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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

14-691/S-020

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 14-691/SCS-020	**Submission Date:** May 21, 2001
Drug Name:	Alkeran® (melphalan)
Formulation:	Tablet, 2 mg
Applicant:	Glaxo Wellcome Inc. Five Moore Drive PO Box 13398 Research Triangle Park, NC 27709
Reviewer:	John Duan, Ph.D.
Type of Submission:	Response to Comments on Labeling

This is a Clinical Pharmacology and Biopharmaceutics (CPB) review on the applicant's responses to the Agency's comments on the labeling of Alkeran® tablets.

I. BACKGROUND

Alkeran® tablets (N14-691) are indicated for the palliative treatment of multiple myeloma and for the palliation of non resectable epithelial carcinomas of the ovary. Several dosage regimens have been employed, including 6 to 10 mg daily, 0.15 to 0.25 mg/kg daily, for 4 to 10 days as a treatment course. The dose is required to be adjusted on the basis of blood counts.

Alkeran tablets have been marketed in the United States since 1964. The drug product is currently manufactured at the facility in Greenville, North Carolina, by Glaxo Wellcome. The applicant has decided to transfer the production facility from Greenville, North Carolina, to Dartford, United Kingdom (UK). At the same time, since Alkeran® Tablets were developed almost 40 years ago, the applicant intends to reformulate and update the drug product prior to transferring the product to the new facility. Based on the agreements reached at the meeting dated November 20, 1996 and the teleconference dated March 14, 1997, the applicant submitted an IND [redacted] dated May 16, 1997, to the Agency to provide a basis for the review of clinical trials to compare two existing formulations of melphalan 2.0 mg with a new worldwide formulation manufactured at a new facility in Dartford, UK.

The current submission indicates that the applicant accepts the labeling comments made by the Agency. The revised draft labeling with these changes is provided.

II. COMMENTS

The applicant accepts the Agency's comments and provides the revised draft labeling.

IV. RECOMMENDATIONS

No action is necessary.

/S/

John Duan, Ph.D. Date

Reviewer
Division of Pharmaceutical Evaluation I

/S/

Atiqur Rahman, Ph.D Date

Team Leader
Division of Pharmaceutical Evaluation I

CC:

NDA 14-691	original
HFD-150	Division File
HFD-150	MPelosi
HFD-150	PCortazar
HFD-150	CLiang, EDuffy
HFD-860	MMehta, ARahman, JDuan
HFD-340	Vishwanathan
CDR	

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/s/

John Duan
7/17/01 09:39:07 AM
BIOPHARMACEUTICS

Atiqur Rahman
8/1/01 03:28:40 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 14-691/SCS-020	**Submission Date:** December 6, 2000
Drug Name:	Alkeran® (melphalan)
Formulation:	Tablet, 2 mg
Applicant:	Glaxo Wellcome Inc. Five Moore Drive PO Box 13398 Research Triangle Park, NC 27709
Reviewer:	John Duan, Ph.D.
Type of Submission:	Supplemental New Drug Application

This is a review of the Clinical Pharmacology and Biopharmaceutics (CPB) studies submitted in support of reformulated Alkeran® tablets.

I. SYNOPSIS

Alkeran® tablets (N14-691) are indicated for the palliative treatment of multiple myeloma and for the palliation of non resectable epithelial carcinomas of the ovary. Several dosage regimens have been employed, including 6 to 10 mg daily, 0.15 to 0.25 mg/kg daily, for 4 to 10 days as a treatment course. The dose is required to be adjusted on the basis of blood counts.

Alkeran tablets have been marketed in the United States since 1964. The drug product is currently manufactured at the facility in Greenville, North Carolina, by Glaxo Wellcome. The applicant has decided to transfer the production facility from Greenville, North Carolina, to Dartford, United Kingdom (UK). At the same time, since Alkeran® Tablets were developed almost 40 years ago, the applicant intends to reformulate and update the drug product prior to transferring the product to the new facility. Based on the agreements reached at the meeting dated November 20, 1996 and the teleconference dated March 14, 1997, the applicant submitted an IND [redacted] dated May 16, 1997, to the Agency to provide a basis for the review of clinical trials to compare two existing formulations of melphalan 2.0 mg with a new worldwide formulation manufactured at a new facility in Dartford, UK.

The current submission includes the results of a clinical study to show similarity of the new worldwide formulation to the present US and UK formulations. In addition, the dissolution test results for the proposed reformulated product and the current US commercial product are also provided.

This review is completed by Question Based Review approach focusing on the comparison between the new world wide formulation and the US formulation and also on the dissolution profile of the new formulation.

1. Has the bioequivalence between the reformulated products and the currently marketed formulation been established?

The applicant provided the current U.S. and the proposed formulations as shown below.

Current US Formulation		Proposed Reformulation	
Composition	Weight per Tablet	Composition	Weight per Tablet
Melphalan, USP	2.0 mg	Melphalan	2.00 mg
Sugar, NF		icrocrystalline Cellulose, NF	
Lactose		Crospovidone, NF	
Magnesium Stearate, NF		Colloidal Silicon Dioxide, NF	
Povidone, USP		Magnesium Stearate, NF	
Starch, Potato,			
Total Core Weight		Total Core Weight	
Coating		Coating	
No coating			
Total Tablet Weight	140 mg	Total Tablet Weight	103 mg

The results of a bioequivalence study submitted in this sNDA showed that treatments with the new worldwide tablet formulation (proposed reformulation) and the present US formulation led to similar plasma concentration profiles. The analysis of the pharmacokinetic parameters, C_{max} and AUC, showed that the 90% confidence intervals were within the 80 to 125% bioequivalence range, except for the upper-limit of the C_{max} of the new worldwide formulation compared to the present US formulation which was 127%. The results are summarized in the following table.

Table. Summary of Melphalan Plasma Concentration Data

Melphalan Geometric LS Mean (95% CI)

	ALKERAN US	ALKERAN World-Wide	Treatment Comparison	Estimate	90% CI
C_{max} (ng/mL)	178.3 (161.3, 197,1)	200.7 (181.6, 221.8)	C/A	1.13	(1.00 - 1.27)
AUC_{last} (ng•h/mL)	440.1 (418.0, 463.3)	475.3 (451.5, 500.3)	C/A	1.08	(1.02 - 1.15)
AUC_{∞} (ng•h/mL)	448.9 (426.6, 472.3)	483.2 (459.3, 508.3)	C/A	1.08	(1.01 - 1.14)

A = present US formulation, C = new worldwide formulation

The reviewer rechecked the calculations based on the raw data provided by the applicant. Thus, the new worldwide formulation of ALKERAN® is considered to be bioequivalent to the present US formulation in terms of AUC; however, the C_{max} of reformulated product is 13% higher in comparison to the current US formulation.

2. Is the assay for the study valid?

The in-study assay validation results based on the analytical report are presented in the following table.

Analyte	Melphalan
Method	
Quantifiable Range	
Precision (%CV)	< 14.5%
Accuracy (%bias)	< ±6.3%

A summary of the pre-study assay validation data is presented in the following table from IND S-005 and S-014 dated February 24, 1998 and March14, 2000, respectively.

Calibration model	Linear weighted 1/X
Quantifiable range	
precision (%CV)	< 6.1%
Accuracy (% bias)	< ±9.7%
Matrix stability	At least 16 days
Solution stability	At least 23 days

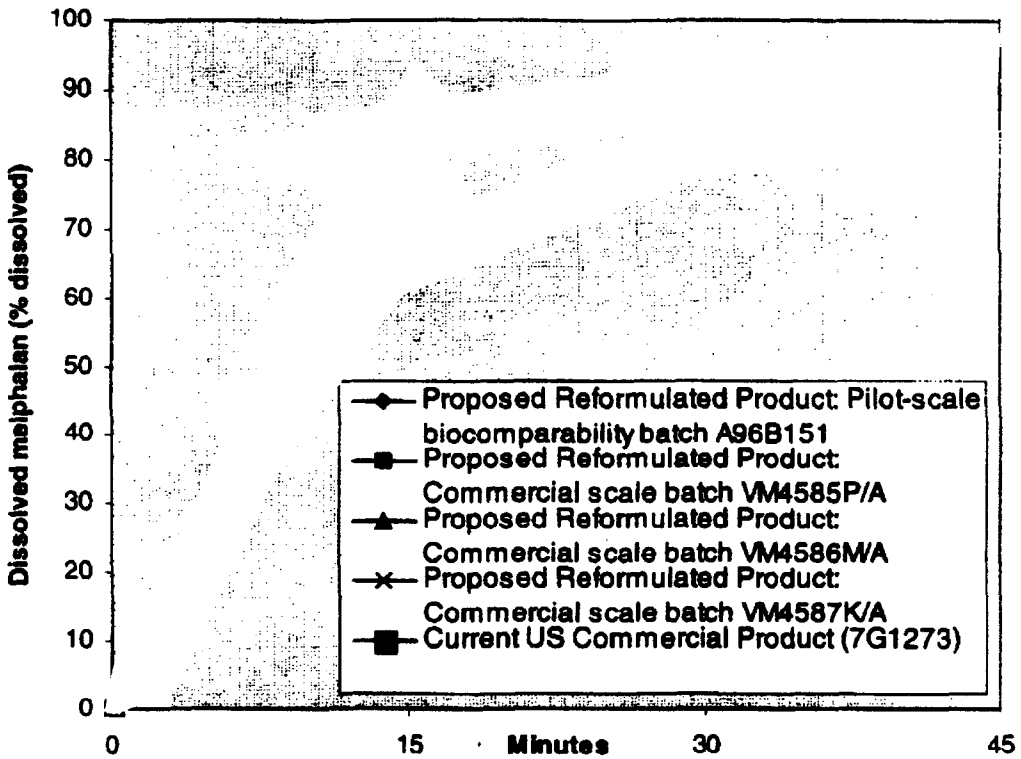
The assay methods and validations are acceptable based on the current standards.

3. Are the dissolution data and specification acceptable?

The justification for setting the dissolution specifications was provided in IND S-003 dated October 29, 1997, which is attached to the current NDA submission (see Appendix II). These include stability of melphalan in different dissolution media at 37°C and 22°C, dissolution results for reformulated Alkeran tablets in different dissolution media. As indicated in the review comments for the IND submission, it is appropriate to use 0.1 N HCl as dissolution medium based on the stability profile of melphalan. In the current sNDA, dissolution test results under the following conditions for the proposed reformulated ALKERAN® (melphalan) Tablets, 2 mg (pilot-scale biocomparability batch A96B 151 and three commercial scale batches, VM4585P/A, VM4586M/A, and VM4587K/A) and the current US commercial product (batch 7G1273) are provided.

Apparatus:	USP <711> Apparatus II
Media:	900 mL 0.1 N hydrochloric acid
Paddle Speed:	50 ± 2 rpm
Temperature:	37.0 ± 0.5°C

The applicant provided the results as shown in the following Figure.



Based on the dissolution data from the new formulation, the applicant proposes the following dissolution specifications.

Meets USP requirements where Q = 80% dissolved in 30 minutes at the following instrumental conditions.

Apparatus:	USP <711> Apparatus II
Media:	900 mL 0.1 N hydrochloric acid
Paddle Speed:	50 ± 2 rpm
Temperature:	37.0 ± 0.5°C

According to the data provided, the specification is acceptable.

II. GENERAL COMMENTS

1. The new worldwide formulation of ALKERAN® is considered to be bioequivalent to the current US formulation in terms of AUC; however, the C_{max} of reformulated product is 13% higher in comparison to the current US formulation.

2. The dissolution specifications of the reformulated tablets are as follows.

Meets USP requirements where Q = 80% dissolved in 30 minutes at the following instrumental conditions.

Apparatus:	USP <711> Apparatus II
Media:	900 mL 0.1 N hydrochloric acid
Paddle Speed:	50 ± 2 rpm
Temperature:	37.0 ± 0.5°C

III. LABELING COMMENTS

The following statements in CLINICAL PHARMACOLOGY section:

In a separate study in 18 patients given single oral doses of 0.2 to 0.25 mg/kg of ALKERAN, the mean dose adjusted (± SD) plasma C_{max} was 212 ± 74 ng/mL, the AUC was 498 ± 137 ng•h/mL, the $t_{1/2}$ was 1.12 ± 0.15 hours, and the t_{max} was 1.0 ± 0.5 hours.

Should be changed to:

Draft

IV. RECOMMENDATIONS

Please forward the General Comments and the Labeling Comments to the applicant.

/S/

John Duan, Ph.D. Date

Reviewer
Division of Pharmaceutical Evaluation I

/S/

Atiqur Rahman, Ph.D Date

Team Leader
Division of Pharmaceutical Evaluation I

CC:	NDA 14-691	original
	HFD-150	Division File
	HFD-150	MPelosi
	HFD-150	PCortazar
	HFD-150	CLiang, EDuffy
	HFD-860	MMehta, ARahman, JDuan
	HFD-340	Vishwanathan
	CDR	

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

APPENDIX II. INDIVIDUAL STUDY SYNOPSIS

1. Biocomparability study, ALKA1001

Study title: A biocomparability study of ALKERAN (Melphalan) 2mg Tablets in patients with multiple myeloma, ovarian cancer or other refractory malignancies.

Investigator & location: [redacted]

Study period: December 15, 1997 to April 9, 1998.

Study formulation:

- Test product: ALKERAN® Tablets (new worldwide formulation), 2 mg (batch # A96B151)
- Reference product: ALKERAN® Tablets (US formulation), 2 mg (batch # 7G1273), and ALKERAN® Tablets (UK formulation), 2 mg (batch # J3690A).

Objectives:

- To compare the pharmacokinetic profile of the new worldwide formulation of melphalan to the present US and UK formulations of ALKERAN® Tablets.
- To asses the biocomparability of the new worldwide formulations of melphalan relative to the present US and present UK formulations of ALKERAN® Tablets.
- To evaluate the acute toxicity profile of the new worldwide formulation of melphalan relative to the present US and present UK formulations of ALKERAN® Tablets.

Subjects: Eighteen subjects were screened and evaluated at single oral doses of 0.2 –0.25 mg/kg.

Study Design:

This was an open-label, single dose, randomized, 3-way crossover biocomparability study in patients with multiple myeloma, ovarian carcinoma or other refractory malignancies.

Plasma melphalan concentrations were monitored to evaluate pharmacokinetics. The criteria for evaluation for safety were physical examination, vital signs, ECG, laboratory test results and reported adverse events.

The pharmacokinetic analyses were descriptive statistics for log-transformed and untransformed C_{max}, AUC_{last}, $AUC_{0-\infty}$, and $t_{1/2}$ as well as untransformed t_{max} and %AUC extrapolated. ANOVA (analysis of variance) was used to assess the pharmacokinetic comparisons among formulations for dose adjusted C_{max}, $AUC_{0-\infty}$ and AUC_{last}. The effects due to sequence, subject within sequence, period and treatment were evaluated. Based upon the residual variation of ANOVA, 90% confidence intervals for the ratio of geometric least-squares means of test and reference were calculated. Bioequivalence was concluded if the

90% confidence intervals of C_{max} and AUC for the ratio of geometric means of test and reference intervals fell within the standard bioequivalence range of 80-125%. Non-parametric methods were used to compare t_{max} across formulations.

Results:

Assay performance: The in-study assay validation results based on the analytical report are presented in the following table.

Analyte	Melphalan
Method	
Quantifiable Range	ng/mL
Precision (%CV)	< 14.5%
Accuracy (%bias)	< ±6.3%

A summary of the pre-study assay validation data is presented in the following table from IND 53,336 S-005 and S-014 dated February 24, 1998 and March14, 2000, respectively.

Calibration model	Linear weighted 1/X
Quantifiable range	g/mL
precision (%CV)	< 6.1%
Accuracy (% bias)	< ±9.7%
Matrix stability	At least 16 days
Solution stability	At least 23 days

The assay methods and validations are acceptable based on the current standards.

Pharmacokinetics:

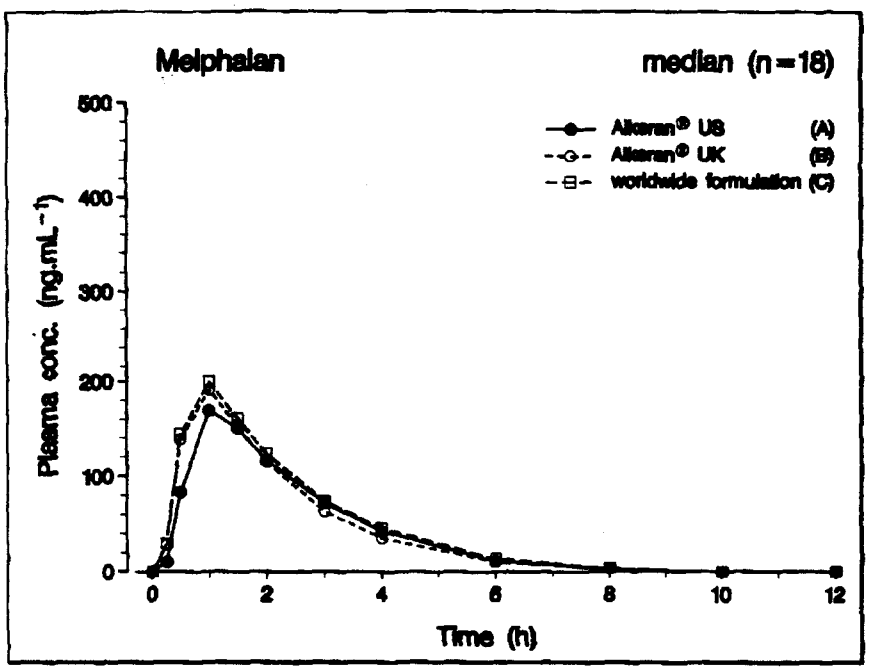
The pharmacokinetic results of the study show that treatment with the new worldwide tablet formulation leads to similar plasma concentration profiles as seen with those of the present US and UK formulations. The median melphalan plasma concentration time profile and the dose normalized profile are shown in the following figures. The statistical analysis of the pharmacokinetic parameters, C_{max} and AUC, showed that the 90% confidence intervals were within the 80 to 125% bioequivalence range except for the upper-limit of the Cmax of melphalan of the new worldwide formulation compared to the present US formulation which was 127% (see Tables below).

Table **Summary of Dose-Normalized Melphalan Plasma Concentration Data**

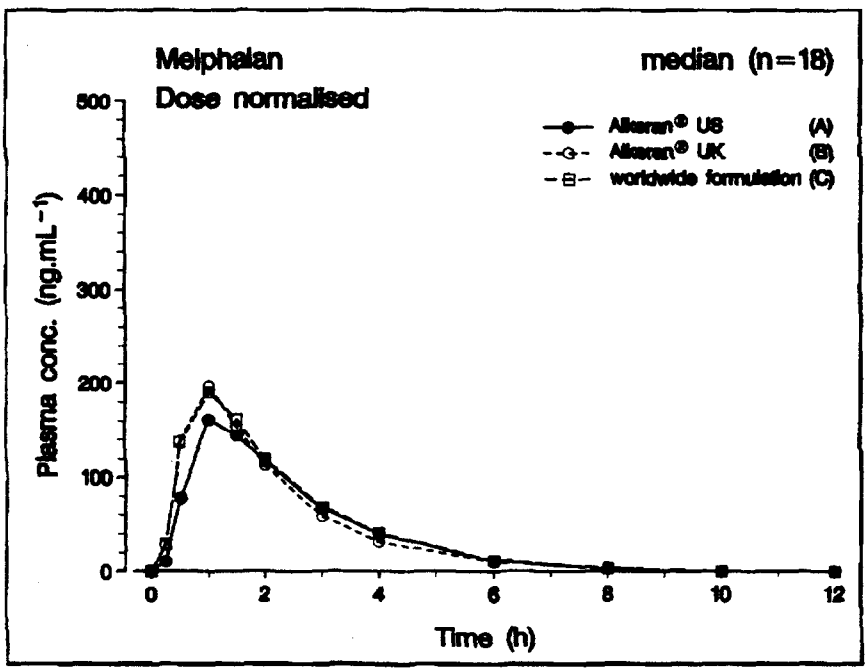
	Melphalan Geometric LS mean (90% CI)*					
	ALKERAN US	ALKERAN UK	ALKERAN World-Wide	Treatment Comparison	Estimate**	90% CI
C_{max} (ng/mL)	178.3	205.4	200.7	C/A	1.13	(1.00 – 1.27)
	(161.3, 197.1)	(185.8, 227.1)	(181.6, 221.8)	C/B	0.98	(0.87 – 1.10)
				A/B	0.87	(0.77 – 0.98)
AUC_{last} (ng*h/mL)	440.1	473.5	475.3	C/A	1.08	(1.02 – 1.15)
	(418.0, 463.3)	(449.8, 498.6)	(451.5, 500.3)	C/B	1.00	(0.95 – 1.07)
				A/B	0.93	(0.87 – 0.99)
AUC_{∞} (ng*h/mL)	448.9	480.4	483.2	C/A	1.08	(1.01 – 1.14)
	(426.6, 472.3)	(458.6, 505.4)	(459.3, 508.3)	C/B	1.01	(0.95 – 1.07)
				A/B	0.93	(0.88 – 0.99)
t_{max} (h)	1.0	1.0	1.0	C/A	-0.25	(-0.5 – 0.0)
				C/B	0.0	(-0.25 – 0.0)
				A/B	0.25	(0.0 – 0.5)

A = present US formulation, B = present UK formulation, C = new worldwide formulation
*median (min., max.) for t_{max}
**median difference for t_{max}

Median Melphalan Plasma Concentration Time Profile



Median Melphalan Plasma Concentration Time Profile, Dose Normalized



The dissolution of the new worldwide formulation is faster at 15 and 30 minutes than that of the present US formulation. However, this does not appear to impact bioavailability of these two formulations.

Safety

There were total of 12 adverse events reported during the conduct of the study, all of which are drug related. The adverse events include vomiting and myelosupprsssion. During treatment with the new worldwide formulation five adverse events were reported: vomiting (two), anemia (serious adverse event), granulocytopenia and thrombocytopenia. With the present UK ALKERAN formulation, three adverse events were reported: anemia, granulocytopenia and thrombocytopenia (serious adverse event). With the present US ALKERAN formulation, four adverse events were reported vomiting (two), anemia and granulocytopenia.

Comments:

1. The new worldwide tablet formulation is considered biocomparable to the present US formulation based on the data provided.

2.Dissolution tests

Composition of the formulations:
The current U.S. and the proposed formulations are provided by the applicant as shown below.

Current US Formulation		Proposed Reformulation	
Composition	Weight per Tablet	Composition	Weight per Tablet
Melphalan, USP	2.0 mg	Melphalan	2.00 mg
		Microcrystalline Cellulose, NF	
Lactose		Crospovidone, NF	
Magnesium Stearate, NF		Colloidal Silicon Dioxide, NF	
Povidone, USP		Magnesium Stearate, NF	
Starch, Potato,			
Total Core Weight		Total Core Weight	
Coating		Coating	
No coating			
Total Tablet Weight	140 mg	Total Tablet Weight	103 mg

Dissolution results:
Dissolution test for the proposed reformulated ALKERAN® Tablets, 2 mg and the current US commercial product were compared. The applicant provided the results in the Table and Figure below.

Results for the US commercial batch 7A2311 did not meet the proposed percent dissolved chlorambucil specification according to USP Stage II testing (Q= —% at 30 minutes). The applicant considered that this difference in dissolution profile was attributed to the current commercial product's sugar film-coating, which is different than the —— coating in the reformulated product.

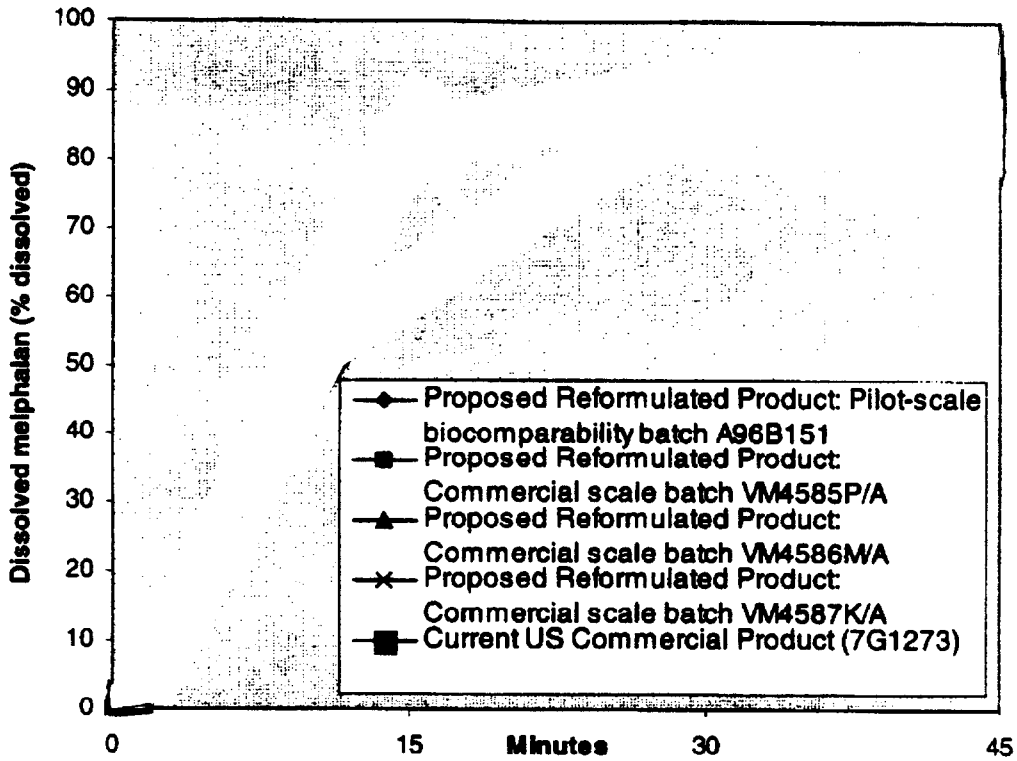
The proposed dissolution method and specification for the reformulated product is not intended for use with the current US commercial formulation. There is no dissolution specification registered for the current US commercial product. There is only a disintegration specification for the current US commercial product of "meets USP requirements in not more than 45 minutes (no disks)".

Table. Rate of Dissolution Comparison for ALKERAN® (melphalan) Tablets, 2 mg: Proposed Reformulated Product versus Current US Commercial Product

		Percent Melphalan Dissolved (based on labeled claim)	
Batch	**Time**	**Individual Tablets**	**Avg**
Reformulated Product	15 min		81
(Pilot-scale biocomparability	30 min		88
batch A96B151)	45 min		90
Reformulated Product	15 min		83
(Commercial scale batch	30 min		93
VM4585P/A)	45 min		93
ReformuJated Product	15 *min*		*84*
(Commercial scale batch	30 min		94
VM4586M/A)	45 min		95
Reformulated Product	15 min		85
(Commercial scale batch	30 min		94
VM4587K/A)	45 min		94

Current US Commercial Product (7G1273)	15 min	64
	30 min	86
	45 min	89

Figure. Comparative dissolution profiles of current US commercial product (Batch 7A2311) and proposed reformulated product (batch A97B57).



Based on the data, the applicant suggested the following dissolution specifications.

Typical Instrumental Conditions for Dissolution

Apparatus: USP <711> Apparatus II
Media: 900 mL 0.1 N hydrochloric acid
Paddle Speed: 50 ± 2 rpm
Temperature: 37.0 ± 0.5°C

Specifications
Meets USP requirements where Q = 80% dissolved in 30 minutes.

Comments:

1. In IND submission [redacted]S-003 dated October 29, 1997, the applicant provided the justification of the selection for the dissolution conditions, which is attached to this review.
2. According to the data provided, the specifications are acceptable.

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commercial

information

Table 3 **Dissolution Results at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B152 using Water**

	% Melphalan Dissolved		
Tablet	15 Minutes	30 Minutes	45 Minutes
1 2 3 4 5 6 7 8 9 10 11 12			
Average Minimum Maximum	44	47	42

Figure 3 **Dissolution Profile at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B152 using Water**

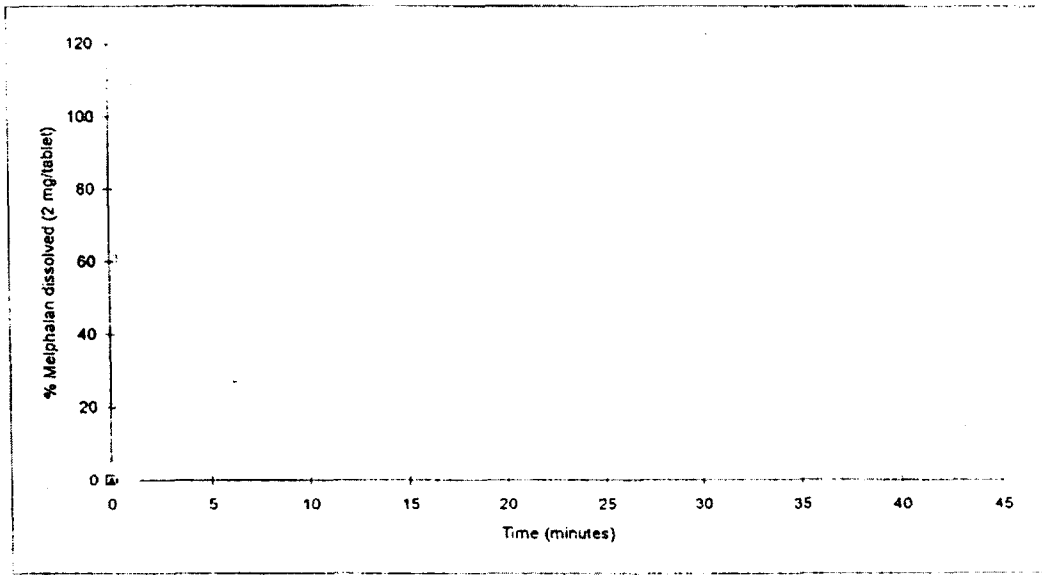


Table 4 **Dissolution Results at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B152 using Simulated Intestinal Fluid (without enzymes)**

Tablet	% Melphalan Dissolved 15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Average	40	44	40
Minimum			
Maximum			

Figure 4 **Dissolution Profile at 50 rpm Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B152 using Simulated Intestinal Fluid (without enzymes)**

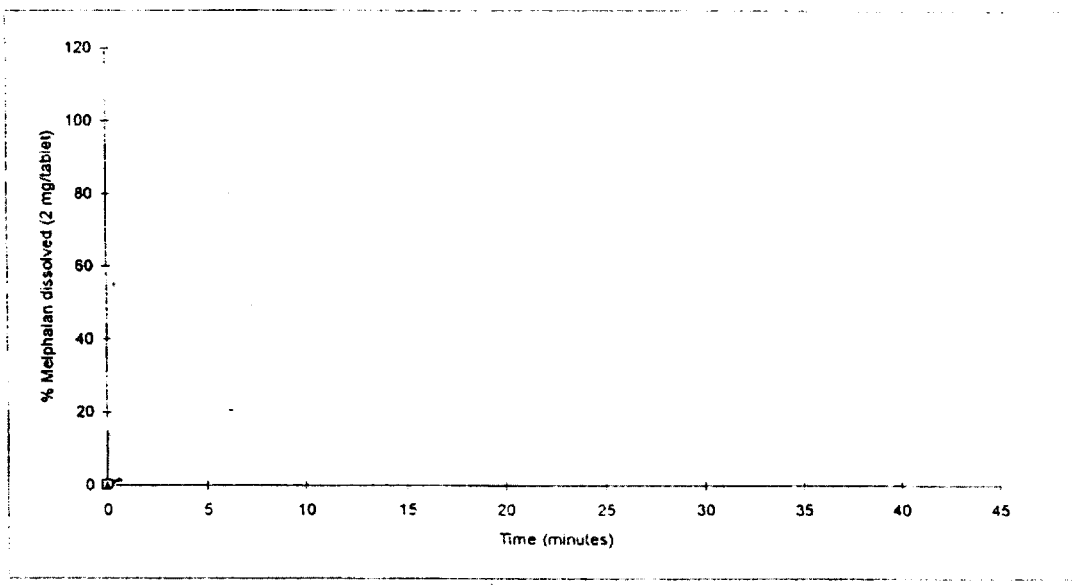


Table 5 **Dissolution Results at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B152 using 0.1 N Hydrochloric Acid**

	% Melphalan Dissolved		
Tablet	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Average	85	94	95
Minimum			
Maximum			

Figure 5 **Dissolution Profile at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B152 using 0.1*N* HCl**

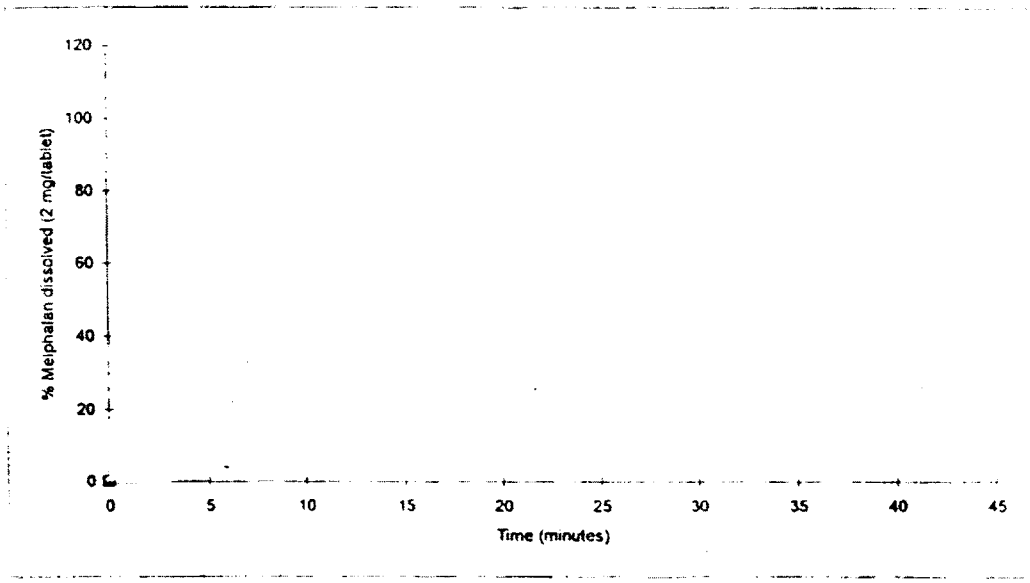


Table 6 **Dissolution Results at 50 rpm for US Alkeran (melphalan) 2 mg Tablets, Batch 7D2006, using 0.1*N* Hydrochloric Acid**

	% Melphalan Dissolved		
Tablet	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Average	66	87	92
Minimum			
Maximum			

Figure 6 **Dissolution Profile at 50 rpm for US Alkeran (melphalan) 2 mg Tablets, Batch 7D2006, using 0.1*N* Hydrochloric Acid)**

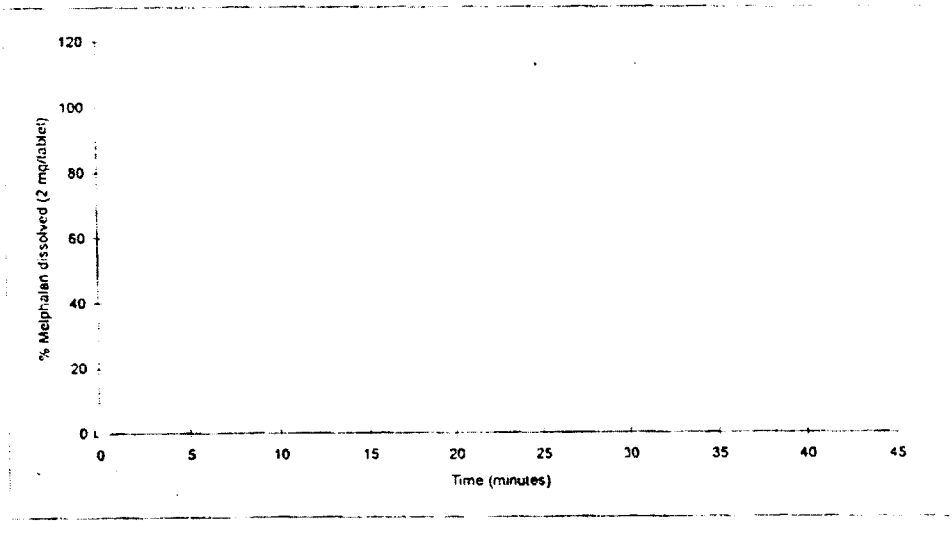


Table 7 **Dissolution Results at 50 rpm for UK Alkeran (melphalan) 2 mg Tablets, Batch T2892A, using 0.1*N* Hydrochloric Acid**

	% Melphalan Dissolved		
Tablet	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Average	58	80	90
Minimum			
Maximum			

Figure 7 **Dissolution Profile at 50 rpm for UK Alkeran (melphalan) 2 mg Tablets, Batch T2892A, using 0.1*N* Hydrochloric Acid**

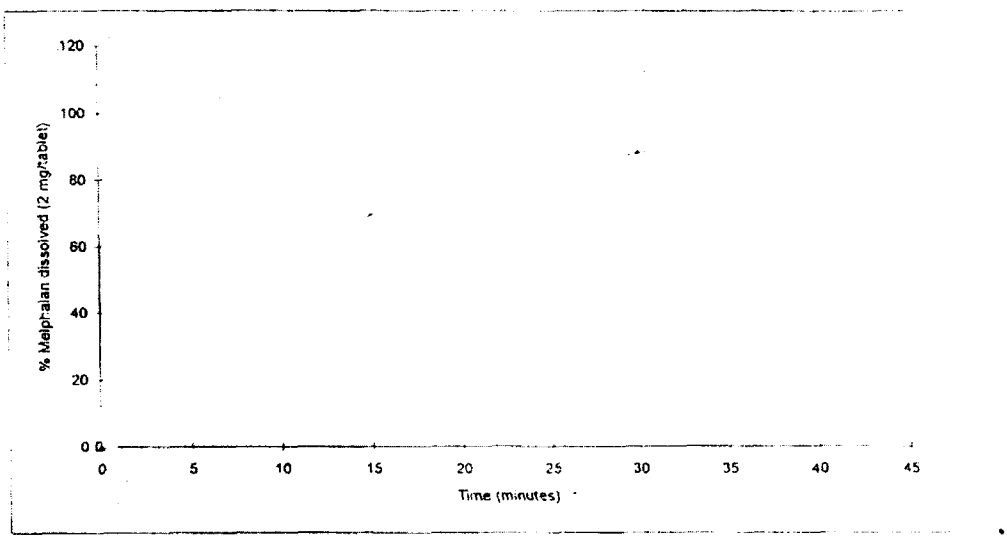


Table 8 **Dissolution Results at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B151 using 0.1*N* Hydrochloric Acid**

	% Melphalan Dissolved		
Tablet	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Average	89	96	96
Minimum			
Maximum			

Figure 8 **Dissolution Profile at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B151 using 0.1*N* Hydrochloric Acid**

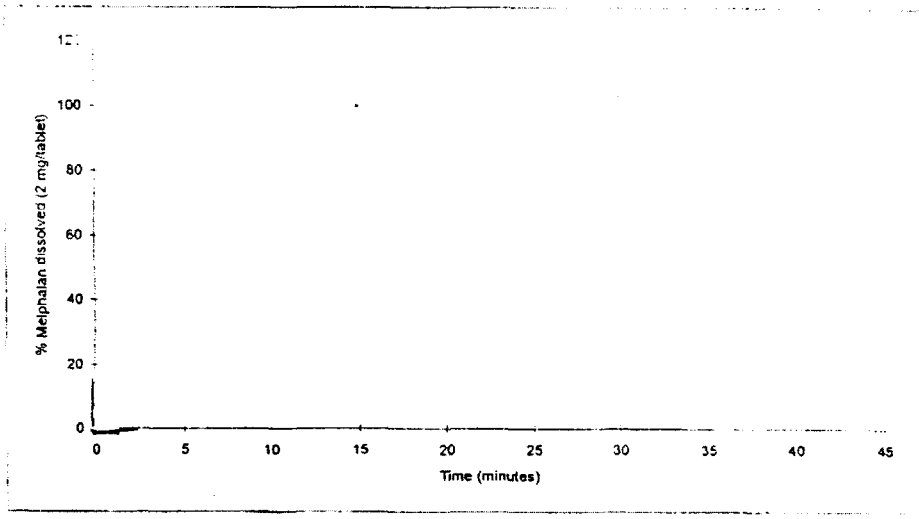


Table 9 **Dissolution Results at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B152 using 0.1*N* Hydrochloric Acid**

	% Melphalan Dissolved		
Tablet	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Average	89	93	92
Minimum			
Maximum			

Figure 9 **Dissolution Profile at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B152 using 0.1*N* Hydrochloric Acid**

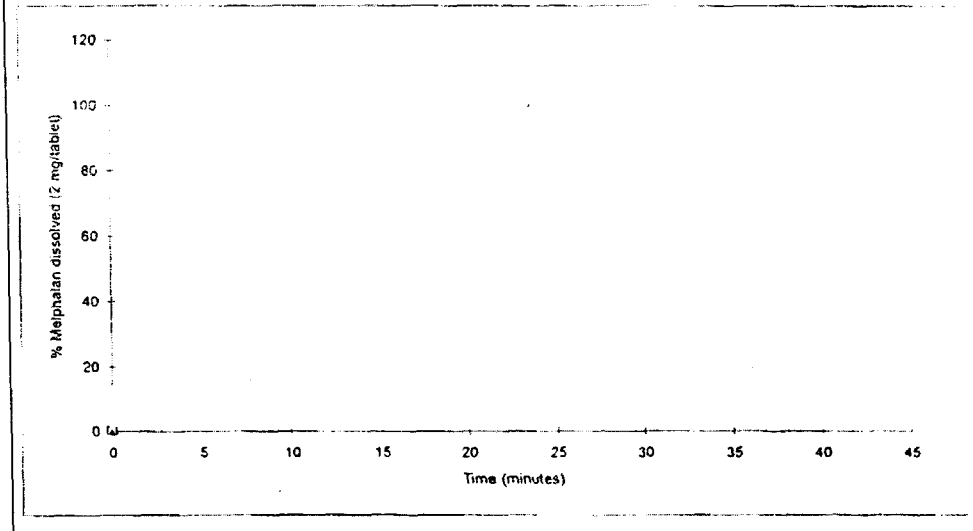
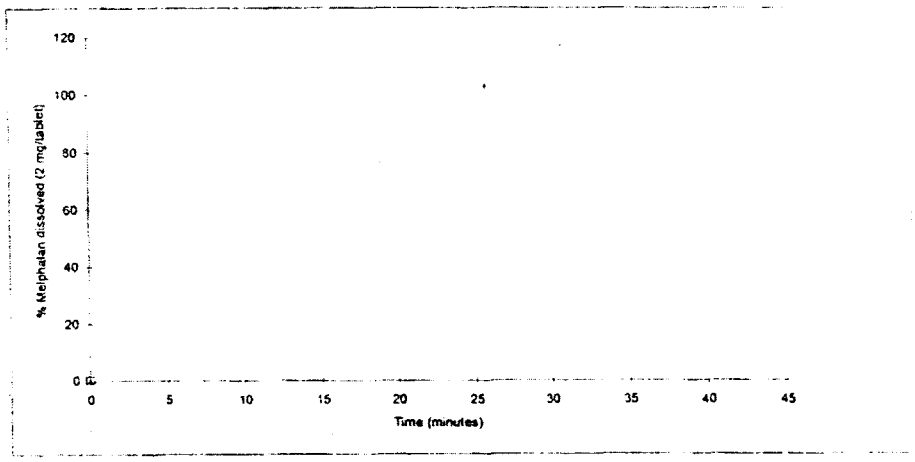


Table 10 **Dissolution Results at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B153 using 0.1*N* Hydrochloric Acid**

	% Melphalan Dissolved		
Tablet	15 Minutes	30 Minutes	45 Minutes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Average	89	94	93
Minimum			
Maximum			

Figure 10 **Dissolution Profile at 50 rpm for Alkeran (melphalan) 2 mg film-coated Tablets, Batch A96B153 using 0.1*N* Hydrochloric Acid**



/s/

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