REFERENCES

Aguiar, A.J., Wheeler, L.M., Fusari, S., and Zelmer, J.E. Evaluation of Physical and Pharmaceutical Factors Involved in Drug Release and Availability from Capsules. J. Pharm. Sci. 57(1986) : 1844.

Anon. Lopid$^{(R)}$ (Gemfibrozil) : Compendium of Pharmacological and Clinical Studies. Warner Lambert Company, 1982.

Fluehler, H., Hirtz, J., and Moser, H.A. An Aid to Decision-Making in Bioequivalence Assessment. J. Pharmacokinet. Biopharm. 9(1981) : 235-243.

Frick, M.H., et al. Helsinki Heart Study : Primary-Prevention Trial with Gemfibrozil in Middle-Aged Men with Dyslipidemia. N. Eng. J. Med. 317(1987) : 1237-1245.

Gordon, T., Castelli, W.P., Hjortland, M.C., Kannel, W.B., and Dawber, T.R. High Density Lipoprotein as a Protective Factor against Coronary Heart Disease. Am. J. Med. 62(1977) : 707-714.

Hall, M.J., Nelson, L.M., Russell, R.I., and Howard, A.N. Gemfibrozil - The Effect on Biliary Cholesterol Saturation of a New Lipid - Lowering Agent and Its Comparison with Clofibrate. Atherosclerosis 39(1981) : 511-516.

Hamberger, C., et al. In Vitro Binding Study of Gemfibrozil to Human Serum Proteins and Erythrocytes : Interaction with Other Drugs. Int. J. Clin. Pharmacol. Res. 6(1986) : 441-449.

Hengy, H., and Kolle, E.U. Determination of Gemfibrozil in Plasma by High Performance Liquid Chromatography. Arzneim. Forsch. 35(II) (1985) : 1637-1639.

Jain, A.K., Ryan, J.R., Lacorte, W.S.S., and McMahan, F.G. Clinical Evaluation of Gemfibrozil, A New Antilipemic Agent. Clin. Pharmacol. Ther. 29(1981) : 254-255.

Kovanen, P.T., Koskinen, P., and Manninen, V. A Comparison of Different Formulations and Dosage Administrations of Gemfibrozil. Am. J. Cardiol. 57(1986) : 31 G.-34 G.

Martin, M.J., Hulley, S.B., Browner, W.S., Kuller, L.H., and Wentworth, D. Serum Cholesterol, Blood Pressure, and Mortality : Implications from a Cohort of 361,662 Med. Lancet 2(1986) : 933-936.

Miller, G.J., and Miller, N.E. Plasma High-Density-Lipoprotein Concentration and Development of Ischaemic Heart Disease. Lancet 1(1975) : 16-19.

Nash, D.T. Gemfibrozil - A New Lipid Lowering Agent. J. Med. 11(1980) : 107-116.

Notari, R.E. Biopharmaceutics and Clinical Pharmacokinetics. 4 th ed. New York : Marcel Dekker, 1987.

Okerholm, R.A., et al. The Metabolism of Gemfibrozil. Proc. Roy. Soc. Med. 69 Suppl. 2(1976) : 11-14.

Peto, R., Yusuf, S., and Collins, R. Cholesterol - Lowering Trial Results in the Epidemiologic Context. Circulation. 72(1985) : III-451.

Randinitis, E.J., et al. Gas Chromatographic Determination of Gemfibrozil and Its Metabolites in Plasma and Urine. J. Chromatogr. 307(1984) : 210-215.

Rodda, B.E., and Davis, R.L. Determining the Probability of an Important Difference in Bioavailability. Clin. Pharmacol. Ther. 28(1980) : 247-252.

Ross, R. The Pathology of Atherosclerosis - An Update. N. Eng. J. Med. 314(1986) : 488-500.

Sedman, A.J., and Wagner, J.G. CSTRIP a Fortran IV Computer Program for Obtaining Initial Polyexponential Parameter Estimates. J. Pharm. Sci. 65(July 1976) : 1006-1010.

Shargel, L., and Yu, A.B.C. Applied Biopharmaceutics and Pharmacokinetics. New York : Appleton - Century - Crofts., 1980.

Skelly, J.P. Bioavailability and Bioequivalence. J. Clin. Pharmacol. 16(Part 2) (October 1976) : 539-545.

Smith, T.C. Toleration and Bioavailability of Gemfibrozil in Healthy Men. Proc. Roy. Soc. Med. 69(1976) : 24-27.

The United States Pharmacopoeia XXII. Rockville MD. : United States Pharmacopoeial Convention, Inc., 1990.

Todd, P.A., and Ward, A. Gemfibrozil A Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Use in Dyslipidaemia. Drugs 36(1988) : 314-339.

Tuomilehto, J., et al. A Clofibrate Controlled Trial of Gemfibrozil in the Treatment of Hyperlipidaemias. Proc. Roy. Soc. Med. 69 Suppl. 2 (1976) : 38-40.

Vega, G.L., and Grundy, S.M. Gemfibrozil Therapy in Primary Hypertriglyceridemia Associated with Coronary Heart Disease. Effects on Metabolism of Low Density Lipoproteins. JAMA 253 (April 1985) : 2398-2403.

Wagner, J.G. Generic Equivalence and Inequivalence of Oral Product. Drug. Intell. Clin. Pharmacol. 5(1971) : 115.

Westlake, W.J. Use of Confidence Intervals in Analysis of Comparative Bioavailability Trials. J. Pharm. Sci. 61(1972) : 1340-1341.

APPENDIX A

TEST PRODUCTS

Table 33 Test Products

Brand name	Manufacturer/Distributor	Mfg. date	Batch No.
GEMFIBRIL	Siam Pharmaceutical Co., Ltd.	15-1-91	10 UA 001
HIDRIL	Berlin	31-8-90	900088
LOCHOLES	T.O. Chemical	14-5-90	341101
LOPID	Parke-Davis/Warner-Lambert	2-1-91	088011

APPENDIX B

DISSOLUTION MEDIA

Composition of dissolution media

0.2 M Phosphate buffer pH 7.5 ± 0.1

Monobasic Potassium Phosphate (0.2 M)	250	ml
Sodium Hydroxide (0.2 N)	205	ml
Carbondioxide Free Water q.s.	1000	ml

APPENDIX C

The typical calibration curves and data for gemfibrozil concentrations in phosphate buffer (pH 7.5 ± 0.1) and pooled human plasma are presented in Tables 34 and 35 and Figures 17 and 18, respectively.

Table 34 Typical Calibration Curve Data for Gemfibrozil Concentrations in Phosphate Buffer (pH 7.5 $\pm$ 0.1) Estimated Using Linear Regression[a]

Standard No.	Conc. (mcg/ml)	Absorbance at 276 nm.	Inversely[b] Estimated Conc. (mcg/ml)	% Theory[c]
1	4.00	0.055	3.85	96.31
2	20.00	0.154	20.08	100.41
3	40.00	0.276	40.08	100.20
4	60.00	0.397	59.92	99.86
5	80.00	0.519	79.92	99.90
6	100.00	0.643	100.25	100.25
7	120.00	0.765	120.25	100.20
8	150.00	0.945	149.75	99.84
			Mean	99.62
			S.D.	1.35
			C.V.[d]	1.36%

a. $r^2 = 0.9999$, $Y = 0.0061 X + 0.0315$

b. $\text{Inversely Estimated Concentration} = \dfrac{\text{Absorbance} - 0.0315}{0.0061}$

c. $\% \text{ Theory} = \dfrac{\text{Inversely Estimated Concentration}}{\text{Known Concentration}} \times 100$

d. $\% \text{ C.V.} = \dfrac{\text{S.D.}}{\text{Mean}} \times 100$

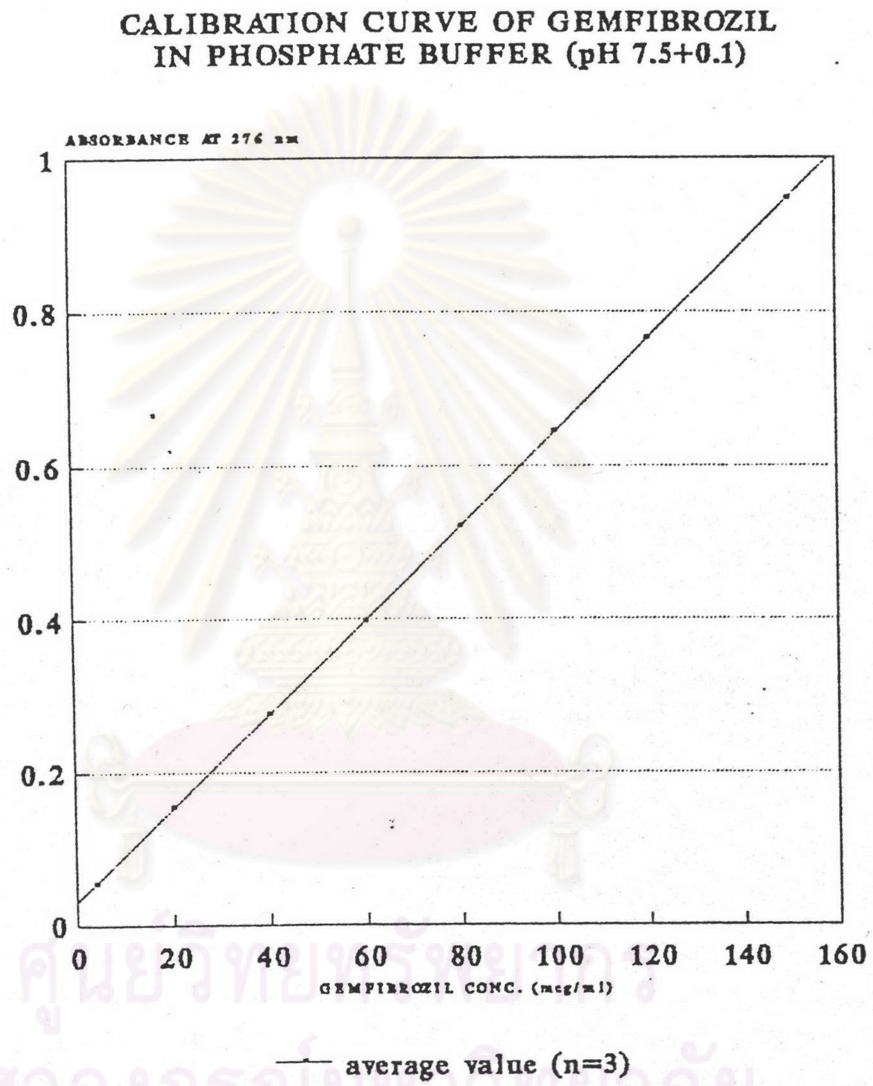

Figure 17 Calibration curve of gemfibrozil in phosphate buffer (pH 7.5 ± 0.1)

Table 35 Typical Calibration Curve Data for Gemfibrozil Concentrations in Pooled Human Plasma Estimated Using Linear Regression[a]

Standard No.	Conc. (mcg/ml)	Peak Height Ratio	Inversely[b] Estimated Conc. (mcg/ml)	% Theory[c]
1	1.00	0.1706	0.98	99.44
2	2.00	0.2998	1.99	99.49
3	6.00	0.8012	5.89	98.20
4	10.00	1.3104	9.85	98.54
5	14.00	1.8977	14.42	103.04
6	20.00	2.5995	19.82	99.43
7	30.00	3.8998	30.01	100.02
8	60.00	7.7524	59.99	99.98
			Mean	99.64
			S.D.	1.54
			C.V.[d]	1.55%

a. $r^2 = 0.9999$, $Y = 0.1285 X + 0.0441$

b. $\text{Inversely Estimated Concentration} = \dfrac{\text{Peak Height Ratio} - 0.0441}{0.1285}$

c. $\text{\% Theory} = \dfrac{\text{Inversely Estimated Concentration}}{\text{Known Concentration}} \times 100$

d. $\text{\% C.V.} = \dfrac{\text{S.D.}}{\text{Mean}} \times 100$

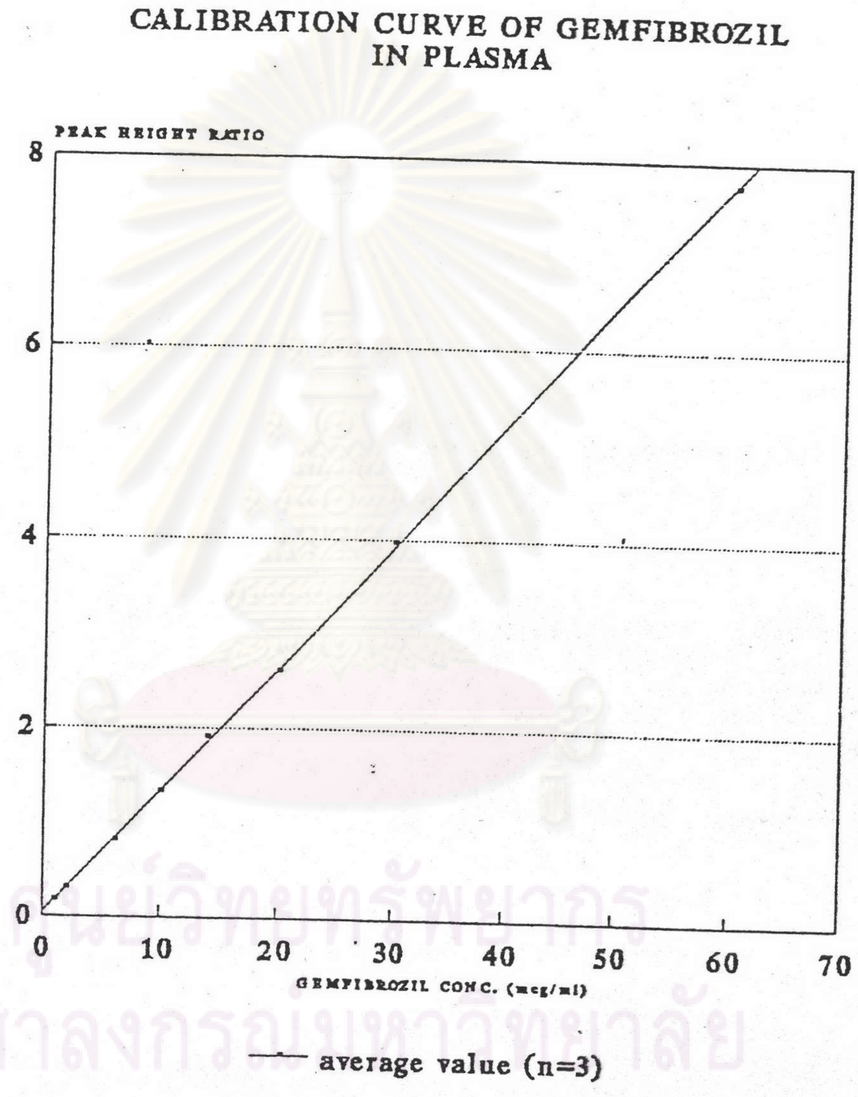

Figure 18 Calibration curve of gemfibrozil in pooled human plasma

APPENDIX D

SUBJECTS

Table 36 Demographic Data

Subject No.	Age (yr.)	Weight (kg.)	Height (cm.)
1	30	60	161
2	20	56	170
3	39	62	171
4	32	47	157
5	20	55	163
6	30	67	177
7	27	59	178
8	27	52	163
9	38	67	170
10	40	67	167
11	34	52	175
12	37	64	170
Mean	31.17	59.00	168.50
S.D.	6.85	6.70	6.53

APPENDIX E

STATISTICS

1. <u>Mean</u> ($\bar{X}$)

$$\bar{X} = \frac{\Sigma X}{N}$$

2. <u>Standard deviation</u>

$$S.D. = \frac{\Sigma (X - \bar{X})^2}{N - 1}$$

3. <u>Standard error of mean</u> (S.E.M.)

$$S.E.M. = \frac{S.D.}{N}$$

4. <u>Testing the difference among treatment means</u>

Completely randomized design

	Treatments					Total	Mean
	1	2	3	....	k		
	X_{11}	X_{12}	X_{13}	....	X_{1k}	T_1	X_1
	X_{21}	X_{22}	X_{23}	....	X_{2k}	T_2	X_2
	.	.	.	....	.	...	...
	X_{n1}	X_{n2}	X_{n3}	....	X_{nk}	T_n	X_n
Total	T_1	T_2	T_3	....	T_k	T	X
Mean	X_1	X_2	X_3	....	X_k		

where T = Total of all observations

X = Overall mean

k = Number of treatments

n = Number of sampling units in each treatment

$\mu_1, \mu_2, \mu_3, \ldots.\mu_k$ = Population mean

The null hypothesis $H_o : \mu_1 = \mu_2 = \ldots..\mu_k$

The alternative hypothesis $H_a : \mu_1 \neq \mu_2 \neq \ldots..\mu_k$

Analysis of variance (ANOVA) for testing differences among treatment mean

Source of variation	d.f.	SS	MS	F
Among group	k-1	SS_{among}	MS_{among}	F_T
Within group	Σn-k	SS_{within}	MS_{within}	
Total	Σn-1	SS_{total}		

where : d.f. = Degree of freedom

SS = Sum of Square

MS = Mean square

F_T = Variance ratio

Sum of squares :

1. Compute a correction term (C.T.)

$$C.T. = \frac{T^2}{\Sigma n}$$

2. Total sum of squares (SS_{total})

$$SS_{total} = \sum_{i=1}^{k} \left(\sum_{j=1}^{n} X^2_{ij} \right) - C.T.$$

3. The among group sum of squares (SS_{among})

$$SS_{among} = \sum_{i=1}^{k} \frac{(T^2_i)}{n_i} - C.T.$$

4. The within group sum of squares (SS_{within})

$$SS_{within} = SS_{total} - SS_{among}$$

$$\text{Mean squares} = \frac{\text{Sum of squares}}{\text{Degree of freedom}}$$

$$\text{Variance ratio} = \frac{\text{Among group mean squares}}{\text{Within group mean squares}}$$

F has (k-1), (Σn-k) degree of freedom.

If F value calculated is less than $F_{0.05}$, the null hypothesis is accepted and the alternative hypothesis is rejected. If F value is greater than $F_{0.05}$, the alternative hypothesis stands which shows that there are significant differences among treatment means ($p < 0.05$).

5. Testing the difference of two means

If the result of the difference testing among treatment means by analysis of variance is significant ($p < 0.05$), the testing of difference between the mean of the reference treatment and the each other treatment mean is performed by t-test.

The null hypothesis : $H_o : \mu_1 = \mu_2$

The alternative hypothesis : $H_a : \mu_1 \neq \mu_2$

$$t = \frac{X_1 - X_2}{S_d}$$

where $X_1 - X_2$ = difference of the two means

S_d^2 = pooled error variance

when n in each treatment is equal,

$$S_d = \sqrt{\frac{2\ MS_{within}}{n}}$$

when n in each treatment is not equal,

$$S_d = \sqrt{MS_{within} \frac{(n_1 + n_2)}{n_1 n_2}}$$

where n_1, n_2 = number of samples in treatment 1, 2 respectively

$t_{0.05}$ has (Σ n-k) degree of freedom.

If t value calculated is greater than $t_{0.05}$ from the table, it indicated that there is statistically significant difference of these means ($p < 0.05$).

6. Correlation coefficient test

The correlation coefficient is a quantitative measure of the relationship of correlation between two variables, x and y.

$$r = \frac{\Sigma\ (x - x)(y - y)}{\sqrt{\Sigma\ (x - x)^2\ \Sigma\ (y - y)^2}}$$

where r = Correlation coefficient

N = the number of x and y pairs

Test of Zero Correlation

Let ρ = the true correlation coefficient, estimated by r

The null hypothesis $H_o = \rho = 0$

The alternative hypothesis $H_a = \rho \neq 0$

$$t_{N-2} = \frac{\left| r \quad N-2 \right|}{\sqrt{1 - r^2}}$$

The value of $t_{0.05}$ is referred to a t distribution with (N-2) degree of freedom. If t calculated is greater than $t_{0.05}$, the null hypothesis is rejected and the alternative hypothesis is accepted. If t is not significant, the null hypothesis stands.

VITAE

Miss Ratanareka Yamasmit was born on May 24th 1967, in Bangkok. She obtained her degree in Bachelor of Science in Pharmacy (Second Class Honors) in 1990 from the Faculty of Pharmaceutical Sciences, Chulalongkorn University.