REQUEST: CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Please submit the following items to the sNDA.

1. An overall population pK report that describes the patient population demographics, methods, results and study conclusions.

2. A report that describes your population pK model building efforts. This report should include your criteria for choosing your final model, the reason for the structural model chosen, and a description of how any covariates tested were included or eliminated. This latter item is often best summarized in a table that includes the minimum objective function (or other criteria) listed for each model assessed.

3. Definitions of the column headings for the NONMEM datafile.

4. The final NONMEM datafile, **if it is different** from the electronic file already submitted.

5. [redacted]

6. The NONMEM output file.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dianne Spillman
2/11/02 02:03:33 PM
CSO
Response requested by 2-22-02.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Carol Curme	**From:**	Dianne Spillman
Fax:	(952) 541-9209	**Fax:**	(301) 594-0499
Phone:	(952) 513-6974	**Phone:**	(301) 594-5746
Pages (including cover):	1	**Date:**	February 8, 2002
Re:	NDA 20-954 / S-004 – Clinical Info Request #1		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Carol –

Following is a clinical request.

> The study report mentions that the study was conducted in 10 centers. However, appendix 16.1.3 lists only 8 investigators and their addresses. Please clarify this apparent discrepancy.

Please provide a response to this request via fax, followed by a hard-copy submission to the NDA. Thank you.

Regards,

Dianne Spillman
Project Manager, Oncology Drugs

☑ Checked in DFS 2-8-02... NDA 20-954 / SE2-004
cc: R.Dagher/D.Griebel
c:\...\20954\S-004\faxes\020208m-fax-ir1.doc

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/s/

Dianne Spillman
2/8/02 05:56:54 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-954/S-004

PRIOR APPROVAL SUPPLEMENT

Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

Attention: Carol S. Curme, J.D., RAC
Senior Manager of Regulatory Affairs

Dear Ms. Curme:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Busulfex® (busulfan) injection

NDA Number: 20-954

Supplement Number: S-004

Review Priority Classification: Priority (P)

Date of Supplement: December 21, 2001

Date of Receipt: December 28, 2001

This supplement proposes the following change: revisions to the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the package insert to incorporate pediatric information on dosing, pharmacokinetics and safety.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 26, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 28, 2002.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Dianne Spillman, Regulatory Project Manager, at (301) 594-5746.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dianne Spillman
2/13/02 02:07:48 PM
signing for D.Pease

ORPHAN MEDICAL

SE4-004-BZ

January 11, 2002

Richard Pazdur, M.D.
Division of Oncology Drug Products [HFD-150]
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II
1451 Rockville Pike
Rockville, MD 20852
Phone: (301) 827-1537

Subject: **Busulfex® (busulfan) Injection; NDA #20-954**
User Fee #3,396, Orphan Designation #94-830

AMENDMENT: Labeling Supplement Requiring FDA Pre-Approval under 21 CFR 314.70(b)

SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Dear Dr. Pazdur:

Orphan Medical, Inc. submits this amendment to the labeling supplement for Busulfex® (busulfan) Injection that was submitted on December 21, 2001 in electronic format. The labeling supplement requested changes to the package insert for Busulfex to incorporate pediatric information on dosing, pharmacokinetics and safety. The supplement was submitted in response to the FDA's formal Written Request for pediatric information dated March 27, 2000, made pursuant to Section 505A of the FFDCA, and therefore, the deadline for submission was December 31, 2001.

Last week, Dr. Randy Levin (FDA/CDER) contacted me regarding the format of the electronic supplement and requested several changes to the submission (changes described in Attachment 1). Both Dr. Levin and I confirmed with the Division's Project Manager, Dianne Spillman, that the revised electronic submission could be submitted as an amendment if resubmitted within a reasonable time.

Orphan Medical requests that the FDA accept this submission as an amendment to the pediatric supplement, so that the company can obtain pediatric exclusivity per FDAMA.

The enclosed CDROM includes an electronic copy of the revised supplement, and the original 356h and cover letter. If you have any additional questions concerning the supplement or this amendment, please contact me directly.

Sincerely,

Carol S. Curme, J.D., RAC
Senior Manager of Regulatory Affairs
(952) 513-6974

cc: (cover letter only)
Dr. Marlene Haffner (Office of Orphan Products Development)
Gary Buehler, Office of Generic Drugs
Dayton Reardan, Ph.D., RAC, Vice-President of Regulatory Affairs

Requested Changes to the Electronic Submission

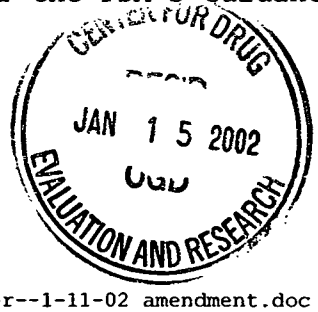
Request 1: Remove folders without any content. Remove N10Stat, and provide both clinical and statistical data in a folder called "clinstat." The Table of Contents (TOC) for the supplement should be the same level as the 356h.
Action Taken: The folders for Sections 4, 7, 9, 10, 15 and 17 were removed from the supplement. The folder name "8clinical" was retained. Renaming this folder to "clinstat" would be very time-consuming because hypertext links throughout Section 8 would require revision. The pdf file of the TOC is now at the same level as the 356h.

Request 2: Place pdf files for items 13-20 into a folder called "Other" (unless it's an empty folder).
Action Taken: A folder titled "Other" was created and Sections 13-20 were moved to this folder. Sections 15 and 17 were not moved to "Other" because they were removed from the supplement.

Request 3: Provide cover letter in pdf format.
Action Taken: The cover letter is provided in this format.

Request 4: In the subfolder for the clinical study report (OMC-BUS5-FSR), combine 5 pdf files (divided by page numbers) into a single file for final study report. Remove the subfolders titled "programs" and "StatDoc." The CRF tabulations should be moved to the CRT folder (separate file for each patient). Consider removing information that is already included in the clinical study report (Appendices, Tables).
Action Taken: The clinical study report, consisting of 5 pdf files, was not combined into one file. The study report was divided into 5 pdf files so that each file is less than 50 MB. The pdf file "OMC-BUS-5 FSR 1-531" includes the table of contents with hyperlinks to each section of the report. Combining the files into one would require redoing bookmarks and hypertext links, and thus would require a significant amount of time. This was explained via e-mail to Dr. Levin, who responded on January 7, 2002 that the FDA would accept the final study report as 5 separate files in this instance.

The subfolder OMC-BUS-5-FSR now only contains the 5 pdf files of the clinical study report. Other information was removed because it was misplaced or not required per the FDA's Guidance.



Request 5: Provide the SAS datasets as uncompressed SAS transport files. Include these in the 11CRT folder. Each dataset should be provided as a separate file, not combined into one. These files should be provided as XPORT files, not CPORT. Refer to the guidance that describes how to define the variables in a pdf file.

Action Taken: The file containing the datasets (BUS5) has been decompressed into 43 SAS transport files, and are now included in Section n11CRT. This Section also includes the dataset for the population pharmacokinetics study (Nonmemv5.xpt) and the CRT Tabulations. Data definition tables are included for both study reports per the FDA's Guidance: Providing Regulatory Submissions in Electronic Format - NDAs.

Request 6: In n12crf, each case report form should be provided separately, not combined into one document.

Action Taken: The case report forms are now provided as separate pdf files per patient.

ORIGINAL

ORPHAN MEDICAL

NDA NO. 20-954 REF NO. 004

NDA SUPPL FOR SE8-004

SE8-004 PM

December 21, 2001

Richard Pazdur, M.D.
Division of Oncology Drug Products [HFD-150]
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II
1451 Rockville Pike
Rockville, MD 20852
Ph: (301) 827-1537

Subject: **Busulfex® (busulfan) Injection; NDA #20-954**
Labeling Supplement Requiring FDA Pre-Approval under 21 CFR 314.70(b)
SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED
User Fee #3,396, Orphan Designation #94-830

Dear Dr. Pazdur:

Orphan Medical, Inc. submits this labeling supplement for Busulfex® (busulfan) Injection to request changes to the package insert to incorporate pediatric information on dosing, pharmacokinetics and safety. These changes to the labeling are supported by an open-label uncontrolled clinical trial performed in 24 pediatric patients treated with Busulfex as part of a preparative regimen prior to allogeneic hematopoietic progenitor cell transplantation (HPCT) for a variety of malignant and nonmalignant diseases (OMC-BUS-5).

This supplement is being submitted in response to the FDA's formal Written Request for pediatric information dated March 27, 2000, made pursuant to Section 505A of the FFDCA. As this submission fulfills the requirements of the Written Request, Orphan Medical requests an additional 6 months of marketing exclusivity to be added to the patent for Busulfex (Patent No.'s 5,430,057 & 5,559,148) and the orphan drug exclusivity period regardless of whether this supplement is approved or not.

Orphan Medical requests priority review for the approval of Busulfex®. This expedited review is being sought for the following reasons:

- Busulfan is included in the FDA document "List of approved drugs for which additional pediatric information may produce health benefits in the pediatric population" – docket no. 98N-0056.

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952-513-6900 • Fax: 952-541-9209 • www.orphan.com

- Busulfex would provide a significant improvement to oral busulfan for use as part of a preparative regimen for HPCT in pediatric patients. In HPCT, it is critical to provide precise dosing of the preparative regimen, but this is not possible with oral busulfan due to inherent bioavailability, absorption and administration problems.
- There is an urgent need for dosing instructions for pediatric patients in the Busulfex package insert.
- Many transplant physicians are already administering Busulfex to pediatric patients. Although Orphan Medical neither promotes nor actively tracks such use, such off-label use is implied by distribution to pediatric hospitals and inquiries from pharmacists and physicians regarding dosing of Busulfex in children. Orphan Medical is currently unable to proactively provide guidance on dosing pediatric patients, and as a result, the health and safety of this vulnerable population may be compromised.

Previously there has been no consensus within the HPCT community regarding the most appropriate method for dosing busulphan in pediatric patients. This supplement includes a population PK analysis that represents the first standardized approach for busulfan dosing in pediatrics and on which the dosing guidelines are based. It is acknowledged that this dose regimen was not employed in trial OMC-BUS-5, but is nonetheless considered valid and to represent an improvement over other regimens routinely used in clinical practice.

Orphan Medical is proposing a dosing guideline for pediatric patients which utilizes a stratified weight-based approach as shown below:

[

]

Use of this nomogram should allow approximately 70% of patients to achieve the clinically desired busulfan concentration range at Dose 1, compared to rates less than 50% for other regimens. In addition, reduced intra-patient variability suggests that the AUC will be maintained across the 4-day, 16-dose regimen.

To achieve the appropriate therapeutic exposure of busulphan, and given the increased clearance of busulphan in pediatric patients, the pediatric dosing guidelines include doses above that recommended for adults (0.8mg/kg). They will therefore result in increased exposure to both busulfan and the excipient N,N-

dimethylacetamide (DMA). Use of such doses should not represent an increased safety risk in consideration of the following:

- The toxicology of busulphan at such doses is well understood in the context of HPCT
- The maximum daily exposure to DMA in the proposed guidelines (6200mg/m^2) is below that reported to result in non-serious side effects (Weiss, 1962)
- A review of the safety data from OMC-BUS-5, where average doses of up to 1.32 mg/kg (maximum individual doses of 1.6 mg/kg) were used, found no evidence of new, unexpected toxicity or toxicity that could be solely attributed to DMA.

The Busulfex and cyclophosphamide dosing regimen used in OMC-BUS-5 was well-tolerated by all patients. The profile of adverse experiences was similar to that seen in the adult trials even though several pediatric patients were dose-adjusted to receive a busulfan dose 1½ to 2 times higher than the approved adult dose. The incidences of death and relapse in the pediatric clinical trial at 100 days post-transplant were similar to that for the adult trial where patients underwent allogeneic transplant (OMC-BUS-4)

Efficacy results (myeloablation, time to engraftment, disease-free survival, and survival) confirm the results seen in adults and indicate that Busulfex is efficacious as a preparative regimen for pediatric HPCT.

Despite these positive results, Orphan Medical is not seeking an indication due to the restriction to specific disease.

The supplement is being filed electronically per the FDA's Guidance: Providing Regulatory Submissions in Electronic Format (Jan. 1999). If you have any questions pertaining to this supplemental NDA, please contact me directly.

Sincerely,

Carol S. Curme

Carol S. Curme, J.D., RAC
Senior Manager of Regulatory Affairs
(952) 513-6974

cc: (cover letter only)
Dr. Marlene Haffner (Office of Orphan Products Development)
Gary Buehler, Office of Generic Drugs
Dayton Reardan, Ph.D., RAC, Vice-President of Regulatory Affairs

8341

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Orphan Medical, Inc.
13911 Ridgedale Drive
Suite 250
Minnetonka, MN 55305

2. TELEPHONE NUMBER *(Include Area Code)*

(952) 513-6900

3. PRODUCT NAME

Busulfex® (busulfan) Injection

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

20-954 / S-001

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

3,396

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☒ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Carol S. Cramer	Senior Manager of Regulatory Affairs	12-20-01

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA: 20-954	Efficacy Supplement Type: SE-2	Supplement Number: 004
Drug: Busulfex®(busulfan) Injection	Applicant: Orphan Medical Inc.	
RPM: Sean Bradley, R.Ph.	HFD-150	Phone: 301-594-5750/
Application Type: 505(b)(1)	Reference Listed Drug (20-954, Busulfex® (busulfan) Injection:	

❖ Application Classifications:	
• Review priority	Priority
• Chem class (NDAs only)	Cytotoxic Agent
• Other (e.g., orphan, OTC):	Orphan
❖ User Fee Goal Dates:	June 28, 2002
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	(X) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	N/A
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	N/A
Exclusivity (approvals only)	
• Exclusivity summary	Still ~~NEA~~ needed
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of*	( ) Yes, Application #_____ ( ) No

sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H (X) N/A
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling) agreed upon by applicant	✓
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	21JUN02 Labeling meeting
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other (Pre-sNDA)	20JAN00
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
❖ Clinical review(s) *(indicate date for each review)*	28JUN02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Page 26 of Medical Review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	Joint Medical/Statistical Review
❖ Biopharmaceutical review(s) *(indicate date for each review)*	28JUN02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
❖ CMC review(s) *(indicate date for each review)*	01MAY02
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	01MAY02
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation (X) N/A
❖ Methods validation	( ) Completed ( ) Requested (X) N/A
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-954

MAR 27 2000

Orphan Medical
13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

Attention: Carol S. Curme, J.D., RAC
Manager, Regulatory Affairs

Dear Ms. Curme:

To obtain needed pediatric information on Busulfex® (busulfan) injection, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following study:

- *Type of study:* Phase 2 study of Busulfex pharmacokinetics in at least 20 patients with malignant and non-malignant diseases treated in combination with cyclophosphamide as a conditioning regimen for allogeneic bone marrow transplant, with pharmacokinetic and safety characterization, including complete clinical data, for all age groups.

- *Age group in which study will be performed:* Infants $\geq$ 1 month to adolescents $\leq$ 16 years.

- *Study endpoints*: Time to engraftment, engraftment, myeloablation, survival, and busulfan pharmacokinetic parameters. The latter should include busulfan concentration and AUC to delineate appropriate dose selection and dose adjustments in children of age categories known to have differing busulfan clearances.

  Endpoints such as volume of distribution, half-life, extent of plasma protein binding, and variability of free and protein bound busulfan pharmacokinetics should be presented. These endpoints may be supported with a presentation of the pediatric busulfan pharmacokinetic literature.

- *Drug information*
  dosage form: Intravenous injection
  route of administration: Intravenous

- *Safety concerns:* Veno-occlusive disease, pneumonitis, time to engraftment, GvHD, infections, and transfusion requirements

- *Statistical information:* Descriptive statistics

- *Labeling that may result from the study:* Appropriate sections of the label may be changed to incorporate the dosage, pharmacokinetic, and safety findings of the study.

- *Format of reports to be submitted:* Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition to your study report, please submit a summary of your post-marketing experience including safety and efficacy update.

- *Timeframe for submitting reports of the study:* Reports of the above studies must be submitted to the Agency on or before December 31, 2001. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above study to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Dianne Spillman, Regulatory Project Manager, at (301) 594-5746.

Sincerely Yours,

/S/

Robert Temple, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Archival NDA 20-954 / IND 46,232
HFD-150/division file
HFD-150/D.Spillman /S/
HFD-150/D.Griebel
/J.Johnson
/N.Chidambaram
/E.Duffy
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/S.Ibrahim
/A.Rahman
/N.Li
/G.Chen
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HFD-600/Office of Generic Drugs
HFD-2/M.Lumpkin
HFD-104/D.Murphy
HFD-002/T.Crescenzi
HFD-6/KRoberts

Drafted by: D.Griebel/1-12-00
Edited by: review team/1-13-00 pre-sNDA meeting
D.Spillman/2-23-00/3-8-00
Initialed by: D.Pease/2-24-00
S.Ibrahim/2-24-00
A.Rahman/2-24-00
G.Chen/2-24-00
D.Griebel/2-29-00
J.Johnson/2-29-00 /S/
R.Pazdur/2-29-00

Discussed @ PdIT: 3-15-00
PdIT edits incorporated by: D.Griebel/3-15-00 /S/ 3-23-00

Final: dds/3-22-00
filename: c:\...\20954\ltrs\ped-excl-ltr - wR

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

MEETING MINUTES

MEETING DATE: January 20, 2000 **TIME:** 1:00 p.m. **LOCATION:** WOC2/r 6002

IND: 46,232 Meeting Request Submission Date: 11-9-99; sn 074 (MR)
Additional Document Dates: 11-11-99; sn 075 (MR)
11-11-99; NDA correspondence
12-20-99; sn 077 (GC)

DRUG: Busulfex (busulfan) injection

SPONSOR/APPLICANT: Orphan Medical, Inc.

TYPE of MEETING:

1. Pre-sNDA

2. **Proposed Indications:**

FDA PARTICIPANTS:

	Richard Pazdur, M.D.	–	Director, Division of Oncology Drug Products
	Donna Griebel, M.D.	–	Clinical Reviewer
	Gang Chen, Ph.D.	–	Statistical Team Leader
	Ning Li, Ph.D.	–	Statistical Reviewer
	Safaa Ibrahim, Ph.D.	–	Clinical Pharmacology and Biopharmaceutics Reviewer
	Eric Duffy, Ph.D.	–	ChemistryTeam Leader
	Nallaperumal Chidambaram, Ph.D.	–	Chemistry Reviewer
	Dianne Spillman	–	Project Manager
Office of Orphan Product Dev.:	John McCormick, M.D.	–	Deputy Director, Office of Orphan Product Development
	Henry C. Startzman, M.D.	–	Medical Reviewer
	Jim Bona, R.Ph.	–	Reviewing Pharmacist
at pre-meeting:	Steven Hirschfeld, M.D., Ph.D.	–	Clinical Reviewer
	John Johnson, M.D.	–	Clinical Team Leader
	W. David McGuinn, Ph.D.	–	Pharmacology/Toxicology Reviewer
	Dotti Pease	–	Chief, Project Management Staff
	Atiqur Rahman, Ph.D.	–	Clinical Pharmacology and Biopharmaceutics Team Leader
	Victor Santana, M.D	–	Oncology Drugs Advisory Committee (ODAC) member

INDUSTRY PARTICIPANTS:

Orphan Medical:	William Houghton, M.D.	–	Chief Operating Officer
	Dayton Reardan, Ph.D.	–	Vice President, Regulatory Affairs
	Shari Lennon, M.D.	–	Director, Busulfex Development
	Carol Curme, JD, RAC	–	Manager, Regulatory Affairs
	Donna Wall, M.D.	–	Principal Investigator

BACKGROUND DOCUMENTS:

1. November 9, 1999 *IND submission - serial #074*: Meeting Request
2. November 11, 1999 *IND submission - serial #075*: Revised Meeting Request
3. November 11, 1999 *NDA submission:* Meeting request (same as IND submission 075)
4. November 30, 1999 FDA fax: confirmation of January 20, 2000 meeting date
5. December 20, 1999 *IND submission - serial #077*: Briefing document

MEETING OBJECTIVE:

To discuss an [redacted] that is consistent with the FDA's Guidance "FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products"

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

NOTES: Although Drs. Temple and Behrman did not attend the Division internal meeting or the corresponding industry meeting for this project, Dr. Behrman did provide comments on the Division's internal bullets presented during the industry meeting.

Drs. Shari Lennon and Dayton Reardon gave a brief presentation.

During the course of the meeting, there were additional agreements between the Division and Orphan Medical, Inc. (OMI), these agreements are italicized and identified here with a square (▪) bullet.

1. **Orphan Medical proposes to submit a supplement based upon our pediatric clinical trial, OMC-BUS-5, [redacted] Busulfex. Is this sufficient data for [redacted] pediatric [redacted] where the annual incidence is less than 1000 patients in the United States?**

FDA: [redacted]. Pending review it may fulfill your commitment and justify addition to the pediatric section of the package insert of some information on safety, dosing and pharmacokinetics.

[redacted]

- *OMI would like to review the draft WR, if possible.*

- *OMI stated that conducting these studies would be unrealistic (see additional bullets).*

- *OMI should submit letters from pediatricians to corroborate their view that Busulfex should be considered a preparative regimen vs. a disease regimen*

- *These letters should be submitted to the IND as correspondence.*

2. **We intend to have kinetics and dose adjustment information on all pediatric patients in our trial. Will this data be sufficient to describe recommended pediatric dosing?**

FDA: The pharmacokinetic and dosing data are acceptable, however,

- Other pharmacokinetic (PK) parameters, such as total plasma clearance, volume of distribution, and half-life should be also calculated by non-compartmental methods. Protein binding of busulfan in the pediatric patients should be evaluated. The PK parameters and % protein bound should be evaluated separately for children < 4 years of age and for those > 4 years of age. This information should be incorporated in the package insert for Busulfex for Injection.

  - *OMI has most of the information requested and will include it in the report.*

  - *OMI does not have "% protein bound" data, but will investigate the possibility of getting this data.*

- The sponsor is encouraged to explore the relationship between safety endpoints and exposure (i.e., AUC) to busulfan in pediatric patients.

UNRESOLVED ISSUES REQUIRING FURTHER DISCUSSION:

1. Orphan Medical review of draft Written Request.
2. Orphan Medical ——

ACTION ITEMS:

Item	Responsible Person	Due Date	Completion Date
1. Provide copy of FDA minutes to OMI.	D. Spillman, FDA	NLT 2-17-2000	✓ 2-16-00
2. Submit correspondence (arguments/letters) to IND.	D.Reardan, OMI	a few weeks	

The meeting concluded at 1:55 p.m.

ADDENDUM: FDA clarification of question #1, italicized bullet #3.

The changes to the bullet identified above were made after the meeting and are not intended to alter the meaning of the bullet, but to clarify some of the wording.

- *OMI could submit letters from pediatric oncologists to corroborate their view that Busulfex should be considered a general hematopoieic stem cell transplant preparative regimen vs. a disease-specific transplant preparative regimen* [ ] *. These letters should include comments on the adequacy of PK data, the relative importance of establishing a disease-specific indication, and whether engraftment is a clinical endpoint that could be considered a surrogate endpoint.*

/S/ /S/

Concurrence Chair:

Dianne Spillman /date
Project Manager/Minutes preparer

Donna Griebel, M.D. /date
Clinical Reviewer

ATTACHMENTS:

1. Development Plan (1 page) [from 12-20-99 submission #077, page 137]
2. Protocol Outlines (3 pages) [from 12-20-99 submission #077, page 138-140]
3. ———

cc: Original IND 46,232/n-074 (MR)
/n-075 (MR)
/n-077 (GC)
HFD-150/Div.Files
/D.Spillman/2-9-00

Addendum by D.Griebel: 2-10-00/2-15-00
Through R.Pazdur: 2-16-00
F/T by: dds\2-15-00
c:\...\46232\mtgs\minutes\000120psn-mm

MEETING MINUTES = pre-sNDA (PsN)

DDR: **DO NOT DISTRIBUTE COPIES** TO THESE PEOPLE

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fax copy to: /V.Santana (ODAC)
/C.Curme (Orphan Medical representative)

OVERALL DEVELOPMENT PLAN

Indication: [redacted]

[redacted]

Proposed pivotal trial(s): **CLINICAL PROTOCOL NUMBER: OMC-BUS-5**

Proposed supportive trial(s): **Not applicable**

APPEARS THIS WAY
ON ORIGINAL

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