TABLE Summary for the pharmacokinetic parameters of busulfan as reported by different studies

Reference	*Dose mg/kg/day or (mg/m²/day)*	*n*	*Age (yr)*	*$t^1/_2$ (hr) (mean±SD)*	*Clearance (mL/min/kg) (mean±SD)*	*Vd (L/kg)*
50	4	28	>18	2.33	2.9 (1.7)	0.59 (0.44)
61	4	16	>18	2.59	2.64 (0.56)	——
63	4	14	0.2–3.6	1.54	8.4 (4.3)	1.42 (0.83)
62	4	11	4–14	2.33	4.4 (2.2)	1.06 (0.44)
106	(150)	25	2–14	2.94	4.5 (1.4)	1.04 (0.38)
61	4	9	1.3–14	2.43	4.9 (2.2)	——
67	4	33	0.2–2.75	2.83	6.8 (3.0)	1.69 (1.29)
66	4	16	0.5–19	2.40	8.9 (3.7)	——
88 (oral, 2 mg)		7	1.8–6	2.74	5.2 (2.1)	1.15 (0.52)
88 (oral, 2 mg)		8	>13	2.68	3.6 (1.3)	0.64 (0.12)
88 (i.v., 2 mg)		8	1.8–6	2.46	3.62 (0.78)	0.74 (0.10)
88 (i.v., 2 mg)		8	>13	2.61	2.49 (0.52)	0.56 (0.10)
64	4	9	1.3–13	2.30	3.96 (0.97)	0.78 (0.19)
64	(150)	12	1.4–13.5	2.48	3.44 (1.13)	0.70 (0.10)

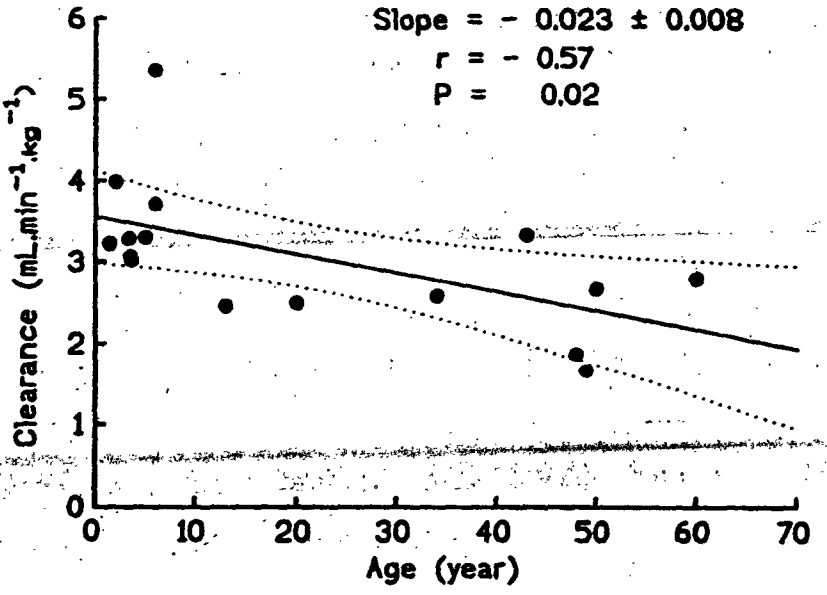

Figure 1 The relationship between clearance corrected for body-weight and age.

busulfan varied between 0.27 hr to 0.68 hrs[50,60] and the lag time (the time needed before the absorption start) was reported to be as short as 0.02 hr and as long as 1 hr. This probably can be explained by the different methods of administration and/or the difference in the transit time in the gastrointestinal tract for adults and children.[63]

It was found[64] in 21 children, who underwent bone marrow transplantation and were preconditioned with oral busulfan either as crushed tablets or as whole tablets, that the administration of crushed tablets resulted in a significantly shorter lag time compared to that obtained when the children were given the whole tablets. However, this study showed no significant difference between the absorption half-lives. An accelerated absorption was reported by Schuler *et al.*[98] when the patients were pre-treated with metoclopramide which has been reported

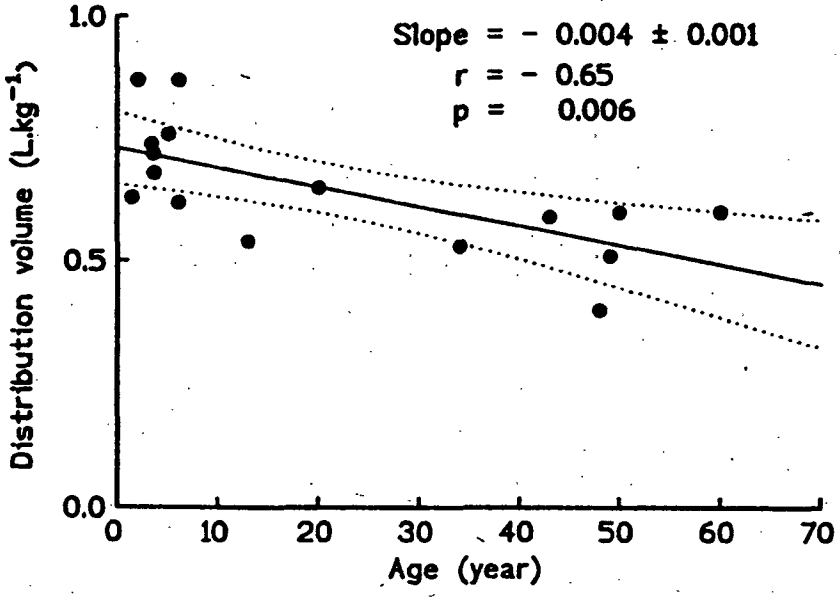

Figure 2 The relationship between distribution volume normalized for body-weight and age.

to accelerate the absorption of cyclosporine A (CsA), paracetamol and morphine.[99-100]

DRUG INTERACTIONS WITH BUSULFAN

There is very little information available about the interaction of busulfan with other drugs, probably due to the limited clinical use of the drug. Interaction of busulfan with other drugs was first reported by Fitzsimmons *et al.*[101,102] They found that pretreatment of mice with the anticonvulsants high-dose phenytoin, phenobarbital or Aroclor 1254 increased the proportion of animals that survived marrow-ablative doses of busulfan. Both myelotoxicity and neurotoxicity decreased. A continuous decrease in the steady state level of plasma concentrations was observed in 40% of the patients treated with high-dose busulfan. We have[103] followed the pharmacokinetic parameters after the first and the last dose of deuterium-labelled busulfan in BMT patients treated with either phenytoin or diazepam as prophylactic anticonvulsant therapy. Patients who received phenytoin showed a significantly higher clearance and shorter elimination half-lives after the last dose compared to the first dose. No significant differences were observed between the first and the last dose in the patients treated with diazepam.

These studies showed that phenytoin as an anticonvulsant alters the pharmacokinetics of busulfan and most likely its pharmacodynamics. On the other hand, busulfan can also alter the pharmacokinetics of phenytoin resulting in less drug efficacy.[104,105] For adequate anticonvulsant prophylaxis, drugs such as diazepam, clonazepam or other anticonvulsants with less enzyme-inductive properties than phenytoin should be used.

METABOLIC PATHWAY OF BUSULFAN

Animal studies

The metabolic fate of busulfan has been studied after the administration of radiolabelled compound to rats, mice and rabbits. The first metabolic study was performed by Roberts and Warwick[81] and showed that 3-hydroxysulfolane was the major metabolite and it corresponds to about 60% of the total radioactivity in urine. Trams *et al.*[82] reported three major metabolites in rat which accounted for 70–80% of the total radioactivity excreted into the urine. Several minor metabolites were also isolated and 12–14% of the injected ^{14}C-busulfan was excreted as expired $^{14}CO_2$. Studies using ^{35}S-labelled busulfan[83,84] showed that the methanesulfonate groups of busulfan were excreted almost quantitatively into the urine. The probable mechanism for this metabolic pathway was suggested to proceed through the reaction with glutathione or the cysteinyl moiety to form a sulfonium ion.[106-108] Utilizing a rat liver perfusion technique, we were able to isolate (γ-glutamyl-β(S-tetrahydrothiophenium) alanyl-glycine (sulfonium ion of glutathione) from both the perfusate and the bile.[57] The reaction between glutathione and busulfan was shown to be enzymatic and mediated by glutathione-S-transferase. Marchand and Abdel Monem[109] have

shown that busulfan as well as 1,4-diiodobutane are conjugated with glutathione to form a sulfonium ion.

After the administration of ^{14}C-busulfan to the rat about 70% of the total injected radioactivity was excreted into rat urine.[58] The major metabolite was identified as 3-hydroxysulfolane (39%, Fig3), tetrahydrothiophene-1-oxide (13%) and sulfolane (20%), about 6% was the intact drug and 2% was a hydrolysed product (tetrahydrofuran; ref 92). About 14% of the radioactivity in the urine was not identified, although a part co-eluted with the sulfonium ion of N-acetyl-L-cysteine. The hydrolysis of this fraction yielded about 40% tetrahydrothiophene. In another study,[110] 3-hydroxysulfolane and tetrahydrothiophene were isolated from rat urine (57% and 5%, respectively) after the administration of 1,4-dibromobutane. Tetrahydrothiophene was suggested to be formed in vivo via sulfonium ion and subsequently transformed into 3-hydroxysulfolane. When ^{14}C busulfan was injected into the rat,[111] the total radioactivity was eliminated slowly from both brain and plasma with half-lives of 8 and 9 hr, respectively. About 50% of the total radioactivity isolated after 24 hours in both plasma and brain was identified as sulfolane and 11% as tetrahydrothiophene-1 oxide. 3-Hydroxysulfolane was found in both plasma (30%) and brain (18%). About 18% of the radioactivity in the rat brain was unidentified metabolites and about 6% in both plasma and brain was identified as intact busulfan.

Human studies

The metabolic fate of busulfan is not as well documented in man as in animals. The first metabolic study in humans[86] utilized ^{14}C-busulfan or ^{35}S-busulfan and showed that of the ^{35}S-busulfan 45–60% was excreted into the urine as an alkali salt of methanesulfonic acid. About 25–30% of the radioactivity from the injected ^{14}C-busulfan was excreted into the urine. Vodopick *et al.*[85] were able to separate twelve metabolites after the administration of ^{3}H-busulfan to man but they were not identified. We were able to isolate: 3-hydroxysulfolane, sulfolane and tetrahydrothiophene 1-oxide as the first urinary metabolites in patients undergoing bone marrow transplantation.[60] Tetrahydrothiophene was also identified after the urine was hydrolysed. The results indicate that glutathione is involved in busulfan metabolism in humans as well as in rats. All the above mentioned studies of the metabolism of busulfan can be summarized in Figure 3.

Tetrahydrothiophene, tetrahydrothiophene 1-oxide, sulfolane and 3-hydroxysulfolane did not have cytotoxic activity when tested on V79 cell line.[58] However, the glutathione sulfonium ion and N-acetyl-L-cysteine sulfonium ion are alkylating agents and it remains to be shown whether these metabolites have a cytotoxic effect and hence pharmacological activity. Also it remains to be answered if the biotransformation of busulfan takes place in the human brain.

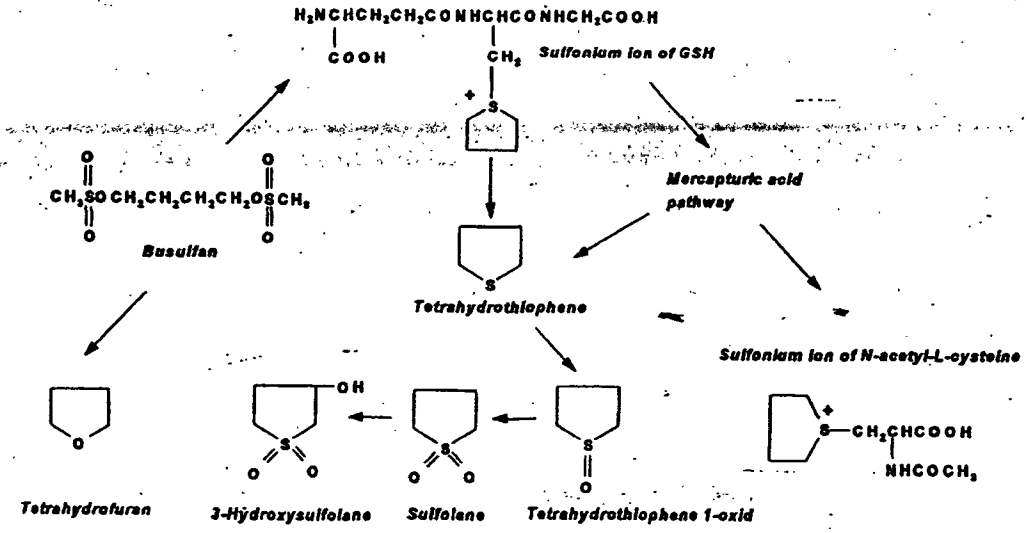

Figure 3 The metabolic pathway of busulfan.

ALTERATION IN BUSULFAN KINETICS WITH THE AGE

Since its introduction as a part in the myeloablative regimen busulfan dosage has usually been 1 mg/kg four times a day and for four days. Despite equal doses for adults and children according to body-weight, many investigators have shown that young children and infants have lower systemic exposure to busulfan than adults. This difference may have serious consequences: for example higher rates of engraftment failures and higher rates of early relapse[65-69] Grochow *et al.*[63] have shown that children (0.13–5 years) had a 2.4-fold higher distribution volume and 2.2-fold higher clearance rate compared to adults. We have reported[61] a lower through plasma concentration during the four days therapy for children below the age of five as compared to adults (Fig. 4) and older children (210 and 612 μg/L, respectively). Vassal *et al.*[62] reported a higher clearance rate and a higher distribution volume for 11 young children than in adults. Moreover, a higher clearance was observed in children between 0.5 and 3 years as compared to children between 7 and 19 years. It was also reported that the elimination half-lives of busulfan decreased continuously from infancy until early childhood.[66]

Hobbs *et al.*[42] were first to change their preparative regimen to 80 mg/m²/day × 4 days with a minimum dose of 4 mg/kg/day and a maximum of 5 mg/kg/day. Lucarelli *et al.*[41] reported a higher relapse rate in children with β-thalassemia when the patients were treated with 14 mg/kg and that better results were achieved when the dosage was increased to 16 mg/kg. Vassal *et al.*[112] recommended 600 mg/m² (150 mg/m²/day) in children, which corresponds to 24.8 mg/kg (range 17.8–29.2 mg/kg). Their results demonstrate that the new dosage significantly increased the systemic exposure compared to the usual dosage of 16 mg/kg. However, a higher rate of VOD and neurotoxicity also accompanied the new dosage. Yeager *et al.*[113] used 40 mg/m² busulfan every 6 hr for 16 doses, which corresponds to 26.4 mg/kg (range 24.3–28.2) and is about 60% higher than the normal dosage of 16 mg/kg. None of the patients treated with this dosage developed neurological toxicities and no late graft failure was seen. When Shaw *et al.*[64] optimized the therapy of busulfan to a single dose of 150 mg/m² × 4 days, the rate of VOD was low and no neurological toxicities were observed. Their results also showed a higher systemic exposure indicating the linearity in busulfan kinetics.

Considering the age-dependent pharmacokinetics of busulfan, it seems clear that the dosage on the basis of body weight is no longer relevant in pediatric patients. Dosage based on body surface area provides better systemic exposure in children equivalent to that observed in

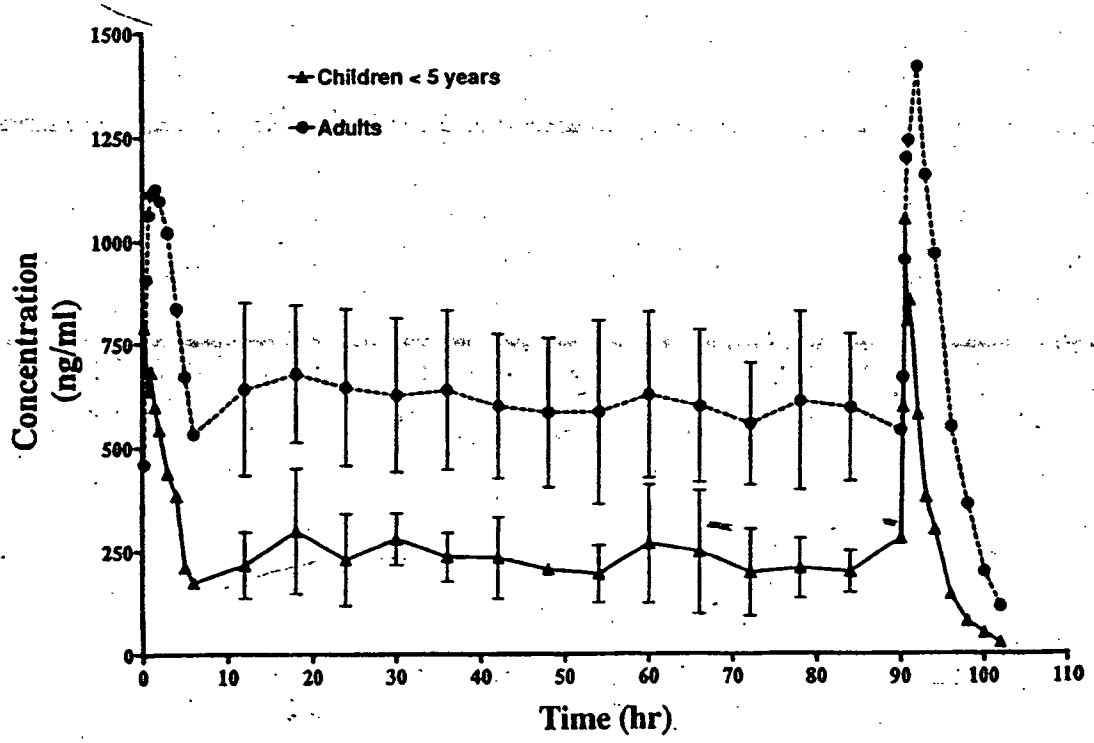

Figure 4 Busulfan concentrations in plasma (minimum concentrations) during four days therapy.

adults. However, further improvements to reduce interpatient variability in systemic exposure and hence a better efficacy and controlled toxicity is required.

CLINICAL RELEVANCE OF PHARMACOKINETICS AND PHARMACODYNAMICS

Several studies have attempted to correlate the various pharmacokinetic parameters and pharmacodynamic response to busulfan and/or busulfan's side effects. Hepatic venooclusive disease (VOD) is a hepatotoxic lesion involving obstruction of small intrahepatic venules and damage to the surrounding centrilobular hepatocytes. It is a complication that develops in 20–40% of patients undergoing bone marrow transplantation for malignancy.[47,114] The VOD is fatal in about 50% of those patients. Grochow *et al.*[50] found a significant correlation between high systemic exposure of busulfan expressed as AUC of the first dose and the occurrence of VOD. All six patients who developed VOD had an AUC greater than the mean (2012 ± 1223 μmol.min/L). Méresse *et al.*[115] reported that a total dose of busulfan exceeding 16 mg/kg was the most important risk factor in a multivariate analysis of 136 children pre-conditioned with myeloablative regimen containing busulfan. Vassal *et al.*[112] showed that increasing busulfan dosage in young children from 16 mg/kg to 600 mg/m^2 and thereby increasing the systemic exposure to busulfan significantly increased the incidence of VOD from 7% to 22%, which is comparable to the incidence of VOD in adults. This new dosage suggested by Vassal *et al.*[116] also increased the incidence of neurotoxicity from 1.7% to 15.4% in 123 patients studied. However, the neurotoxicity could be prevented by anticonvulsive prophylaxis. Moreover, we have shown recently the relation between busulfan concentration and alopecia.[117] These studies have helped to identify interindividual pharmacokinetic differences which can in part explain differences in the incidence or severity of busulfan- related toxicites. However, more studies are needed to identify other therapy-related toxicities such as interstitial pneumonia, mucositis and late CNS toxicities.[116–122]

The administration of regimens containing TBI results in a high rate of side effects such as cataract, multiple endocrine abnormalities and growth disturbances in children.[122] Sanders and the Seattle Marrow Transplant Team[121] have reported that the endocrine function abnormalities influencing subsequent growth and development in children after marrow transplantation rarely occur after preparation with cyclophosphamide alone. It appears that the addition of busulfan to cyclophosphamide does not result in growth, development or thyroid function abnormalities. However, gonadal function and disturbances in pubertal development may be influenced by high-dose busulfan. Vassal *et. al.*[62] detected busulfan in the cerebrospinal fluid (CSF) of nine young bone marrow transplantation recipients with a mean CSF-to-plasma concentration ratio of 0.95. We showed[60] that the CSF/plasma ratio in 5 adult patients was 1.3. Busulfan rapidly entered into the CSF compartment in one adult patient[123] and the concentrations in CSF and plasma were comparable during the four days of therapy. No accumulation of the parent drug was observed.

Busulfan labelled with the positron-emitting radionuclide ^{11}C[124] was used to investigate the distribution in cynomolgus monkey with positron emission tomography (PET). Busulfan was shown to rapidly cross the blood-brain barrier (BBB). After 30 min, the radioactivity remaining in the brain was about 50% of the amount initially extracted. However, the radioactivity was accumulated in the liver and lungs during 60 min scanning. In man, ^{11}C-busulfan also rapidly entered the brain (Fig. 5) and about 20% of the total injected dose was extracted. The high cerebral uptake of busulfan is most probably due to the lipophilic character of the drug and the low extent of protein binding.[60,89] This high cerebral extraction of busulfan in humans can have therapeutical implications concerning its ability to eradicate leukemic cells in the CNS or its use in the treatment of childhood malignant brain tumors.[125] Equally important is the insight gained into the side effects often seen in high-dose therapy such as seizures and other neurological effects (mental developing) in children undergoing bone marrow transplantation. Therefore, more data, long time follow up and correlation with both dose and concentrations of busulfan are required. Since the introduction of busulfan/cyclophosphamide as a new conditioning regimen prior to BMT[126] a lower relapse rate but a higher incidence of complications and toxicities was reported for AML patients. Tutschka *et al.*[126] reported that the reduction of cyclophosphamide from 200 to 120 mg/kg reduced the complications without compromising the antileukemic effect. The incidence of IP and VOD was reported to be 12% and 2%, respectively. A significant decrease of the cumulative liver toxicities and hemorrhagic cystitis using the modified regimen was confirmed by other investigators.[55,118]

In contrast to the above mentioned studies, Morgan *et al.*[127] have reported a relatively higher toxicity (VOD, IP and hemorrhagic cystitis) using the modified regimen as compared to cyclophosphamide/TBI. A multiple logistic regression analysis indicated that the preparative regimen

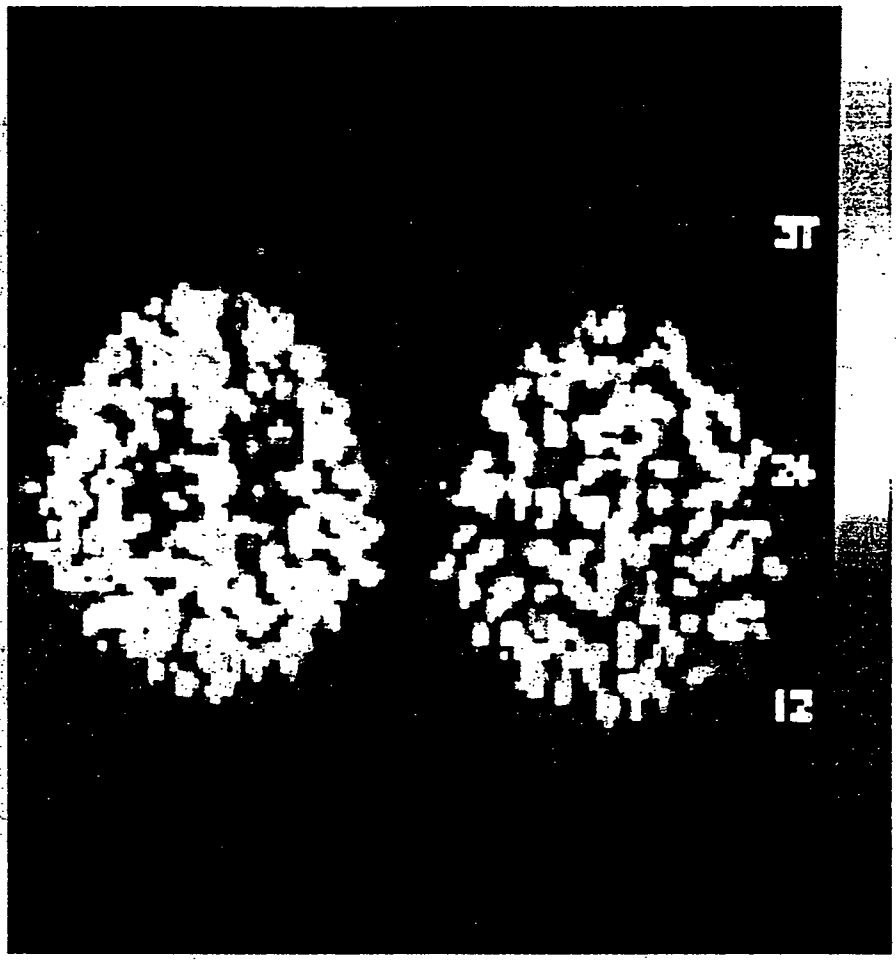

Figure 5 PET image of 11C-busulfan in the human brain from 0–5 min (left) and from 25–35 min (right) after injection. (See Color Plate XXVII at the back of this issue.)

was the only significant factor. Randomized multi-center study in France[128] and by Ringdén *et al.*[129] found that a higher toxicity accompanied the use of BU/Cy compared to Cy/TBI. A multi-international collaboration with a high number of patients to understand the factor/factors underlying these conflicting results may be helpful in optimizing busulfan therapy with high efficacy and lower toxicity. One way to optimize the optimal dose of busulfan is to use therapeutic drug monitoring. However, therapeutic drug monitoring in connection with bone marrow transplantation poses a number of difficulties and considerations:

1) In conventional chemotherapy, the dose is optimized after the first cycle of treatment according to the toxic side effects. In BMT, the treatment is given once and the toxicities and drug efficacy are determined a long time after the treatment. 2) Correlations between the drug exposure (either as a plasma concentration or AUC or any other pharmacokinetic parameter) and the toxicity and/or efficacy must be found. 3) Busulfan is usually used in combination with other drugs which may either enhance or decrease toxicity. 4) High rate of inter- and intra-individual variability in absorption reported by many authors causes problems with limited sampling procedures. Therefore, a reliable limited sample procedure is needed. 5) The disease (malignancy or non malignancy) have been shown to have an effect on the pharmacokinetics of the drug and they have to be considered. 6) A very rapid and sensitive method to assay busulfan after the first dose is required to allow the dose adjustment.

A better understanding of the disposition of busulfan in combination with cyclophosphamide in BMT may potentially improve the therapeutic outcome.[130] The interpatient

variations in disease, circadian rhythms, abnormalities in liver functions and the bioavialibility are now known. At the present time, the use of dose adjustment is probably the most reliable way to enhance the efficacy and lower the drug-related toxicity. However, an approach would be to develop a parenteral preparation of busulfan to be administered as an infusion.

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Bradley, Sean

From: Carol Curme [CCURME@orphan.com]
Sent: Wednesday, June 26, 2002 1:19 PM
To: 'bradleys@cder.fda.gov'
Subject: RE: Busulfex S-004: Response to Fax 062502

Importance: High


Busulfex pi 26JUN02-2.doc

Dear Sean,

The package insert in the previous response to the FDA did not include instructions on blood sampling. The insert was corrected to include this information (pp. 16-17) (see attachment). If possible, please print out this copy of the insert for the meeting today. Please excuse us for this error and associated inconvenience.

Sincerely,

Carol Curme

-----Original Message-----
From: Carol Curme
Sent: Wednesday, June 26, 2002 11:04 AM
To: 'bradleys@cder.fda.gov'
Subject: Busulfex S-004: Response to Fax 062502

Dear Sean,

Here is our response to the FDA's fax dated June 25, 2002. An e-mail with the referenced journal articles and a list of meeting attendees will follow.

Sincerely,
Carol

June 26, 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 Facsimile, dated May 24, 2002
Regarding the Supplement of Pediatric Information
User Fee #3,396, Orphan Designation #94-830

Dear Dr. Pazdur:

Orphan Medical submits this response to the FDA's facsimile dated June 25, 2002, in which the Agency presented its second version of labeling for Busulfex to incorporate pediatric information. Orphan Medical provides comment to the FDA's proposed dose-adjustment formulae and their rationale in Attachment 1: DISCUSSION OF DOSE-ADJUSTMENT STRATEGY.

A copy of Orphan Medical's revised package insert is attached. The FDA's instructions for dose-adjustment have been replaced by an AUC-based calculation reflective of current clinical practice. Other minor changes to labeling are shown on pages 14, 15, 28, and 30.

In addition, Orphan Medical seeks clarification of the clearance and volume terms included for pediatric patients in the Pharmacokinetics section. The figures for clearance — ml/min/kg) and volume of distribution (—) appear to be substantially greater than those cited in published literature (Schuler 2001, Hassan 1996) (Attachment 4). These units were not included in the previous FDA insert. Given this discrepancy, Orphan Medical wishes to confirm the accuracy of these values.

Please reference Table III, p. 948 in the Schuler article, and Table I, p. 398 in the Hassan article. The Schuler article is included as a reference for intravenous busulfan.

We look forward to our teleconference with the FDA at 12:45 (CST) today to discuss these issues.

Sincerely,

Carol S. Curme, R.A.C.
Senior Manager of Regulatory Affairs
Phone: (612) 513-6974

Cc: Dayton Reardan, Ph.D., Vice-President Regulatory Affairs
Sean Bradley, FDA Project Manager

ATTACHMENT 1: DISCUSSION OF DOSE-ADJUSTMENT STRATEGY

FDA'S RECOMMENDATION:

For Pediatric patients ≤ 12 kgs:

For Pediatric patients > 12 kgs:

Rationale: "Therapeutic Drug Monitoring: Although dose adjustment based on several samples/AUC is scientifically preferable, it is believed that this recommendation would not be practicable/feasible in a clinical setting. Therefore, dose adjustment based on the original FDA suggestion of C2hr has been re-inserted, but in the mathematical form used by Orphan Medical (instead of the dose adjustment nomogram)"

ORPHAN MEDICAL'S RESPONSE:

OMI agrees with FDA's suggestion to include a formula to assist in dose adjustment however we suggest that a dose-adjustment formula based on AUC is more appropriate to reflect current clinical & pharmacokinetic practice in the USA. In addition use of AUC improves accuracy and precision and thereby ensures increased safety in interpretation and clinical application of these time-critical clinical data. These points are discussed below.

Current Clinical / Pharmacokinetic Practice

The internationally accepted standard for dose-adjustment of busulfan based regimens is AUC or estimation of C_{ss} values derived from AUC. (C_{ss} = concentration at steady state = AUC divided by dosing interval).

In the US several established institutions (Attachment 2) perform busulfan pharmacokinetic analysis for their own patients, or on behalf of other clinical centers. Transplant centers routinely collect 6 or more busulfan plasma samples for analysis - 3 samples are considered the minimum for calculation of AUC. The PK laboratories (or the clinical sites) use validated computer programs, such as WinNonlin, to calculate and report busulfan AUC, C_{ss} and other PK parameters. The AUC or C_{ss} results are then used by clinicians to determine if dose adjustment is required. The usual formula for dose adjustment is

"dose (mg) = Actual Dose (mg) x Target AUC(µMol•min)/Actual AUC(µMol•min)"

A sample laboratory report from [redacted] is provided in Attachment 3. [redacted] is considered a reference laboratory for busulfan pharmacokinetic analysis and acted as the central PK laboratory for the Busulfex development program.

In consideration of the above, OMI is not aware of any clinical center or accredited pharmacokinetic laboratory in the USA who use single sample plasma-concentration data to dose-adjust busulfan-based treatment. Further we are not aware of any published literature where a single busulfan plasma-concentration sample is applied for dose-adjustment.

Dose Adjustment using one plasma sample

We acknowledge that limited sampling strategies (LSS) are widely accepted and clinically appropriate. All published and current clinical applications of LSS utilize at least 3 data points which is considered clinically appropriate for the following reasons

1) at least 3 data points are needed to determine AUC which (as described above) is the key PK parameter for estimation, analysis and comparison of individualized systemic exposure.
2) validated computer models allow identification of potentially erroneous samples, and allow AUC estimation even if 1 sample was erroneously collected

In addition, clinical application of the proposal to use a single 2hr sample may not be ideal for the following reasons:

1) due to institutional variations in nursing & IV administration practice or technical difficulties C2hr may not always represent the end of the Busulfex infusion
2) even in patients whose infusions run exactly 2 hrs, the scheduled sample may not always be taken at the correct (2hr) time-point due to competing medical priorities
3) there is no mechanism to correct the dose-adjustment calculation for late samples (samples not taken at 2 hrs)
4) this single time point may not be applicable in patients whose clearance and volume term are not highly correlated (in contrast to the BUS-5 patients, n=24).

Summary and Alternative Proposal

In conclusion OMI feels that the FDA proposal is not consistent with current clinical & pharmacokinetic practice, would require significant educational efforts and may be associated with a greater margin for error (compared to AUC based methods). In view of the above OMI proposes to revert to our proposed labeling of 13th June 2002 in relation to dose adjustment:

"Therapeutic drug monitoring and dose adjustment following the first dose of BUSULFEX is recommended. ——— ———

——— dose (mg) = Actual Dose (mg) x Target AUC(μMol•min)/Actual AUC(μMol•min)"

OMI feels that this approach is reflective of current clinical practice and allows increased safety in interpretation and clinical application of these time-critical clinical data..In addition provision of a formula for calculation of AUC is not required given that most labs automatically calculate this parameter for the clinician.

Attachment 2: Major US Busulfan PK Testing Facilities

The US facilities who represent the majority of on-shore busulfan pharmacokinetic testing are listed below:

- [redacted]

124 pages redacted from this section of the approval package consisted of draft labeling

Redacted 11

pages of trade

secret and/or

confidential

commercial

information

DUPLICATE

ORPHAN MEDICAL

June 17, 2002

Richard Pazdur, M.D.
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SE2-004
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JUN 19 2002
HFD-150 / CDER

SUBJECT: **Busulfex® (busulfan) Injection**
NDA #20-954 / S-004
User Fee #3,396, Orphan Designation #94-830
Follow-up Information to May 22, 2002 Submission; Response to FDA Facsimile dated May 28, 2002; Meeting Request dated June 6, 2002 Regarding the Supplement of Pediatric Information

Dear Dr. Pazdur:

Orphan Medical, Inc. submits in duplicate this response to the FDA, regarding the supplement of pediatric information (NDA #20-954/S-004), which includes the following components: 1) Follow up information to Orphan Medical's May 22, 2002 submission, which was made in response to the FDA's facsimile dated April 25, 2002; 2) Response to the FDA's facsimile dated May 28, 2002; and 3) Orphan Medical's meeting request dated June 6, 2002, for a Teleconference with the FDA's Division of Oncology Drug Products on June 7, 2002.

To expedite the FDA's review, Orphan Medical previously submitted a response to the Agency's facsimile dated May 28, 2002, by e-mail to Sean Bradley, Regulatory Project Manager, Division of Oncology Drug Products, on May 29, 2002. Orphan Medical's meeting request dated June 6, 2002 (Attachment 4) was also previously submitted by e-mail to Sean Bradley on June 6, 2002. With the exception of the enclosed follow-up information to the May 22, 2002 submission, the content of this submission is the same as that previously submitted by e-mail.

On May 22, 2002, Orphan Medical submitted a response to the FDA's facsimile dated April 25, 2002. This facsimile included a request for Orphan Medical to provide the institutional guidelines for prophylaxis and treatment of acute GVHD for each clinical trial site. In the May 22, 2002 submission, it was stated that the Institutional Guidelines for Site 14, Rainbow Babies and Children's Hospital, Cleveland, Ohio, had been requested by our Contract Research Organization, and that these guidelines would be forwarded to the Division upon receipt by Orphan Medical. Orphan Medical has since received the GVHD guidelines for this site, which are included in Attachment 1.

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

On May 28, 2002, the FDA requested via facsimile, a copy of the adverse drug experience report of myocardiopathy, manufacturer report number 01-009. Orphan Medical previously submitted this report to the FDA on May 17, 2001. A copy of the facsimile request is included in Attachment 2. A copy of the adverse drug experience report is included in Attachment 3. This report was previously sent by e-mail to Sean Bradley, on May 29, 2002.

On June 6, 2002, Orphan Medical requested, by e-mail to Sean Bradley, a June 7, 2002 teleconference with the FDA's Division of Oncology Drug Products, to obtain clarification of the FDA's proposed dosing recommendations for Busulfex® in pediatric patients. A copy of the e-mail, and a signed copy of the meeting request, is included in Attachment 4. On June 7, 2002, Orphan Medical agreed with the FDA to cancel the requested meeting.

If you have any questions or require additional information, please contact me directly.

Sincerely,

Carol D. Curme

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

cc: Dayton T. Reardan, Ph.D., R.A.C., Vice-President of Regulatory Affairs
Sean Bradley, R. Ph., FDA Regulatory Project Manager

ORPHAN MEDICAL

DUPLICATE

SE2-004
BL

June 17, 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

RECEIVED
JUN 19 2002
HFD-150 / CDER

Subject: **Busulfex® (busulfan) Injection; NDA #20-954/S-004**
Response to Facsimile, dated May 24, 2002
Regarding the Supplement of Pediatric Information
User Fee #3,396, Orphan Designation #94-830

Dear Dr. Pazdur:

Orphan Medical submits this response to the FDA's facsimile dated May 24, 2002, in which the Agency presented its recommended labeling for Busulfex to incorporate pediatric information. A response to the FDA's proposed labeling was previously submitted by e-mail on June 14, 2002. This formal response includes minor revisions to the list of attachments.

The red-line version of the FDA's insert is in Attachment 1. Orphan Medical's proposed package insert, in Attachment 2, is a red-line version of the draft insert that was submitted in the efficacy supplement dated December 21, 2001. Orphan Medical's package insert with changes accepted, in Attachment 3, was submitted to the FDA by e-mail in Word 6.0/95 on June 14, 2002.

The table in Section 1 of this response highlights the differences between the FDA's recommended changes and Orphan Medical's revised package insert, and provides a rationale for our position. These differences are referenced by paragraph and sentence of the draft insert with accepted changes. We recommend that the reviewer reference the FDA's red-line insert when reading this table. Topics that require a more detailed discussion are addressed in Section 2.

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The most significant difference between the FDA's proposed labeling and Orphan Medical's version is the dosing section that now includes: 1) [redacted] dosing regimens; and 2) a recommendation for dose adjustment that involves the calculation of a target dose using an AUC value based on three blood samples collected at different time points after infusion. Orphan Medical and the FDA discussed these points last week, and a facsimile from the FDA dated June 7 suggests that the FDA may be amenable to these changes. In addition to these changes, Orphan Medical has added specific instructions on collecting blood samples for pharmacokinetics analysis. This was added in response to the FDA's recommendation for dose-adjustment in the labeling. Based on our experience, we believe that these explicit instructions will minimize errors in calculating a target dose.

In the FDA's Request #10 (dated June 10, 2002), we were asked to provide some labeling instruction that explicitly describes how AUC should be calculated. Orphan Medical suggests in the label the AUC should be calculated from at least 3 blood samples. However, Orphan Medical does not feel that it is appropriate to provide instruction on how to calculate AUC given the variety of methods and computer programs available.

If you have any questions about this response, please feel free to contact me directly.

Sincerely,

Carol S. Curme

Carol S. Curme, R.A.C.
Senior Manager of Regulatory Affairs
Phone: (952) 513-6974

cc: Dayton Reardan, Ph.D., Vice-President Regulatory Affairs
Sean Bradley, FDA Project Manager

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:** June 13, 2002
Re: NDA 20-954/S-004 FDA Draft Labeling	

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

Carol –

Here is another FDA suggested labeling for Busulfex for your review:

In the PRECAUTIONS section, Special Populations, Pediatric subsection, 3rd paragraph:

[illegible]

1

If you have any questions regarding this transmission, please contact me at 301-594-5750.

Sean Bradley, R.P.h.

Regulatory Project Manager

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:**	June 10, 2002
Re:	NDA 20-954/S-004 Clinical Info Request #12		

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

Carol –

Further to your therapeutic drug monitoring proposal (three samples, adjust based on AUC), could you please provide FDA with:

- a rationale for the sampling times chosen
- a rationale and some Labeling instruction that explicitly describes how AUC should be calculated.

If you have any questions regarding this transmission, please contact me at 301-594-5750.

Sean Bradley, R.Ph.

Regulatory ~~Project~~ Manager

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	JUN 12 2002
Pages, including cover sheet:	1	**Date:** June 7, 2002	
Re:	NDA 20-954/S-004-FDA Responses to labeling questions		

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

Carol –

Here are our responses to your labeling questions. Have your team review the answers and if there is any questions, then will discuss these issues further this afternoon. If our answers are clear to your team and you feel today's meeting isn't necessary, please let me know.

Regards,

Sean Bradley, R.Ph.

Regulatory Project Manager

4 pages redacted from this section of the approval package consisted of draft labeling

Please label this as an SNC. S-004 NDA 20-954/S004 SEB.

DUPLICATE

RECEIVED
JUN - 7 2002
HFD-150 / CDER

SUPPL NEW CORRESP
SNC to S-004

June 6, 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

NDA 3 10 JUN 02

Subject: Busulfex® (busulfan) Injection; NDA #20-954/S-004
Request for Teleconference
Regarding the Supplement of Pediatric Information
User Fee #3,396, Orphan Designation #94-830

Dear Dr. Pazdur:

Orphan Medical, Inc. requests a teleconference with the FDA's Division of Oncology Drug Products to obtain clarification of the FDA's proposed dosing recommendations for Busulfex in pediatric patients. The proposed date for the teleconference is June 7 at 9:00 am (CST) and 10:00 am (EST).

Our consultant (pharmacokineticist) will be at a separate location from Orphan Medical. We propose to call the FDA with our consultant on the other line. If you accept this meeting request, please provide the phone number of the conference room with the FDA's attendees.

Information for the teleconference request is provided on the following pages. We appreciate the opportunity to discuss these issues with the FDA on such short notice. If you have any questions or require additional information, please contact me directly.

Sincerely,

Carol S. Curme, R.A.C.
Senior Manager of Regulatory Affairs
Phone: (612) 513-6974

Cc: Dayton Reardan, Ph.D, Vice-President Regulatory Affairs
Sean Bradley, FDA Project Manager

Requested Meeting Date: June 7, 2002

Meeting Time: 9:00 - 10:00 am (CST)

List of Attendees from Orphan Medical:

—	Pharmacokinetics consultant, — —
David Fuller, M.D.	Vice-President of Medical Affairs, Orphan Medical
Shari Lennon	Director of Busulfex Development, Orphan Medical
Carol Curme	Senior Manager of Regulatory Affairs, Orphan Medical

List of Requested Agency Staff:

Medical Reviewer or Team Leader
BioPharm Reviewer or Team Leader

Background Information:

Orphan Medical submitted an efficacy supplement (S-004) in December 2001, which included a draft package insert with pediatric information that was based on our clinical trial of 24 pediatric patients (OMC-BUS-5). The package insert included dosing recommendations for pediatric patients that was derived from a population pharmacokinetic analysis. The proposed dosing regimen derived from the analysis consisted of the following four dosing categories based on actual body weight.

Proposed dose-regimen for IV busulfan in pediatrics

[redacted]

On May 15, 2002, the FDA provided Orphan Medical with a pharmacometric report that included a critique of Orphan Medical's population pharmacokinetic analysis, followed by a description of the FDA's analysis using different methodology. The result of the FDA's analysis was two possible dosing regimens for pediatric patients:

- A dosing regimen based on actual body weight (ABW) whereby patients ≤ 12 kg receive 1.1 mg/kg busulfan and patients > 12 kgs receive 0.8 mg/kg busulfan; and
- [redacted]

On May 24, 2002, Orphan Medical received the FDA's suggested labeling for Busulfex. The FDA made the following dosing recommendations under the PRECAUTIONS section, Pediatric subsection:

- [redacted]
- [redacted]

BUSULFEX can then be corrected to achieve the target exposure by the following adjustment:

List of Questions:

Orphan Medical presents the following list of questions with regard to the FDA's dosing recommendations:

1. The BMT community aims to give pediatric patients the same busulfan exposure as adult patients. Calculation of the Busulfex dose is based on either actual body weight (mg/kg) or body surface area (mg/m^2). Therefore, it is important to provide a dosing recommendation for both methods. Orphan Medical understands and accepts the FDA recommendation for the mg/kg dosing (1.1 or 0.8 mg/kg for patients $\leq$ 12 kg or > 12 kg, respectively). However, the FDA recommended — — not seem to correlate to the recommended mg/kg doses.

Orphan Medical seeks to understand the methodology and recommendation for the — in order to facilitate communication with the BMT community, as well as reconcile the — dose for pediatric patients with the FDA approved adult dose of 0.8 mg/kg.

2. Orphan Medical supports the FDA recommendation for therapeutic drug monitoring and dose adjustment following the first dose of Busulfex. Consistent with dosing practices in the

pediatric transplant community, we would recommend that both ___ dosing be provided as described above. The proposed nomogram for dose adjustment is applicable to patients dosed per ___. In view of this, we would like to propose an alternative approach (see below) that is consistent with current clinical practice in the pedatric transplant community and is applicable to either ___ -based dosing. Would the agency please comment on this proposal?

Alternate Pharmacokinetic (PK) testing and dose adjustment approach:

PK testing:

Collection of three blood samples at the following time points: 2 hr (end of infusion), 4hr and 6hr post (immediately prior to the next scheduled Busulfex administration).

Dose Adjustment:

___ Dose (mg dose based on either mg/kg or mg/m^2) = Actual dose administered (mg) x Actual AUC (uMol-min) /Target AUC

Rationale for Alternate PK testing and dose adjustment approach:

This alternate approach allows the clinician the opportunity for evaluation and review of the patient's pharmacokinetic profile (rather than a single busulfan concentration time point) and provides an opportunity for feedback on the dosing recommendation. This alternate approach should increase the safety of this process in two specific ways: 1) with collection of greater than one blood sample, chances of a successful result increase. With the collection of only one sample, while we acknowledge that this is theoretically possible, in the clinical setting can introduce chance of error in sample collection and

thus affect recommended dosing adjustments. 2) collection of greater than one sample will allow calculation of each individual patient's pharmacokinetic profile, thus increasing on an individual basis, a dose adjustment which may more reliably achieve the intended therapeutic target exposure. Further, by allowing the clinician the opportunity to review the data in a manner that is consistently and currently used in the pediatric community (i.e., either AUC or Css [Concentration at steady state] individual patient clinical considerations can be taken into account when a dose adjustment appears warranted. Introduction of a single busulfan concentration level and clinical interpretation of this single point will be unfamiliar and may hinder the ability to individualize dosing for a patient.

Further, the nomogram proposed for — -based dosing is based on a patient population where the clearance (CL) and volume of distribution (V) parameters were similar. It appears that with use of the proposed nomogram, if CL and V are not similar, the nomogram does not consistantly guide dose adjustment into the target range. Further, based on a single blood concentration value, it appears that if a patient has a C2hr value other than 1000 ng/ml, dose adjustment will be required. Could the agency comment on this?

3. Please provide your formula for calculation of — resulting in — for pediatric patients of both genders.

4. To better appreciate the FDA NONMEM analysis, Orphan Medical requests a copy of the full report, including the output tables and listings.

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:**	May 28, 2002
Re:	NDA 20-954/S-004 Clinical Info Request #11		

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

Carol –

Please submit a copy of the ADE report of myocardiopathy previously submitted to the FDA on 5-17-01.

If you have any questions regarding this transmission, please contact me at 301-594-5750.

Sean Bradley, R.Ph.

Regulatory Project Manager

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:	33	**Date:**	May 24, 2002
Re:	NDA 20-954/S-004 FDA Draft Labeling		

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

Carol –

Here is a copy of the FDA suggested labeling for Busulfex for your review.

If you have any questions regarding this transmission, please contact me at 301-594-5750.

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

Bradley, Sean

From: Carol Curme [CCURME@orphan.com]
Sent: Friday, May 24, 2002 9:40 AM
To: 'bradleys@cder.fda.gov'
Subject: FW: Busulfex 20-954/S004 ADE info

This is my second attempt to send you this message.

-----Original Message-----
From: Carol Curme
Sent: Friday, May 24, 2002 8:35 AM
To: 'bradleys@cder.fda.gov'
Cc: 'dagherr@cder.fda.gov'
Subject: Busulfex 20-954/S004 ADE info

Dear Sean,

This e-mail is in response to Dr. Dhager's question about a listing of post-marketing adverse experiences in the efficacy supplement (S-004). This information can be found in Section 8.8 (ISS), Table 8.9. Section 8.6.3 (Commercial Marketing Experence) includes a hypertext link to Table 8.9.

In reference to Dr. Dhager's question about GVHD criteria, the tables in Section 10.1.1 appear to be consistent with the Case Report Form in the original protocol and in subsequent amendments.

Please let me know if you require any further assistance to you.

Sincerely,

rol S. Curme, RAC
nior Manager of Regulatory Affairs
Orphan Medical, Inc.
phone: 952-513-6974
fax: 952-541-9209
e-mail: ccurme@orphan.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Orphan Medical, Inc.	May 22, 2002
TELEPHONE NO. *(Include Area Code)* (952) 513-6900	**FACSIMILE (FAX) Number** *(Include Area Code)* (952) 541-9209

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

13911 Ridgedale Drive, Suite 250
Minnetonka, MN 55305

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code , telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 20-954

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
busulfan (USAN)	Busulfex® (busulfan) Injection

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
sterile liquid	60 mg ampoule	intravenous

(PROPOSED) INDICATION(S) FOR USE: for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☒ Prior Approval (PA)

REASON FOR SUBMISSION Response to FDA Facsimiles dated April 22, 23, & 25, 2002

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

All sites are ready for inspection. SUBSTANCE:
PRODUCT:

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 46,232; DMF — DMF — ; DMF — DMF — DMF — DMF — DMF — DMF — DMF — DMF — DMF

This application contains the following items: *(Check all that apply)*	
XX	1. Index
XX	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j) (2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
(	20. OTHER *(Specify)* Response to FDA Facsimiles dated April 22, 23, & 25, 2002

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Carol S. Curme	Carol S. Curme, J.D., RAC, Senior Manager of RA	5/22/2002

ADDRESS *(Street, City, State, and Zip Code)*	Telephone Number
13911 Ridgedale Drive, Suite 250, Minnetonka, MN 55305	(952) 513-6900

Public reporting burden for this collection of information is estimated to average 24 hours 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:

partment of Health and Human Services
d and Drug Administration
ER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

FORM FDA 356h (4/00)

ORPHAN MEDICAL

ORIGINAL

NDA SUPP AMEND

SE2-004
BL

May 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

RECEIVED
MAY 23 2002
HFD-150 / CDER

Subject: Busulfex® (busulfan) Injection; NDA #20-954/S-004
Response to FDA's Facsimiles dated April 22, 23, & 25, 2002
Regarding the Supplement of Pediatric Information
User Fee #3,396, Orphan Designation #94-830

Dear Dr. Pazdur:

Orphan Medical, Inc. submits in duplicate this response to the FDA's facsimiles dated April 22, 23, & 25, 2002, regarding the supplement of pediatric information (NDA #20-954/S-004). Copies of these facsimiles are included in Attachment 1. Orphan Medical's responses to the FDA's questions presented in the three facsimiles are included in this submission.

To expedite the FDA's review, Orphan Medical previously submitted responses to the Agency's inquiries by facsimile or e-mail. With the exception of Response #3 (with Attachment 8) of Orphan Medical's facsimile dated May 6 (i.e., regarding institutional guidelines), the content of this submission is the same as that previously submitted in the following correspondences:

- Email Response dated April 30, 2002 to FDA Facsimile dated April 22
- Email Response dated May 5, 2002 to FDA Facsimile dated April 23
- Fax Response dated May 6, 2002 to FDA Facsimile dated April 25

In addition to the responses described above, this submission includes a CDRom containing files of the proposed package insert (MSWord 6.0/95) and a corrected version of the annotated package insert (Adobe Acrobat 4.0). These exact files were previously submitted to the FDA by e-mail on April 29, 2002.

13911 Ridgedale Drive Suite 250 • Minnetonka, Minnesota 55305
952-513-6900 • Fax: 952-541-9209 • www.orphan.com

This was done in response to Dianne Spillman's (FDA's Project Manager) request by telephone on April 22, 2002. In that message, Ms. Spillman stated that the FDA would require an electronic copy of the package insert that was compatible with MSWord 1997. She also informed me of omitted text in the annotated package insert under PRECAUTIONS: Hematologic. This omission has been corrected.

Please contact me directly, should you have any questions or concerns.

Sincerely,

Carol S. Curme, J.D., R.A.C.
Senior Manager of Regulatory Affairs
Direct line: (952) 513-6974
Main no.: (952) 513-6900

cc: Dayton Reardan, Ph.D., R.A.C., Vice-President of Regulatory Affairs
Sean Bradley, R. Ph., Regulatory Project Manager

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:**	May 20, 2002
Re:	NDA 20-954/S-004 Clinical Info Request #10		

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

Carol –

As discussed during our May 10, 2002 teleconference it is the reviewers' position that patient 23501 did meet the clinical criteria for VOD as outlined in the protocol. Furthermore, although the patient's liver biopsy report does not indicate the presence of definitive histologic changes associated with VOD, it is known that the pathologic lesions of VOD can be patchy in nature. Finally, the criteria outlined in the protocol do not require the presence of histologic findings

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
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: 19	**Date:** May 15, 2002
Re: NDA 20-954/S-004 Pharmacometric Review	

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

Carol –

Attached you will find an abridged version of the Pharmacometric report for Busulfex. It is our practice to forward this to you as a courtesy.

If you have any questions regarding this transmission, please contact me at 301-594-5750.

Sean Bradley, R.Ph.
Regulatory Project Manager

1 pages redacted from this section of the approval package consisted of draft labeling

MEMO OF TELECON

IND: NDA 20-954/S004 **Drug:** Busulfex (busulfan) Injection

Date: May 10, 2002 **Time:** 3:58 PM, EST **Phone:** 952-513-6974

Sponsor: Orphan Medical

FDA

Ramzi Dagher, M.D. Medical Reviewer
Sean Bradley, R.Ph. Project Manager

ORPHAN MEDICAL

Carol Curme, R.A.C. Senior Manager of Regulatory Affairs

Discussion Summary

Dr. Dagher had two major issues that he wanted to discuss with Ms. Curme regarding Orphan Medical's sNDA submission:

1. Regarding the assessment of Graft Versus Host Disease (GVHD), the staging criteria faxed to the Agency 06MAY02 is not similar to the staging criteria described in the original protocol in the following areas: two tables of comparison versus one, diarrhea is measured in different units, and SGOT is not in the case report forms.

2. Regarding the incidence of Veno-occlusive disease (VOD), we will be considering patient #23501 as (+) VOD based on the criteria listed in the protocol

Action Items:

1. Orphan Medical will send clarification regarding the differences in the staging criteria for GVHD.

The teleconference concluded at 4:15 PM, EST. There were no unresolved issues.

/S/ 12 JUN 02
Sean Bradley, R.Ph., Project Manager

/S/
Ramzi Dagher, M.D., Medical Reviewer

ORPHAN MEDICAL

FAX TRANSMISSION

13911 Ridgedale Drive
Minnetonka, Minnesota 55305
Voice: 952-513-6900
Facsimile: 952-541-9209

Date: May 6, 2002

Deliver to: Sean Bradley, R. Ph., Regulatory Project Manager

Fax #: (301) 827-4590

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

Number of Pages Including Cover Page: 15

Dear Sean,

Please find a copy of Orphan Medical's response to the FDA's questions presented in the facsimile dated April 25, 2002. This response will be followed by a hard-copy submission to the sNDA.

Sincerely,

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

ORPHAN MEDICAL

May 6, 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 the FDA's Facsimile dated April 25, 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 presented in the facsimile dated April 25, 2002, relating to the supplement of pediatric information. A copy of this facsimile is included in Attachment 1. Orphan Medical's responses to the questions presented in the facsimile are presented on the following page.

Please contact me directly with any questions or concerns.

Sincerely,

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

cc: Dayton Reardan, Ph.D., RAC, Vice-President of Regulatory Affairs
Sean Bradley, R. Ph., Project Manager

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RESPONSE TO THE FDA'S QUESTIONS

Facsimile dated April 25, 2002

FDA's request: 1. Please provide results of the skin biopsies obtained in the following patients with GVHD: 03501, 09502 and 10502.

RESPONSE: The skin biopsy reports for the patients with GVHD listed above are included in Attachment 2.

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?

RESPONSE: The criteria for assessment of GVHD are detailed in the Source Worksheet, Criteria for Assessment of Acute GVHD. This worksheet is included in Attachment 3.

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.

RESPONSE: Per the protocol, GVHD prophylaxis and treatment of acute GHVD were performed per institutional guidelines. These institutional guidelines were provided in the original submission for the majority of the OMC-BUS-5 clinical sites; see Section 8.5.4, OMC-BUS-5 Final Study Report, Appendix 16.1.5: Institutional Standard Care Guidelines. The table included on the following page provides the location of the appropriate guidelines per site.

The institutional guidelines for Site 9 (Children's Memorial Hospital) and Site 14 (Rainbow Babies and Children's Hospital) have been requested by our Contract Research Organization. Orphan Medical is waiting to receive the information.

The institutional guidelines for Site 15 (Emory University School of Medicine) are included in this response as Attachment 4.

Prophylaxis and Treatment of Acute GVHD	Site Number/Principal Investigator	Location in Appendix
UT M.D. Anderson Cancer Center	10/Chan, Ka Wah, MD	2213-2215
University of Connecticut Health Center	04/Feingold, Jay M., MD, PhD	2141, 2149
St. Louis Children's Hospital	02/Hayashi, Robert, MD	2109
Children's Hospital and Health Center	08/Kadota, Richard, MD	2157
All Children's Hospital	03/Klemperer, Martin, MD	2120, 2129-2131
Children's Memorial Hospital	09/Kletzel, Morris, MD	Requested by CRO, awaiting response
Rainbow Babies and Children's Hospital	14/Nieder, Michael, MD	Requested by CRO, awaiting response
Baylor College of Medicine	23/Przepiorka, Donna, MD, PhD	2270-2271, 2273-2274
Cardinal Glennon Children's Hospital	01/Wall, Donna, MD*	2082-2083, 2093
Emory University School of Medicine	15/Yeager, Andrew M., MD	Included in Attachment 4

* This investigator has since relocated to Texas Transplant Institute, San Antonio, Texas

APPEARS THIS WAY
ON ORIGINAL

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 Curne	**From:**	Sean Bradley
Fax:	952-541-9209	**Fax:**	301-827-4590
Phone:	952-513-6874	**Phone:**	301-594-5750
Pages, including cover sheet:	1	**Date:**	April 25, 2002
Re:	NDA 20-954/S-004 Clinical Info Request #9		

☐ **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, CDR, USPHS
Regulatory Project Manager

/S/

Division of Pathology
and Laboratory Medicine

SURGICAL PATHOLOGY REPORT

Name: [redacted] Surgical Number: —

Hospital Number: [redacted] Sex: Female Date: —

Date of birth: — Age: 11 years Physician: —

Clinical data provided: Skin rash, rule out graft versus host, 19 days status post BMT

Gross description: Specimen, labeled "Skin biopsy", consists of a small 2 mm punch biopsy of pale tan skin. The specimen is submitted in toto in one cassette.
KW:bg

Microscopic description: Histologic section consists of skin in which the usual architectural pattern is distorted by vacuolar alteration along the dermal epidermal border. In addition to the vacuolar changes, an occasional necrotic keratinocyte is present. Perivascular lymphocytic inflammatory cell is observed within the papillary dermis.

Diagnosis: Punch biopsy, site unspecified:
- Epidermis with rare necrotic keratinocyte and vacuolar alterations. (See Comment.)

Comment: Although the changes seen may represent early graft-versus-host disease, some drug reactions may demonstrate similar histopathologic changes. Clinical correlation is required.
KW:mp

/S/
M.D
M.D., Pathologist

Date of Report: —

OMC-IBVS-5
03501-LMM

Division of Pathology
and Laboratory Medicine

SURGICAL PATHOLOGY REPORT

Name: [redacted] Surgical Number: —

Hospital Number: [redacted] Sex: Female Date: —

Date of birth: — Age: 11 years Physician: —

Clinical data provided: 11-year-old with mannosidosis, status post BMT, skin rash, rule out GVHD, rule out drug rash

Gross description: Specimen consists of a 2 mm punch biopsy of skin and is not labeled as to the site of the biopsy. The specimen is submitted in toto in one cassette.
WC:sa

Microscopic description: Histologic sections consist of skin demonstrating a moderately dense diffuse lymphocytic infiltrate in the upper dermis with extensive exocytosis. The overlying epidermis shows basal spongiosis and early vesiculation with scattered degenerated keratinocytes. Some of these keratinocytes have pyknotic nucleus and eosinophilic, hyalinized cytoplasm. These necrotic keratinocytes are often associated with one or more satellite lymphocytes. No overt viral cytopathy is seen.

Diagnosis: Punch biopsy of skin:
- Vesicular dermatitis most consistent with graft-versus-host disease.

WC:bg

/S/ _____, M.D. Date of Report: —
M.D., Pathologist

OMC-BUS-5
03501_LMM

SURGICAL FINAL REPORT

*** Converted Case * This report may not match the original report format**

Patient Name: [redacted]
Gender: [redacted]
DOB: [redacted]
MRN:
Location:
Case #:
Surgery Date:
Received:
Reported:

Physician(s): M.D.*
M.D.*

Copy To:

Final Pathologic Diagnosis

DIAGNOSIS: Skin of thigh, biopsy: SKIN CONSISTENT WITH GRAFT VERSUS HOST DISEASE, GRADE I-II.

M.D.

SNOMED CODE:
PRE-OP/POST-OP DIAGNOSIS:
AG
NAG
NOT GIVEN
Imp TUMOR BOARD

Date Signed:
FROZEN SECTION:
AG
NAG
DEF

Sunquest Archived Tests:
DATE OF BIRTH : NONE

Electronically Signed By
Conversion

Previous Specimen(s)

S98-4539 Status: Signed Out Specimen(s) 1: SIGMOID, 2: SIGMOID
C98-314 Status: Signed Out Specimen(s) FLUID NOT SPECIFIED
C98-312 Status: Signed Out Specimen(s) BRONCHIAL
C98-307 Status: Signed Out Specimen(s) CSF
C98-281 Status: Signed Out Specimen(s) BRONCHIAL ASPIR/WASHING
S98-2830 Status: Signed Out Specimen(s) LIVER

Specimen(s) Received

SKIN BX

Other Related Clinical Data

472687

PATHOLOGY REPORT

SURGICAL #:
PATIENT: [redacted]
DATE RECEIVED:
PHYSICIAN:
HOSPITAL #: [redacted]
M.D. LOC:
M.D.DERMATOLOGY
M.D. DERMATOLOGY
PREVIOUS CASE:
PRE-OP DX: R/O GVHD, LEFT THIGH
POST-OP DX: NO DIAGNOSIS GIVEN
CLINICAL DATA: YEAR OLD FEMALE, S/P ALLOGENEIC BMT FOR BETA-THAL MAJOR, DAY +12, NOW WITH ERYTHEMATOUS MACULES AND PATCHES DIFFUSELY
SPECIMEN LABELED: SKIN BIOPSY

Sunquest Archived Tests:
DATE OF BIRTH : NONE

Sunquest SNOMED Translations for original 598-3479:
T02810010I (SKIN OF THIGH, NOS), 240 (GRAFT VS HOST DISEASE) ;GRADE I-II

Gross Description

GROSS DESCRIPTION:

Received in formalin labeled left thigh, is a single cylindrical fragment of brown skin and subcutaneous tissue measuring 0.6 x 0.4 x 0.2 cm. The specimen is bisected and entirely submitted in one cassette.

Microscopic Description

MICROSCOPIC EXAMINATION:

The specimen consists of a portion of skin with vacuolization of the basal layer, and occasional apoptotic body. Focal lympho-cytic infiltrate is present in the dermis, as well as epidermis. The papillary dermis is edematous with perivascular inflammatory infiltrate.

MAY.01'2002 10:51

PATHOLOGY/CYTOLOGY RESULTS MR# M DOB: MDAH:

RECD: FINAL DATE:

J

NOSIS:

SKIN, RIGHT ARM, MEDIAL, BIOPSY:
Mild perivascular chronic superficial inflammatory cell infiltrate. No diagnostic evidence of graft versus host disease.

(B) SKIN, RIGHT ARM, LATERAL, BIOPSY:
Skin with mild focal interface change and occasional apoptotic keratinocytes and mild superficial perivascular inflammatory infiltrate. (See Comment)

Entire report and diagnosis completed by: MD
Report released by: MD #

COMMENT:
Changes are minimal and not diagnostic of graft versus host disease. However, an early phase of graft versus host reaction can not be entirely ruled out.

B=BEGINNING

SELECTION: MED REC NUMBER: &(PF13)MAIN MENU ENTER TO CONT
ORCSUM27

10-502

PATHOLOGY/CYTOLOGY RESULTS MR# 1019

BAC/so
(dd: . . . . .)
:15

;S DESCRIPTION:

(A) SKIN, RIGHT ARM, MEDIAL - A punch biopsy of lightly pigmented skin (0.3 x 0.3 cm with thickness of 0.3 cm). The epidermal surface is unremarkable. INK CODE: Yellow ink applied to cut surfaces.
SECTION CODE: The entire specimen is submitted in cassette B. BS/kk
(B) SKIN, RIGHT ARM, LATERAL - A punch biopsy of lightly pigmented skin with a slightly mottled epidermal surface. The specimen measures 0.3 x 0.3 cm with thickness of 0.3 cm.
INK CODE: Yellow ink is applied to cut surfaces.
SECTION CODE: The specimen is entirely submitted in cassette B. BS/kk

END OF THIS REPORT-PRESS RETURN FOR NEXT REPORT
B=BEGINNING

SELECTION: __ MED REC NUMBER: _____ &(PF13)MAIN MENU ENTER TO CONT

CRITERIA FOR ASSESSMENT OF ACUTE GRAFT VERSUS HOST DISEASE

CLINICAL STAGE OF ACUTE GRAFT VERSUS HOST DISEASE ACCORDING TO ORGAN SYSTEM*

STAGE	SKIN	LIVER (Bilirubin)	GASTROINTESTINAL (Diarrhea)
0	No rash	<2 mg/dl	No changes
1	Maculopapular rash <25% of body surface area	2-3 mg/dl	> 10 ml/kg/24hrs
2	Maculopapular rash 25-50% of body surface area	3.1-6 mg/dl	> 16 ml/kg/24hrs
3	Generalized erythroderma	6.1-15 mg/dl	> 21 ml/kg/24hrs
4	Generalized erythroderma with bullous formation and desquamation	>15 mg/dl	Severe abdominal pain with or without ileus.

OVERALL CLINICAL GRADING OF SEVERITY OF GRAFT VERSUS HOST DISEASE

GRADE	SKIN	LIVER	AND/OR	GASTROINTESTINAL
I	+1 to +2	0		0
II	+1 to +3	+1	and/or	+1
III	+2 to +3	+2 to +3	and/or	+2 to +3
IV	+2 to +4	+2 to +4	and/or	+2 to +4

*If no skin disease, the overall grade is the higher single organ grade.

Prophylaxis of Acute Graft VS Host Disease

Acute GVHD occurs when the bone marrow graft recognizes the patient's body as being foreign and mounts an attack. The primary organs involved include the skin, GI tract and liver. Acute GVHD may be seen as the bone marrow starts to engraft, usually between days 14 -28 but may appear up to 100 days post allogeneic transplant. Immunosuppressive therapy is initiated pre and post BMT to help prevent this complication.

I. Clinical signs and symptoms:
Skin: maculopapular rash which usually starts on the palms and soles
Gut: profuse watery, green diarrhea which usually contains pieces of bowel tissue
Liver: elevation of total bilirubin (greater than 2.0), liver enzymes and alk phosphatase
See BMT toxicity grading sheets in order to document the grade and stage of GVHD

II. Therapeutic interventions:
Cyclosporin
- CSA 3 mg/kg/day IV as continuous infusion to start on day -1 (or as otherwise directed by the protocol).
- Check trough levels day +1 and day +4, then every Monday and Thursday. Keep level between 50 - 400 (monoclonal method). Levels run in the lab Qday at 1100. If the patient has signficant renal or liver toxicity, check the level Qday.
- Change administration of CSA to Q 12 hr dosing when patient is taking po. Mix in 50mg/20 cc D5W (max concentration) and infuse over 2 hours at 0800 and 2000.
- When patient is able to take po meds and has minimal diarrhea, give CSA 50% IV and 50% PO. If tolerated well, then give 100% po. The oral dose is 3 times the intravenous dose. Level should be checked every 3 days while making dose adjustments.
- If there is no GVHD, decrease the dose by 10% every 2 weeks, starting on day 90, (except for patients with aplastic anemia).

Special considerations:
- Administer CSA through CVL lumen marked with yellow adhesive. Drawn the CSA level from the lumen marked with red adhesive.
- Do not mix oral CSA in plastic or styrofoam cups; CSA adheres to plastic.
- Mix CSA in lipophilic solution (chocolate milk) in a glass container.
- Do not stop the CSA infusion for a high level unless the patient has renal toxicity. Decrease the subsequent dose by 10%.
- If a patient has received a mismatched or unrelated BMT it is particularly important that the CSA infusion not be stopped and that the level be maintained in the mid to upper range (200 - 400), especially during the time of engraftment or the patient has AGVHD.
- In general dose adjustments should be made by a range 10 - 15%. Always check to make certain that the specimen was drawn at the correct time and that the CSA infusion was turned off when the specimen was collected before decreasing the dose.

Side effects of CSA:
Hypertension, headaches, gum hyperplasia, tremors, blurred vision, seizures (rare)
Nephrotoxicity: for a creatinine greater than 2 to 2.5 times a patient's baseline, a dose reduction will be made on a sliding scale by a member of the BMT service.

FK506 (Tacrolimus)

- Similar in mechanism to Cyclosporin.
- Give 100mcg/kg/day IVdivided BID. The po dose is 3 times the IV dose.
- Maintain level between 8 - 18ng/ml.

Side effects of FK506:
Hyperglycemia and other side effects listed under Cyclosporin.

Methotrexate: give as directed by protocol. In general:

- 10 mg/m2 IV on days +1, +3, +6 for patients who may be a low risk for AGVHD and would benefit from developing a mild case, in terms of a "graft versus leukemia effect".
- 15 mg/m2 IV on day +1; 10 mg/m2 IV on days +3, +6, +11 for patients with an anticipated high risk of AGVHD.

Treatment of Graft-Versus-Host Disease

If a patient develops a skin rash (grade II) and there is evidence for bone marrow engraftment, a biopsy should be performed to collaborate the clinical diagnosis of GVHD. Early GVHD (grade I - II) may prove to show biopsy negative, even though the working clinical diagnosis may still continue to be GHVD. If there is good clinical evidence of disease in the skin, gut or liver, steroid therapy should be initiated at the discretion of the BMT attending.

Steroids

- For patients with grade II, start methlyprednisolone 2 mg/kg/day IV to be given BID and continue until symptoms improve.
- 7 - 10 days after the symptoms are gone, begin to taper the steroid by 10% every week.
- If there is no evidence of improvement after 7 days, give 5 - 10 mg/kg/day IV BID. If there is improvement with the higher dose of steroids, continue for 1 week, then decrease to 2 mg/kg/day and continue taper by 10% every week.
  Side effects of steroids: gastritis, mood swings, acne, hypertension, hyperglycemia, weight gain, cushingnoid appearance, immunosuppression, asceptic necrosis of the bones.
- If a patient presents with grade III - IV, consider adding ATG as well.

Anti-thymocyte Globulin

- ATG 15 mg/kg/dose BID for 10 doses.
- Mix in 1 mg/cc NS and infuse over 4 - 6 hours.
- Premed with 1 mg/kg methlyprednisolone (take into account existing dose of steroids on board) and benadryl 1 mg/kg (max 50 mg).
- Side effects: fever, chills, flu-like symptoms, puritic rash, allergic reaction(discontinue infusion if patient shows signs of anaphylaxis).

OKT3

- OKT3 is a monoclonal antibody to the T3 antigen of human T lymphocytes.
- It may be used as a replacement for Cyclosporin if previous therapy has failed.
- 2.5 mg IV for patients less than 30 kg; 5 mg IV for patients greater than 30 kg.
- The dose is given Qday for 5 - 10 days.
- Premed with tylenol, benadryl and methlyprednisolone; consider HC 50 - 100 mg 30 minutes after OKT3.
- Side effects: fever, chills, dyspnea, flu-like symptoms

Triamcinolone-