IIIb. Sponsor's analysis

a) Survival data analysis

Survival data for both male and female rats were analyzed by the non-parametric log-rank test (Mantel, 1966; Cox 1972). The trend version of the log-rank test (two-sided; Tarone, 1975) and a chi-square statistic for deviation from trend were also calculated (log-dose scale).

The sponsor claimed that survival did not differ among the groups of male rats. In contrast, there were statistically significant differences in survival among the original study groups of female rats.

b) Tumor data analysis

Summary tables for a number of neoplastic lesions by organ, lesion, and sex were generated. Then, the combined prevalence and death rate method proposed by Peto et al (1980) was applied to conduct trend tests on tumor rates. Intervals for incidental tumors were 0-52, 53-78, 79-92, 93-104, and terminal sacrifice. Moreover, the trend analyses were performed on the following four sets of study groups in both sexes:

first set - groups old control, old-low dose, and old-medium dose;
second set - groups new control and new-low dose;
third set - groups old control and new control;
fourth set - groups combined control (new and old), new-low dose, old-low dose, and old-medium dose.

The sponsor concluded that there were few statistically significant findings with respective to tumor incidence. In addition, the sponsor concluded that the number of statistically significant positive trend is far less than might be expected given the considerable number of tests employed in the primary Peto analyses alone. Hence, the sponsor claimed that the observed tumor incidences are consistent with no carcinogenic effect (or potential) for MDL 73,147EF as assessed in a two-year dietary carcinogenicity study in Sprague-Dawley rats.

IIIc. Reviewer's analysis

This reviewer compared the intercurrent mortality rates using the survival analysis methods described by Cox (1972), and Gehan (1965). In addition, this reviewer did the trend tests on tumor incidence rates using the method described by Peto et al. (1980) and the method of exact permutation trend test, developed by the Division of Biometrics. The data used in this reviewer's analysis were provided by the sponsor on a floppy diskette.

a) Intercurrent mortality data analysis

Table 4 shows the intercurrent mortality data of the rat study. Figure 2a and 2b present the plots

of Kaplan-Meier estimates of the survival distributions of the treatment groups for male and female rats, respectively. The homogeneity of survival distributions of five groups (Old Control, New Control, New-Low Dose, Old-Low Dose, Old-Medium Dose) was tested separately for male and female rats using the Cox test and the Generalized Wilcoxon test. The tests show that only for female rats, there is a statistically significant (at 0.05 level) linear trend ($p=0.0183$ for the Cox test and $p=0.0164$ for the Generalized Wilcoxon test) in the mortality. However, from Table 4, we realized that the mortality rates for the female mice at the end of two-year period study decreased from the old-control group to the old-medium dose group (64%, 64%, 65.33%, 68%, and 45.33% for the old-control, new-control, new-low dose, old-low dose, and old-medium dose groups, respectively). Tables 5A and 5B provide additional details of the p-values for the linear trend and the pairwise tests, respectively.

b) Tumor incidence rates analysis

i) Trend tests among five treatment groups

The sponsor classified the tumor types as 1) `cause of death', 2) `not cause of death', and 3) `undetermined'. Following Peto et al.(1980), the reviewer applied the `death rate method' to the first tumor type and the `prevalence' method to the second and the third tumor types to test the positive linear trend in tumor rates. For tumor types occurring in both categories (fatal and non-fatal) a combined test was performed. All tests were done using the method of exact permutation trend test. The scores used in the reviewer's analyses were 0, 0, 25, 75, and 150 on males and 0, 0, 50, 150, and 300 on females for the old control, new control, new-low dose, old-low dose, and old-medium dose groups, respectively. The time intervals used were 0 - 52, 53 - 78, 79-92, 93-104 weeks, and terminal sacrifice for both sexes.

The following five sets of tumor trend analyses were performed for both sexes:

first set - groups old control, old-low dose, and old-medium dose;
second set - groups new control and new-low dose;
third set - groups old control, new-low dose, old-low dose, and old-medium dose;
fourth set - groups new control, new-low dose, old-low dose, and old-medium dose;
fifth set - groups combined control (new and old), new-low dose, old-low dose, and old-medium dose.

The incidence rates of tumor types with p-values, based on the exact permutation tests, less than .05 are listed below.

Table 3.1(Reviewer) : Tumor types with P-value less than 0.05

FEMALE RATS: NEW CONTROL, NEW-LOW, OLD-LOW, OLD-MEDIUM

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	NC	NL	OL	OM
Adrenal Med	B Medullary Tumor	S	0.0476	0.03425	1	1	2	4

FEMALE RATS: OLD+NEW CONTROL, NEW-LOW, OLD-LOW, OLD-MEDIUM

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	ONC	NL	OL	OM
Liver	M Histiocytic Sarcoma	S	0.0493	0.02815	0	0	3	2

Multiple testing adjustment: A rule proposed by Haseman could be used to adjust the effect of multiple testings. A similar rule proposed by the Division of Biometrics, CDER/FDA was used in this review. This rule states that in order to keep the overall false-positive rate at the nominal level of approximately ten percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .025 level, otherwise the level should be set at .005.

On the basis of Division's p-value adjustment rule, no tumor type was found to have linear positive significant trend. Table 6 provides details of p values on the linear trend tests for the tested tumor types .

IV. Evaluation of validity of the design of the rat study

This reviewer's analysis did not find any tumor was of a significant positive linear trend. However, before drawing the conclusion that the drug is not carcinogenic in rats, it is important to look into the following two issues as pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984). The two issues are:

(I) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor ?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals ?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Statistical Application and Research Branch, Division of Biometrics, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be consider as a sufficient number of animals under an adequate exposure.

In addition, Chu, Cueto, and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and environmental Health. Vol. 8, pp 251-280, 1981), suggested that " To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and the number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto, and Ward (1981), the following criteria are mentioned for dose adequacy.

I) " A dose is considered adequate if there is a detectable loss in weight gain of up to 10 % in a dosed group relative to the controls."

ii) " The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

iii) " In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the Dolasetron rat carcinogenicity study, in the light of the above guidelines.

The following are summary survival data of rats in the old-medium dose (highest dose used in the rat study) group.

Table 4.1 (Reviewer) Survival rates for the old-medium dose group

	End of 52 weeks	End of Study weeks (104)
Male	100%	36 %
Female	100%	54.67%

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From the above summary data, and the survival criteria mentioned above, it may be concluded that there were enough rats exposed for sufficient amount of time to the drug.

The following are summary data of body weight gains of the rat study.

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Table 4.2 (Reviewer) Body weight gains for five dose groups

		Mean body weight(gms)				
		Beginning	End	Weight	Percentage of	
Sex	Group	of study	of study	gain	Old Control	New Control
Male	Old Control	250	793	543		
	New Contro2	266	803	537		
	New-Low	266	692	426	78.45	79.33
	Old-Low	251	687	436	80.29	81.19
	Old-Medium	250	646	396	72.93	73.74

		Mean body weight(gms)				
		Beginning	End	Weight	Percentage of	
Sex	Group	of study	of study	gain	Old Control	New Control
Female	Old Control	189	493	304		
	New Contro2	193	544	351		
	New-Low	193	461	268	88.16	76.35
	Old-Low	189	422	233	76,64	66.38
	Old-Medium	189	360	171	56.25	48.72

Therefore, relative to the old control and new control, male and female rats had average decrement of weight gain in the old-medium dose group equal to 26.67% and 47.5%, respectively.

The mortality rates at the end of the experiment are as follows:

Table 4.3 (Reviewer) Mortality rates for three dose groups

	Old Control	New Control	Old-Medium
Male	68%	72%	64%
Female	64%	64%	45%

The morality rate of the old-medium dose group for the male rats is slightly lower than the average of two controls. However, the morality rate of the old-medium dose group for the female rats is 19% lower than the average of two controls.

Thus, from the survival and body weight gain data it may be concluded that the old-medium dose level may be close to MTD. However, before concluding that the old-medium dose is close to MTD other clinical signs and histopathological effects must also be taken into consideration.

V. Summary

a) The mouse study

For the intercurrent mortality data analysis, the tests showed that only for female mice, there is a statistically significant (at 0.05 level) linear trend ($p=0.019$ in the Cox test and $p=0.037$ in the Generalized Wilcoxon test) in the mortality. However, from Table 1, we realized that the mortality rates for the female mice at the end of two-year period study decreased from the control group to the high dose group (63.64%, 50.91%, 60%, and 38.82% for the control, low dose, medium dose, and high dose groups, respectively).

For tumor incidence rate analysis, the tests show that only in male mice, tumor types Liver/Hepatocellular Adenoma and Liver/Hepatocellular Adenoma & Carcinoma were found to have significant linear positive trends. Moreover, the pairwise comparisons between the control versus high dose groups and the control versus medium dose groups for tumor types Liver/Hepatocellular Adenoma and Liver/Hepatocellular Adenoma & Carcinoma are also significant.

b) The rat study

For the intercurrent mortality data analysis, the tests showed that only for female rats, there is a statistically significant (at 0.05 level) linear trend ($p=0.0183$ for the Cox test and $p=0.0164$ for the Generalized Wilcoxon test) in the mortality. However, from Table 4, we realized that the mortality rates for the female mice at the end of two-year period study decreased from the old-control group to the old-medium dose group (64%, 64%, 65.33%, 68%, and 45.33% for the old-control, new-control, new-low dose, old-low dose, and old-medium dose groups, respectively).

For tumor incidence rate analysis, on the basis of Division's p-value adjustment rule, no tumor type was found to have linear positive significant trend.

Using the criteria for evaluating the validity of experimental designs of negative studies proposed by experts in the field, it may be concluded that the old-medium dose level may be close to MTD. However, before concluding that the old-medium dose is close to MTD other clinical signs and histopathological effects shall also be taken into consideration.

/S/

Wen-Jen Chen, Ph.D.
Mathematical Statistician

Concur: Dr. Huque /S/ 5/14/96

Dr. Smith /S/ 5/14/96

cc:

Archival NDA# 20-623 Dolasetron Mesylate Tablet
HFD-180/Dr. Fred
HFD-180/Dr. Choudary
HFD-180/Dr. Ahmad
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Chen
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Table 1

Intercurrent mortality rates in the mouse study

Sex	Time(wks)	Control	Low	Medium	High
MALE					
	0 - 52	2/ 55 (3.64)	5/ 55 (9.09)	3/ 55 (5.45)	3/ 55 (5.45)
	53- 78	5/ 53 (12.73)	9/ 50 (25.45)	6/ 52 (16.36)	8/ 52 (20.00)
	79- 93	11/ 48 (32.73)	10/ 41 (43.64)	5/ 46 (25.45)	9/ 44 (36.36)
	94-104	6/ 37 (43.64)	6/ 31 (54.55)	6/ 41 (36.36)	4/ 35 (43.64)
	TERM. SACR	31/ 55 (56.36)	25/ 55 (45.45)	35/ 55 (63.64)	31/ 55 (56.36)
FEMALE					
	0 - 52	3/ 55 (5.45)	4/ 55 (7.27)	6/ 55 (10.91)	2/ 55 (3.64)
	53- 78	9/ 52 (21.82)	5/ 51 (16.36)	8/ 49 (25.45)	5/ 53 (12.73)
	79- 93	13/ 43 (45.45)	11/ 46 (36.36)	11/ 41 (45.45)	7/ 48 (25.45)
	94-104	10/ 30 (63.64)	8/ 35 (50.91)	8/ 30 (60.00)	7/ 41 (38.18)
	TERM. SACR	20/ 55 (36.36)	27/ 55 (49.09)	22/ 55 (40.00)	34/ 55 (61.82)

Note: Except the TERM. SACR. row, an entry of this table =number of animals dying in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate;i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

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Table 2A

P-values of tests for overall homogeneity and linear trend in mortality in the mouse study

Test of homogeneity

Sex	Test	P-value
Male	Cox	.3274
	Wilcoxon	.3818
Female	Cox	.0387
	Wilcoxon	.0654

Test of linear trend

Sex	Test	P-value
Male	Cox	.7506
	Wilcoxon	.8834
Female	Cox	.0192
	Wilcoxon	.0365

Table 2B

P-values of pairwise test for the differences in mortality between treated groups in mouse study

Male mouse

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT	GENERALIZED K/W ANALYSIS INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		1.2591	NEG	1.0885		1.0861	.8794		.8783
	PROB	.1309	.2618		.2968		.2973	.3484		.3487
0 VS. 2	CHISQ		.0366	NEG	.0059		.0059	.0229		.0229
	PROB	.4242	.8482		.9387		.9388	.8796		.8797
0 VS. 3	CHISQ		6.5790	NEG	6.3883		6.3533	5.7586		5.7358
	PROB	.0050**	.0103*		.0115*		.0117*	.0164*		.0166*
1 VS. 2	CHISQ		.5519	POS	.8222		.8204	.9880		.9862
	PROB	.2289	.4575		.3645		.3651	.3202		.3207
1 VS. 3	CHISQ		1.6352	NEG	1.7053		1.7033	1.8464		1.8444
	PROB	.1004	.2010		.1916		.1919	.1742		.1744
2 VS. 3	CHISQ		4.8120	NEG	5.4756		5.4474	5.6903		5.6653
	PROB	.0139*	.0283*		.0193*		.0196*	.0171*		.0173*

Female mouse

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT	COX'S TEST INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT	GENERALIZED K/W ANALYSIS INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		1.2591	NEG	1.0885		1.0861	.8794		.8783
	PROB	.1309	.2618		.2968		.2973	.3484		.3487
0 VS. 2	CHISQ		.0366	NEG	.0059		.0059	.0229		.0229
	PROB	.4242	.8482		.9387		.9388	.8796		.8797
0 VS. 3	CHISQ		6.5790	NEG	6.3883		6.3533	5.7586		5.7358
	PROB	.0050**	.0103*		.0115*		.0117*	.0164*		.0166*
1 VS. 2	CHISQ		.5519	POS	.8222		.8204	.9880		.9862
	PROB	.2289	.4575		.3645		.3651	.3202		.3207
1 VS. 3	CHISQ		1.6352	NEG	1.7053		1.7033	1.8464		1.8444
	PROB	.1004	.2010		.1916		.1919	.1742		.1744
2 VS. 3	CHISQ		4.8120	NEG	5.4756		5.4474	5.6903		5.6653
	PROB	.0139*	.0283*		.0193*		.0196*	.0171*		.0173*

Table 3

Tumor rates of the tested tumor types for positive linear trend

MALE MOUSE

Organ Name	Tumor Name	MSFLG**	Exact P-Value	Asymptotic P-value	C	L	M	H
Adrenal	M Pheochromocytoma	S	0.6857	0.65040	0	1	0	0
Gallbladder	B Papillary Adenoma	S	1.0000	0.86990	1	0	0	0
Kidney	B Tubular Adenoma	S	0.4000	0.39835	0	0	1	0
Lacrimal Gl.Pos.	B Adenoma	S	0.1519	0.12545	1	1	5	3
Liver	B Hemangioma	S	0.8320	0.77695	0	2	0	0
Liver	B Hepatocellular Adenoma	S	0.0001*	0.00005	1	4	10	13
Liver	B Hepatocellular Adenoma & Carc.	S	0.0000*	0.00000	8	11	25	26
Liver	B Lipoma	S	0.2541	0.06835	0	0	0	1
Liver	M Hemangiosarcoma	S	0.6857	0.65040	0	1	0	0
Lung	M Hepatocellular Carcinoma	M	0.0514	0.04445	7	7	15	13
Lung	B Alveolar Epith. Cell Adenoma	S	0.2964	0.26640	3	2	4	4
Skin/Subcutis	M Broncho-alveolar Carcinoma	M	0.5464	0.51820	4	4	4	4
Small Intestine	M Hemangiosarcoma	S	0.2541	0.06835	0	0	0	1
Spleen	B Adenoma	S	0.2541	0.06835	0	0	0	1
Spleen	B Hemangioma	S	1.0000	0.88715	1	0	0	0
	M Hemangiosarcoma	S	0.2998	0.24960	0	1	2	1

MSFLG is flag to indicate the current tumor type was classified as a single (S) type (either fatal or non-fatal) or a mixed (M) type (both fatal and non-fatal).

* indicates statistical significance after the adjustment of the multiple test effect.

Table 3

Tumor rates of the tested tumor types for positive linear trend

FEMALE MOUSE

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
Adrenal	B Pheochromocytoma	S	0.5174	0.41090	1	0	0	1
Adrenal	M Pheochromocytoma	S	0.8058	0.74455	0	1	0	0
Brain	B Myxomatous Meningioma	S	0.5102	0.45000	0	0	1	0
Brain	B Oligodendroglioma	S	0.3301	0.09750	0	0	0	1
Kidney	M Myeloid Cell Sarcoma	S	1.0000	0.89250	1	0	0	0
Lacrimal Gl.Pos.	B Adenoma	S	0.7729	0.73935	2	1	3	1
Large Intestine	M Hemangiosarcoma	S	0.5437	0.50250	0	0	1	0
Liver	B Hepatocellular Adenoma	S	0.2810	0.24275	0	4	1	3
Liver	M Erythroid Cell Sarcoma	S	0.6905	0.62970	0	1	0	0
Liver	M Hepatocellular Carcinoma	S	0.2204	0.17110	1	1	0	2
Lung	B Alveolar Epith. Cell Adenoma	S	0.2331	0.20085	2	1	3	4
Lung	M Broncho-alveolar Carcinoma	M	0.3286	0.30425	5	4	5	7
Thymus	M Lymphosarcoma	M	0.2636	0.24115	5	3	8	8
Uterus	B Leiomyoma	S	0.4468	0.40730	2	2	2	3
Uterus	B Stromal Cell Tumor	S	0.2399	0.19385	0	2	1	2
Uterus	B Stromal Polyp (Polypoid Adenoma)	S	0.0730	0.05950	1	3	5	6
Uterus	M Adenocarcinoma	S	0.3301	0.09750	0	0	0	1
Uterus	M Leiomyosarcoma	M	0.1628	0.12520	0	1	1	2
Uterus	M Stromal Cell Sarcoma	S	0.3873	0.34745	3	1	1	3

Table 4

Intercurrent mortality rates in the rat study

Sex	Time(wks)	Old Control	New Control	New Low	Old Low	Old Medium
MALE						
	0 - 52	5/ 75 (6.67)	1/ 75 (1.33)	4/ 75 (5.33)	3/ 75 (4.00)	0/ 75 (0.00)
	53- 78	13/ 70 (24.00)	14/ 74 (20.00)	15/ 71 (25.33)	16/ 72 (25.33)	15/ 75 (20.00)
	79- 92	18/ 57 (48.00)	19/ 60 (45.33)	23/ 56 (56.00)	16/ 56 (46.67)	15/ 60 (40.00)
	93-104	15/ 39 (68.00)	20/ 41 (72.00)	15/ 33 (76.00)	12/ 40 (62.67)	18/ 45 (64.00)
	TERM.SACR	24/ 75 (32.00)	21/ 75 (28.00)	18/ 75 (24.00)	28/ 75 (37.33)	27/ 75 (36.00)
FEMALE						
	0 - 52	3/ 75 (4.00)	2/ 75 (2.67)	4/ 75 (5.33)	4/ 75 (5.33)	0/ 75 (0.00)
	53- 78	9/ 72 (16.00)	15/ 73 (22.67)	15/ 71 (25.33)	12/ 71 (21.33)	7/ 75 (9.33)
	79- 92	21/ 63 (44.00)	10/ 58 (36.00)	14/ 56 (44.00)	18/ 59 (45.33)	15/ 68 (29.33)
	93-104	15/ 42 (64.00)	21/ 48 (64.00)	16/ 42 (65.33)	17/ 41 (68.00)	12/ 53 (45.33)
	TERM.SACR	27/ 75 (36.00)	27/ 75 (36.00)	26/ 75 (34.67)	24/ 75 (32.00)	41/ 75 (54.67)

Note: Except the TERM. SACR. row, an entry of this table =number of animals dying in the time interval/number of animals entering the time interval. An entry in parenthesis = cumulative mortality rate;i.e. cumulative percent of animals dying up to the end of the time interval. An entry in the TERM. SACR. row = number of animals surviving to terminal sacrifice / initial number of animals. An entry in parenthesis in this row = percent of animals (of the initial number) surviving to terminal sacrifice.

Table 5A

P-values of tests for overall homogeneity and linear trend in mortality in the rat study

Test of homogeneity

Sex	Test	P-value
Male	Cox	.3507
	Wilcoxon	.4108
Female	Cox	.0525
	Wilcoxon	.0428

Test of linear trend

Sex	Test	P-value
Male	Cox	.1841
	Wilcoxon	.2498
Female	Cox	.0183
	Wilcoxon	.0164

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Table 5B

P-values of pairwise test for the differences in mortality between treated groups in rat study

Male rat

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		.1270	POS	.0269	.0268	.0000	.0000
	PROB	1.0000	.7216		.8698	.8699	.9977	.9977
0 VS. 2	CHISQ		.8267	POS	1.2142	1.2120	1.5249	1.5221
	PROB	.1817	.3632		.2705	.2709	.2169	.2173
0 VS. 3	CHISQ		.4668	NEG	.1620	.1617	.0227	.0227
	PROB	.2473	.4944		.6874	.6876	.8801	.8802
0 VS. 4	CHISQ		.1188	NEG	.3345	.3341	.5431	.5427
	PROB	.3652	.7303		.5630	.5633	.4612	.4613
1 VS. 2	CHISQ		.1386	POS	.7436	.7425	1.5997	1.5972
	PROB	.3550	.7097		.3885	.3888	.2059	.2063
1 VS. 3	CHISQ		1.4700	NEG	.4573	.4562	.0238	.0237
	PROB	.1126	.2253		.4989	.4994	.8775	.8776
1 VS. 4	CHISQ		.7659	NEG	.7966	.7947	.6670	.6661
	PROB	.1908	.3815		.3721	.3727	.4141	.4144
2 VS. 3	CHISQ		3.0985	NEG	2.2472	2.2387	1.3721	1.3690
	PROB	.0389*	.0784		.1339	.1346	.2415	.2420
2 VS. 4	CHISQ		2.0317	NEG	3.0015	2.9907	3.5388	3.5301
	PROB	.0768	.1540		.0832	.0837	.0599	.0603
3 VS. 4	CHISQ		.0285	POS	.0002	.0002	.2826	.2825
	PROB	.4330	.8659		.9885	.9885	.5950	.5950

Female rat

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ON ORIGINAL

GROUP		EXACT ONE TAIL TEST	2X2 CHI-SQUARE USING N IN DEN	DIRECTION OF 2X2 CHI-SQ	COX'S TEST EXACT INVERSE	COX'S TEST CONSERVATIVE	GENERALIZED K/W ANALYSIS EXACT INVERSE	GENERALIZED K/W ANALYSIS CONSERVATIVE
0 VS. 1	CHISQ		.0285	POS	.1450	.1446	.1997	.1993
	PROB	1.0000	.8659		.7034	.7038	.6549	.6553
0 VS. 2	CHISQ		.0000	POS	.0000	.0000	.1194	.1192
	PROB	.5675	1.0000		.9973	.9973	.7297	.7299
0 VS. 3	CHISQ		.0294	POS	.0266	.0265	.0845	.0844
	PROB	.4319	.8638		.8706	.8706	.7713	.7714
0 VS. 4	CHISQ		4.5463	NEG	5.6835	5.6559	6.5132	6.4898
	PROB	.0163*	.0330*		.0171*	.0174*	.0107*	.0108*
1 VS. 2	CHISQ		.0285	POS	.1841	.1840	.4865	.4863
	PROB	.4330	.8659		.6679	.6679	.4855	.4856
1 VS. 3	CHISQ		.2604	POS	.4045	.4038	.5249	.5243
	PROB	.3050	.6098		.5248	.5251	.4687	.4690
1 VS. 4	CHISQ		3.2411	NEG	3.7326	3.7273	4.4372	4.4319
	PROB	.0357*	.0718		.0534	.0535	.0352*	.0353*
2 VS. 3	CHISQ		.0294	POS	.0091	.0090	.0003	.0003
	PROB	.4319	.8638		.9242	.9242	.9855	.9855
2 VS. 4	CHISQ		4.5463	NEG	5.7737	5.7636	7.1787	7.1659
	PROB	.0163*	.0330*		.0163*	.0164*	.0074**	.0074**
3 VS. 4	CHISQ		6.0877	NEG	6.9976	6.9736	7.7727	7.7521
	PROB	.0067**	.0136*		.0082**	.0083**	.0053**	.0054**

Table 6

Tumor rates of the tested tumor types for positive linear trend

MALE RATS: OLD CONTROL, OLD-LOW, OLD-MEDIUM

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	OC	OL	OM
Adrenal Cor	B Adenoma	S	0.6459	0.55730	2	3	2
Adrenal Med	B Medullary Tumor	S	0.7010	0.66470	17	14	16
Adrenal Med	M Medullary Tumor	S	0.9655	0.94745	6	3	2
Bone	M Osteosarcoma	S	0.6962	0.51885	0	1	0
Brain	M Astrocytoma	M	0.6479	0.53210	1	2	1
Brain	M Mixed Glioma	S	1.0000	0.89425	1	0	0
Heart	M Chondrosarcoma	S	1.0000	0.89400	1	0	0
Heart	M Mesothelioma	S	0.6531	0.49340	0	1	0
Jaw	M Chondrosarcoma	S	1.0000	0.88430	1	0	0
Jaw	M Fibrous Histiocytoma	S	0.6756	0.50665	0	1	0
Kidney	B Adenoma	S	0.3418	0.11535	0	0	1
Kidney	M Liposarcoma	S	0.8988	0.82710	1	1	0
Liver	B Bile Duct Adenoma	S	0.4000	0.13715	0	0	1
Liver	B Hepatocellular Adenoma	S	0.6711	0.54740	1	1	1
Liver	M Hepatocellular Carcinoma	S	0.2658	0.18690	1	2	3
Liver	M Histiocytic Sarcoma	S	0.3375	0.11175	0	0	1
Lung	M Carcinoma	S	1.0000	0.90205	1	0	0
Lung	M Histiocytic Sarcoma	S	0.6886	0.52780	0	1	0
Pituitary	B Adenoma	M	0.4950	0.46910	39	43	40

Table 6

Tumor rates of the tested tumor types for positive linear trend

MALE RATS: NEW CONTROL, NEW-LOW

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	NC	NL
Adrenal Cor	B Adenoma	S	0.9366	0.83465	3	1
Adrenal Cor	M Carcinoma	S	0.4667	0.14250	0	1
Adrenal Med	B Medullary Tumor	S	0.4681	0.37930	12	12
Adrenal Med	M Medullary Tumor	S	0.3725	0.24350	3	5
Bone	M Osteosarcoma	S	0.4286	0.12410	0	1
Bone Sternum	B Osteoma	S	0.5476	0.18170	0	1
Brain	B Meningioma	S	0.5476	0.18170	0	1
Cranial Cav	M Osteosarcoma	S	0.4821	0.15000	0	1
Heart	B Schwannoma	S	1.0000	0.82275	1	0
Pituitary	B Adenoma	M	0.2952	0.25265	38	41
Skin/Sub	B Basal Cell Tumor	S	0.4615	0.14005	0	1
Skin/Sub	B Fibroma	M	0.2954	0.18405	3	5
Skin/Sub	B Hibernoma	S	1.0000	0.82275	1	0
Skin/Sub	B Keratoacanthoma	S	0.5035	0.35345	3	4

Table 6

Tumor rates of the tested tumor types for positive linear trend

MALE RATS: OLD CONTROL, NEW-LOW, OLD-LOW, AND OLD-MEDIUM

Organ Name	Tumor Name	SFLG	Exact P-Value	Asymptotic P-value	OC	NL	OL	OM
Adrenal Cor	B Adenoma	S	0.4288	0.40520	2	1	3	2
Adrenal Cor	M Carcinoma	S	0.7592	0.77295	0	1	0	0
Adrenal Med	B Medullary Tumor	S	0.5712	0.56105	17	12	14	16
Adrenal Med	M Medullary Tumor	S	0.9581	0.94920	6	5	3	2
Bone	M Osteosarcoma	S	0.6619	0.65890	0	1	1	0
Kidney	B Adenoma	S	0.2784	0.07910	0	0	0	1
Liver	M Hepatocellular Carci.	S	0.1648	0.13660	1	1	2	3
Liver	M Histiocytic Sarcoma	S	0.3186	0.27895	0	1	0	1
Lung	M Carcinoma	S	1.0000	0.87930	1	0	0	0
Marrow Ster	M Myeloid Sarcoma	M	0.1197	0.09625	0	1	0	2
Pancreas	B Islet Cell Adenoma	S	0.3739	0.36160	11	5	6	11
Pituitary	B Adenoma	M	0.5787	0.57260	39	41	43	40
Testis	B Interstitial Cell Tu.	S	0.9851	0.94740	2	1	0	0
Thoracic Cav	M Liposarcoma	S	0.5097	0.42730	0	0	1	0
Thymus	B Thymoma	S	0.2784	0.07910	0	0	0	1
Thyroid	B C-cell Adenoma	S	0.8370	0.82515	7	3	4	4

Table 6

Tumor rates of the tested tumor types for positive linear trend

MALE RATS: NEW CONTROL, NEW-LOW, OLD-LOW, OLD-MEDIUM

Organ Name	Tumor Name	MSFLG	P-Value	P-value	NC	NL	OL	OM
Adrenal Cor	B Adenoma	S	0.5125	0.49400	3	1	3	2
Adrenal Cor	M Carcinoma	S	0.7736	0.78045	0	1	0	0
Adrenal Med	B Medullary Tumor	S	0.2627	0.25270	12	12	14	16
Adrenal Med	M Medullary Tumor	S	0.7893	0.77615	3	5	3	2
Bone	M Osteosarcoma	S	0.6437	0.64610	0	1	1	0
Bone Sternum	B Osteoma	S	0.7398	0.70850	0	1	0	0
Brain	B Meningioma	S	0.7398	0.70850	0	1	0	0
Brain	M Astrocytoma	M	0.2433	0.15945	0	0	2	1
Cranial Cav	M Osteosarcoma	S	0.7734	0.77440	0	1	0	0
Heart	B Schwannoma	S	1.0000	0.88820	1	0	0	0
Heart	M Mesothelioma	S	0.5079	0.41825	0	0	1	0
Pancreas	B Islet Cell Adenoma	S	0.2190	0.20720	9	5	6	11
Pancreas	M Acinar Adenocarcinoma	S	0.2872	0.08335	0	0	0	1
Pancreas	M Islet Cell Carcinoma	S	0.2151	0.13155	0	0	1	1
Parathyroid	B Adenoma	S	0.8474	0.85030	0	2	0	0
Paw/Foot	M Giant Cell Tumor	S	0.2925	0.08485	0	0	0	1
Pituitary	B Adenoma	M	0.5353	0.52925	38	41	43	40

Table 6

Tumor rates of the tested tumor types for positive linear trend

MALE RATS: OLD+NEW CONTROL, NEW-LOW, OLD-LOW, OLD-MEDIUM

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	ONC	NL	OL	OM
Adrenal Cor	B Adenoma	S	0.4835	0.47110	5	1	3	2
Adrenal Cor	M Carcinoma	S	0.6212	0.70140	0	1	0	0
Adrenal Med	B Medullary Tumor	S	0.4311	0.42305	29	12	14	16
Adrenal Med	M Medullary Tumor	S	0.9055	0.89380	9	5	3	2
Bone	M Osteosarcoma	S	0.5053	0.52675	0	1	1	0
Bone Sternum	B Osteoma	S	0.5934	0.63950	0	1	0	0
Brain	B Meningioma	S	0.5934	0.63950	0	1	0	0
Brain	M Astrocytoma	M	0.2919	0.22900	1	0	2	1
Brain	M Mixed Glioma	S	1.0000	0.79770	1	0	0	0
Cranial Cav	M Osteosarcoma	S	0.6266	0.69895	0	1	0	0
Heart	B Schwannoma	S	1.0000	0.82950	1	0	0	0
Heart	M Chondrosarcoma	S	1.0000	0.81325	1	0	0	0
Heart	M Mesothelioma	S	0.4000	0.33015	0	0	1	0
Pancreas	B Islet Cell Adenoma	S	0.4013	0.39275	20	5	6	11
Pituitary	B Adenoma	M	0.4597	0.45525	77	41	43	40

Table 6

Tumor rates of the tested tumor types for positive linear trend

FEMALE RATS: OLD CONTROL, OLD-LOW, OLD-MEDIUM

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	OC	OL	OM
Adrenal Cor	B Adenoma	S	0.8720	0.82450	4	3	2
Adrenal Cor	M Carcinoma	S	0.3649	0.21310	0	1	1
Adrenal Med	B Medullary Tumor	S	0.7137	0.64750	5	2	4
Adrenal Med	M Medullary Tumor	S	0.8048	0.71395	1	3	0
Liver	M Hepatocellular Carcinoma	S	0.6821	0.53160	0	1	0
Liver	M Histiocytic Sarcoma	S	0.2798	0.19110	0	3	2
Lymph N. Mes	M Lymphosarcoma	S	0.7086	0.55665	0	1	0
Mammary Gl	B Fibroadenoma	M	0.9997	0.99960	35	21	18
Mammary Gl	M Adenocarcinoma	M	0.3523	0.31675	13	21	17
Marrow Ster	M Myeloid Sarcoma	S	0.3622	0.12250	0	0	1
Omentum/Mes	M Hemangiosarcoma	S	0.4369	0.15640	0	0	1
Omentum/Mes	M Osteosarcoma	S	0.6721	0.51320	0	1	0
Omentum/Mes	M Schwannoma	S	0.6923	0.52880	0	1	0
Pituitary	B Adenoma	S	0.9941	0.99305	52	57	46
Pituitary	M Carcinoma	S	0.7362	0.65055	3	0	3
Thyroid	B C-cell Adenoma	S	0.6998	0.64260	6	4	6

Table 6

Tumor rates of the tested tumor types for positive linear trend

FEMALE RATS: NEW CONTROL, NEW-LOW

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	NC	NL
Adrenal Cor	B Adenoma	S	0.8580	0.74090	4	2
Adrenal Med	B Medullary Tumor	S	0.6847	0.42245	1	1
Adrenal Med	M Medullary Tumor	S	1.0000	0.80865	1	0
Brain	B Meningioma	S	0.4906	0.15410	0	1
Liver	B Bile Duct Adenoma	S	0.4324	0.12595	0	1
Liver	B Hepatocellular Adenoma	S	1.0000	0.91945	2	0
Liver	M Hepatocellular Carcinoma	M	1.0000	0.80865	1	0
Mammary Gl	M Adenocarcinoma	M	0.1068	0.07905	17	24
Pituitary	B Adenoma	M	0.2134	0.17970	53	58
Skin/Sub	B Fibroma	M	0.3638	0.22135	2	4
Skin/Sub	B Keratoacanthoma	S	0.4906	0.15410	0	1
Skin/Sub	M Fibrous Histiocytoma	M	0.5417	0.31440	1	2
Skin/Sub	M Keratoacanthoma	S	0.4906	0.15410	0	1
Thyroid	B C-cell Adenoma	S	0.2539	0.13970	2	4
Uterus	B Polyp	S	0.2686	0.15050	2	4
Uterus	M Adenocarcinoma	S	0.2862	0.09360	0	2

Table 6

Tumor rates of the tested tumor types for positive linear trend

FEMALE RATS:OLD CONTROL, NEW-LOW, OLD-LOW, OLD-MEDIUM

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	OC	NL	OL	OM
Adrenal Cor	B Adenoma	S	0.7618	0.74630	4	2	3	2
Adrenal Cor	M Carcinoma	S	0.2086	0.12480	0	0	1	1
Adrenal Med	B Medullary Tumor	S	0.4693	0.45185	5	1	2	4
Adrenal Med	M Medullary Tumor	S	0.5885	0.56400	1	0	3	0
Brain	M Astrocytoma	M	0.5766	0.44410	1	0	0	1
Heart	B Schwannoma	S	0.3475	0.10510	0	0	0	1
Liver	B Bile Duct Adenoma	S	0.8052	0.77430	1	1	2	0
Liver	B Hepatocellular Adenoma	S	0.2206	0.05230	0	0	0	1
Liver	M Hepatocellular Carcinoma	S	0.5228	0.44745	0	0	1	0
Liver	M Histiocytic Sarcoma	S	0.1105	0.07940	0	0	3	2
Lymph N. Mes	M Lymphosarcoma	S	0.5389	0.46505	0	0	1	0
Lymph N. Misc	M Fibrous_Histiocytoma	S	0.7550	0.75925	0	1	0	0
Mammary Gl	B Adenoma	S	0.8254	0.80825	1	1	1	0
Pituitary	B Adenoma	M	0.9980	0.99775	52	58	57	46
Spleen	M Lymphosarcoma	S	0.5606	0.43410	0	0	2	0
Thymus	M Lymphosarcoma	S	0.9605	0.94400	3	0	1	0
Thyroid	B C-cell Adenoma	S	0.5396	0.52515	6	4	4	6

Table 6

Tumor rates of the tested tumor types for positive linear trend

FEMALE RATS:NEW CONTROL, NEW-LOW, OLD-LOW, OLD-MEDIUM

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	NC	NL	OL	OM
Adrenal Cor	B Adenoma	S	0.7306	0.71475	4	2	3	2
Adrenal Cor	M Carcinoma	S	0.1897	0.11225	0	0	1	1
Adrenal Med	B Medullary Tumor	S	0.0476	0.03425	1	1	2	4
Adrenal Med	M Medullary Tumor	S	0.5887	0.56195	1	0	3	0
Brain	B Meningioma	S	0.7711	0.78170	0	1	0	0
Brain	M Astrocytoma	S	0.2822	0.07755	0	0	0	1
Heart	B Schwannoma	S	0.3475	0.10510	0	0	0	1
Liver	B Bile Duct Adenoma	S	0.6362	0.59065	0	1	2	0
Liver	B Hepatocellular Adenoma	S	0.7753	0.73670	2	0	0	1
Liver	M Hepatocellular Carcinoma	M	0.7281	0.70670	1	0	1	0
Liver	M Histiocytic Sarcoma	S	0.1058	0.07535	0	0	3	2
Mammary Gl	B Fibroadenoma	M	0.9993	0.99900	36	20	21	18
Mammary Gl	M Adenocarcinoma	M	0.8620	0.85620	17	24	21	17
Marrow Ster	M Lymphosarcoma	S	1.0000	0.86185	1	0	0	0
Pituitary	B Adenoma	M	0.9974	0.99700	53	58	57	46
Pituitary	M Carcinoma	M	0.3298	0.29295	2	1	0	3
Thyroid	B C-cell Adenoma	S	0.1257	0.11250	2	4	4	6

Table 6

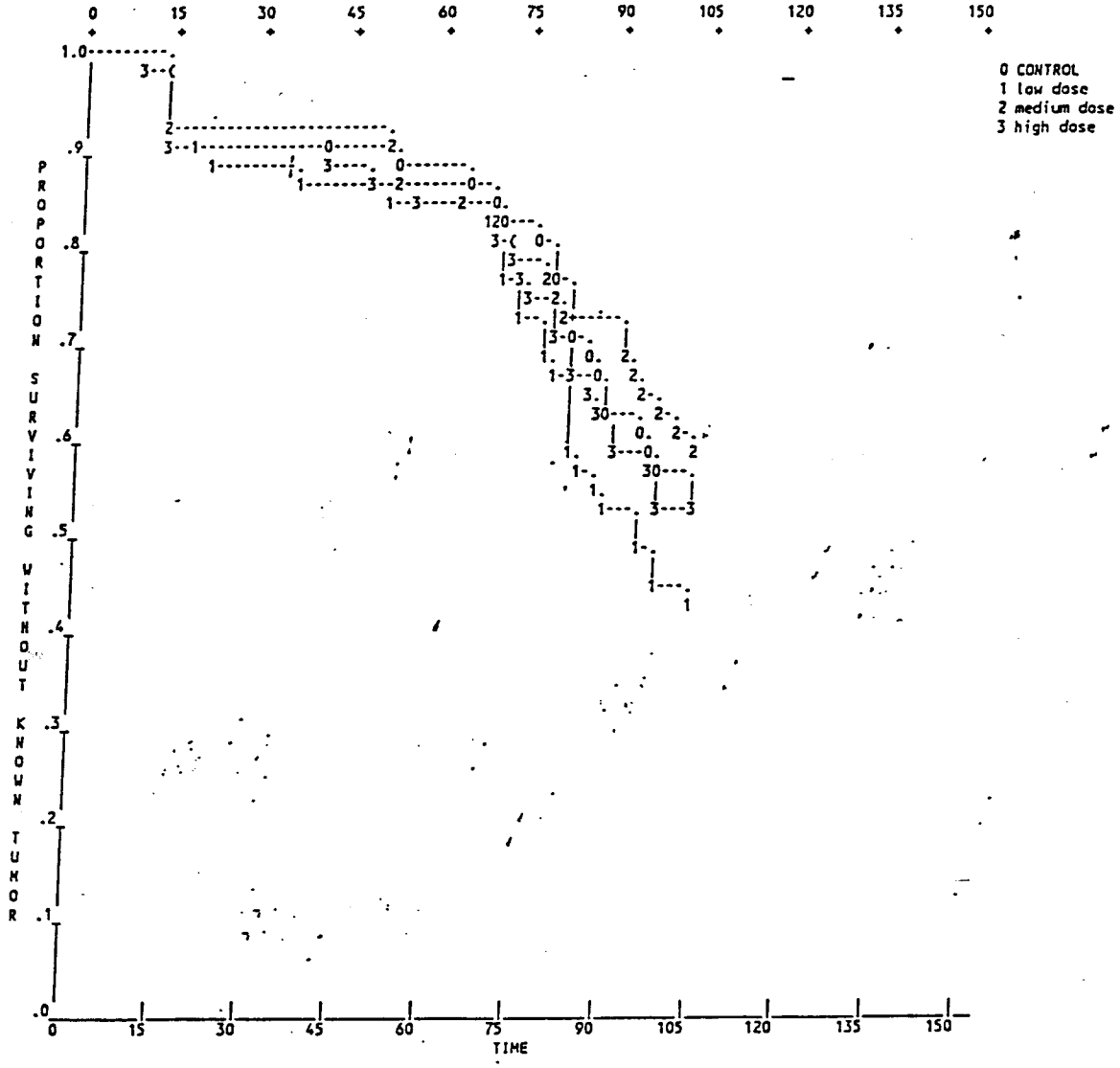
Tumor rates of the tested tumor types for positive linear trend

FEMALE RATS:OLD+NEW CONTROL, NEW-LOW, OLD-LOW, OLD-MEDIUM

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	ONC	NL	OL	OM
Adrenal Cor	B Adenoma	S	0.8221	0.81010	8	2	3	2
Adrenal Cor	M Carcinoma	S	0.1258	0.06655	0	0	1	1
Adrenal Med	B Medullary Tumor	S	0.2729	0.25640	6	1	2	4
Adrenal Med	M Medullary Tumor	S	0.5546	0.53525	2	0	3	0
Brain	B Meningioma	S	0.6276	0.70895	0	1	0	0
Brain	M Astrocytoma	M	0.4753	0.32890	1	0	0	1
Heart	B Schwannoma	S	0.2828	0.07290	0	0	0	1
Liver	B Bile Duct Adenoma	S	0.6245	0.60090	1	1	2	0
Liver	B Hepatocellular Adenoma	S	0.6494	0.57320	2	0	0	1
Liver	M Hepatocellular Carcinoma	M	0.6246	0.60500	1	0	1	0
Liver	M Histiocytic Sarcoma	S	0.0493	0.02815	0	0	3	2
Mammary Gl	B Fibroadenoma	M	0.9999	0.99990	71	20	21	18
Mammary Gl	M Adenocarcinoma	M	0.5872	0.58115	30	24	21	17
Pituitary	B Adenoma	M	0.9959	0.99530	105	58	57	46
Pituitary	M Carcinoma	M	0.5669	0.55085	5	1	0	3
Thyroid	B C-cell Adenoma	S	0.3192	0.30740	8	4	4	6
Uterus	B Polyp	S	0.6649	0.65420	5	4	2	2

Figure 1a

Kaplan-Mier Estimates of the survival distributions
(Male mice)



APPEARS THIS WAY
ON ORIGINAL

Figure 1b

Kaplan-Mier Estimates of the survival distributions
(Female mice)

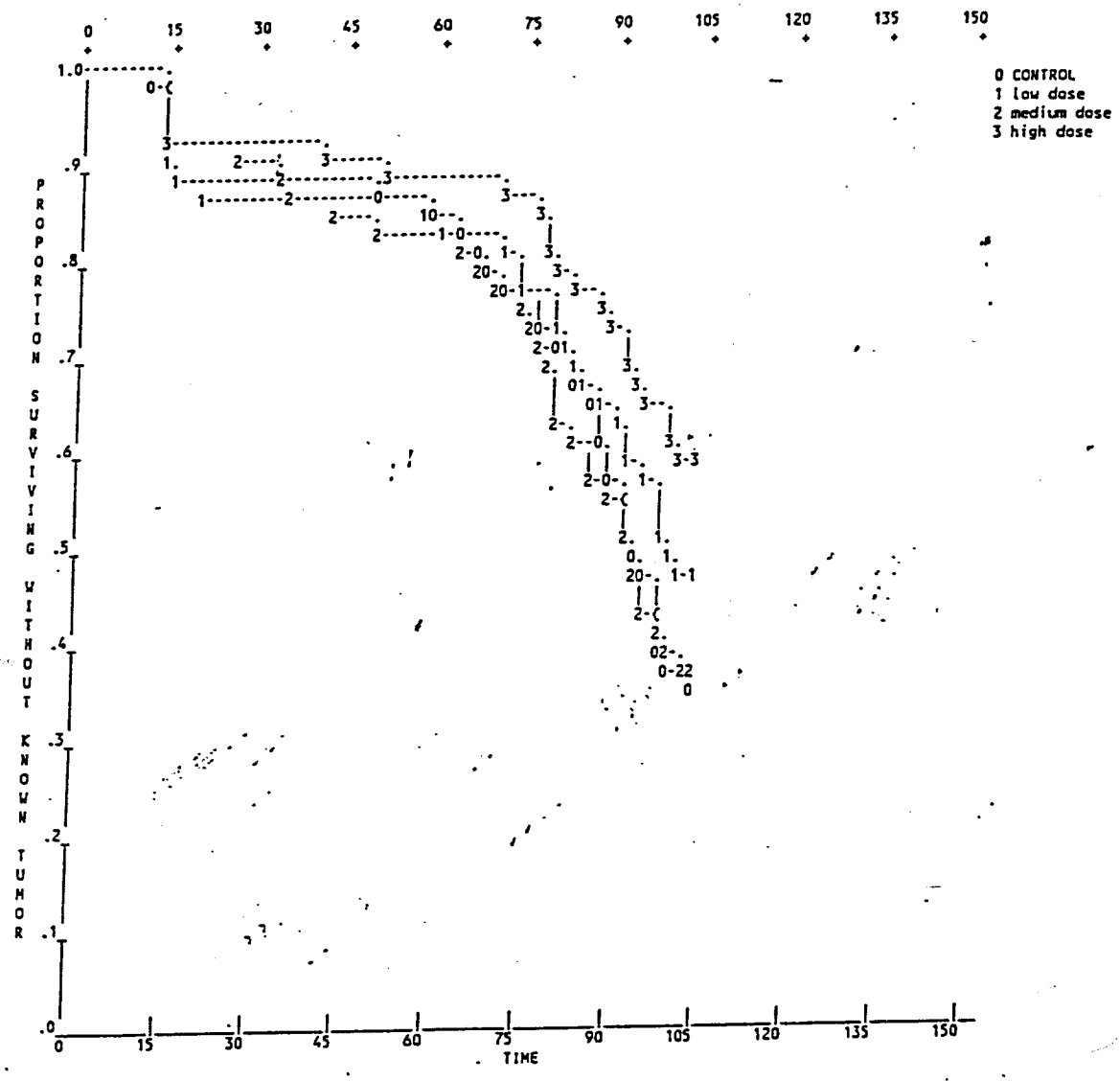


Figure 2a

Kaplan-Mier Estimates of the survival distributions
(Male rats)

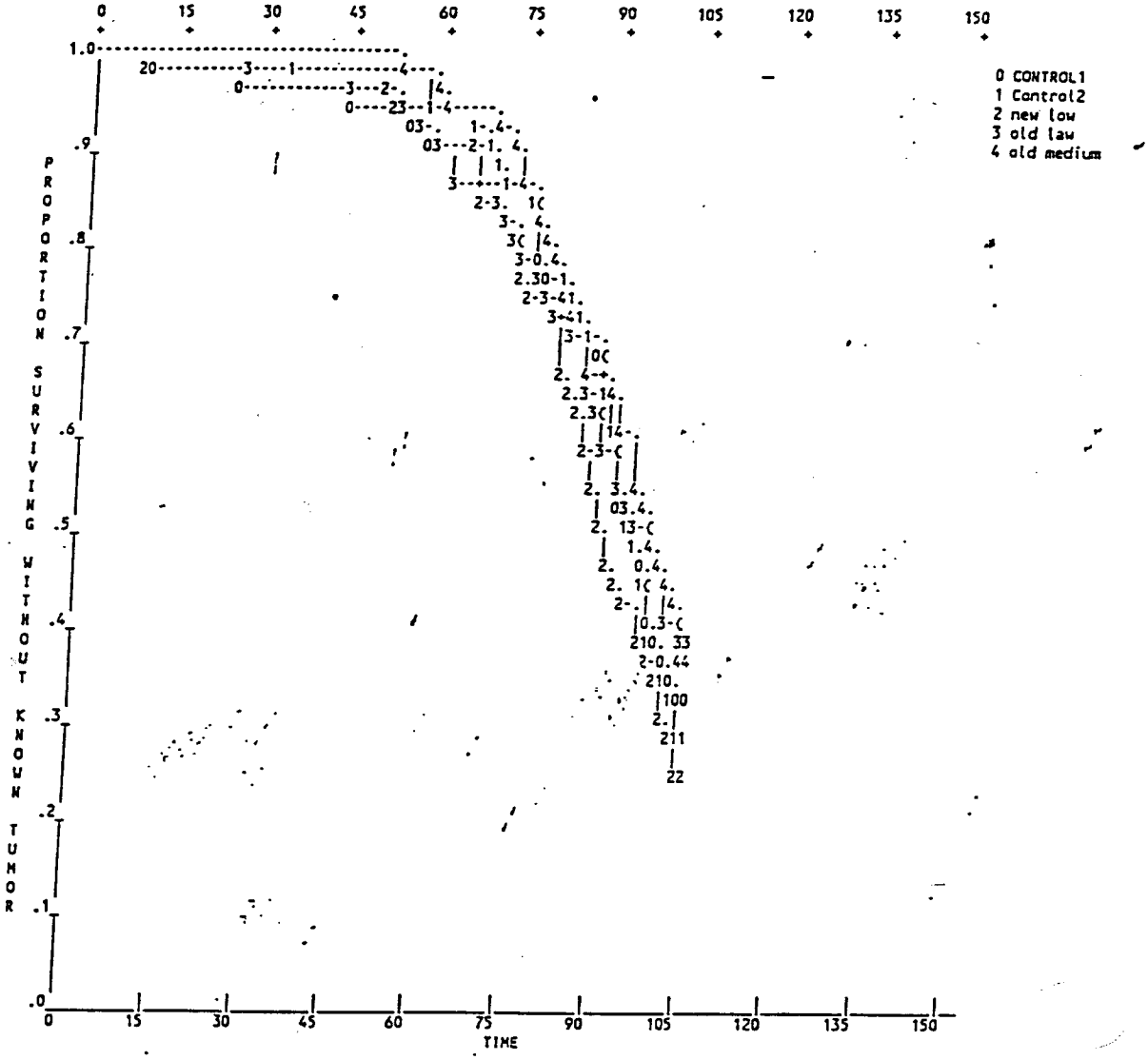
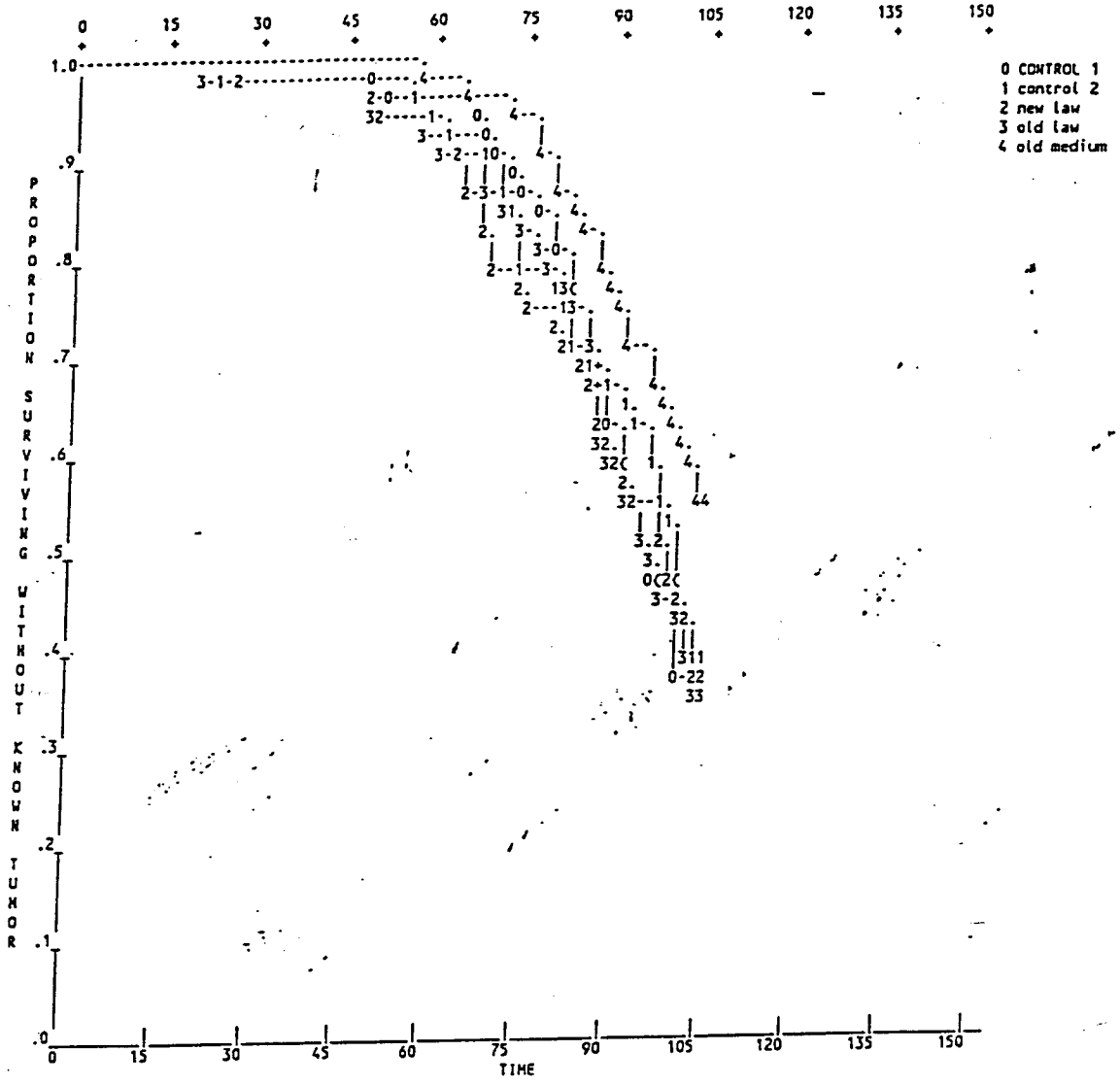


Figure 2b

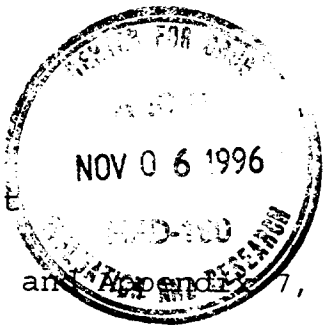
Kaplan-Mier Estimates of the survival distributions
(Female rats)



MEMORANDUM OF STATISTICAL CONSULTATION --- Stability

Date: NOV 1 1996

NDA #: 20-623



Applicant: Hoechst Marion Roussel, Inc.

Name of Drug: Anzemet (dolasetron mesylate) Tablet

Documents Reviewed: Information Amendment p. 7-13 and Appendix 7, Dated September 12, 1996

A. **Background**

The stability analysis for NDA 20-623 was reviewed and documented in the Statistical Review and Evaluation dated August 1, 1996.

It was found that there were insufficient observed data to support a shelf-life at least 24 months in all three packages.

The sponsor has responded to the issues (i.) through (v.) in this Information Amendment.

B. Sponsor's Response

1. **Issue (i.)**

In your stability analysis based on an alternative protocol, there were numerous substitutions: 8 of 21 (38%) for the 100-count HDPE bottle, 8 of 18 (44%) for the 5-count HDPE bottle, and 8 of 15 (53%) for the blister package. Using data with high substitution rates casts doubt about the accuracy of estimated shelf-life. Please explain how the number of substitutions is acceptable for this analysis.

Sponsor's Response to Issue (i.)

The sponsor stated that the sponsor does not need to further defend the data substitutions made under the alternative protocol. They had prior approval to make the data substitution from Division of Gastro-Intestinal Drug Products. They have also provided another analysis that does not use substituted data.

2. **Issue (ii.)**

The p-value for slope comparisons between 5- and 500-count HDPE bottle (HDPE5-HDPE500) was significant at 0.25 level of significance for moisture. This casts doubt that the assumption that there are no difference among 5-, 100-, and 500-count bottle in terms of potency, dissolution, and moisture. Please provide data and/or information which justifies the assumption of no difference among the 5-, 100-, and 500-count bottle in terms of potency, dissolution, and moisture.

Sponsor's Response to Issue (ii.)

Looking at the broader picture, the p-value that is cited for one variable in one package comparison which is below 0.25 provides a relatively weak suggestion of any significant problem with data substitutions made from one package to another under the alternative protocol.

3. **Issue (iii.)**

Please explain the effects on the accuracy of the 95% confidence interval due to substituting the missing time points (3, 6, or 9 months) with later real time data (e.g., 12 month or 13 month).

Sponsor's Response to Issue (iii.)

In terms of statistical expectations, the creation of the additional data would reduce the width of the resulting 95% confidence interval, and thus, increase the shelf-life projected by the statistical analysis.

The sponsor sees no point in attempting to quantify the impacts of data substitution across time on the alternative protocol analysis confidence limits.

4. **Issue (iv.)**

All of the preliminary tests as well as the final test of interaction were performed using a significance level of 0.05.

However, due to poor power to test interaction, using a significance level of 0.25 was suggested in our letter dated October 31, 1995 send to you regarding IND 35,920. Please justify your use of the 0.05 level of significance.

Sponsor's Response to Issue (iv.)

The choice between the 0.25 and 0.05 significance levels will not have much impact in an application with data like that observed for Anzemet tablets, where almost no change was observed in potency, 30-minute dissolution, or moisture over 18 months for any package, strength, or lot.

5. **Issue (v.)**

Your final reduced model used for estimating the shelf-life includes the interaction terms STRENGTH*LOT, YEARS*LOT, AND YEARS*STRENGTH, but does not include the main effects STRENGTH, LOT, and YEARS as suggested in the October 31, 1995 letter mentioned above. In addition, an analysis to estimate common slopes and intercepts cross lots, packages, and strengths could not located. Please justify the final reduced model used in your analysis.

Sponsor's Response to Issue (v.)

The omission of the main effect terms STRENGTH, LOT, and YEARS does not imply a reduced model in this context. Results are shown from the model estimated including these terms and these results are exactly the same as those shown in Amendment dated February 15, 1996. Page 141 of the statistical analysis report K-96-0087-M in terms of model summary statistics and implied shelf-life.

C. **Reviewer's Comments and Evaluation**

1. **Reviewer's Comments on the Sponsor's Responses**

According to this reviewer's information, the Division of Gastro-Intestinal Drug Products never gave the sponsor an approval on their matrix design. For filing of the NDA, the sponsor was allowed to "fill in" missing datapoints for smaller size bottles with information obtained from "sacrificed" larger count

packages.

The sponsor's analysis that does not use substituted data did not have data available from three granulation lots for each package-strength combination. There were only two lots for timepoints 3, 6, 9, 12, and 18 months for each strength for 5-count and 100-count HDPE bottle. There were only two lots for each strength for Alusuisse blister. The estimated shelf-life resulting from two batches may not be reliable.

The sponsor failed to provide further explanation and information about the issues about substitutions listed below.

(1). Please explain how the number of substitutions is acceptable for this analysis.

(2). Please provide data and/or information which justifies the assumption of no difference among the 5-, 100-, and 500-count bottle in terms of potency, dissolution, and moisture.

(3). Please explain the effects on the accuracy of the 95% confidence interval due to substituting the missing time points (3, 6, or 9 months) with later real time data (e.g., 12 month or 13 month).

2. **Reviewer's Evaluation**

The sponsor did not propose 25 or 100 mg strength in the submitted proposed package insert. The sponsor plans to market 50 mg or 200 mg tablets.

This reviewer is focusing the issues of 50 mg only.

This reviewer performed stability analysis of potency, 30 minutes dissolution, and moisture using data with substitutions and without substitutions for 5-count HDPE bottle, 100-count HDPE bottle, and Blister-Alusuisse.

This reviewer ran the Division's routine stability program. With respect to all three quantities:

Potency	90%-110%
30-Minutes Dissolution	≥80%
Moisture	≤8%

For non-substitution data, there were only two lots for timepoints 3, 6, 9, 12, and 18 months for 5-count and 100-count HDPE bottle. There were only two lots for Alusuisse blister. Based on two batch lots, There may be inadequate power for testing the common slope and intercept based on two batch lots. It will be better to assume different slope and different intercept for each of two batches.

Expiration dating periods for the lots in the various package types for 50 mg strength using substituted data and non-substituted data are:

Variable	Package	Lot No.	Substitution Data Est. Expiration Dating Period (Months)	Non-substitution Data Est. Expiration Dating Period (Months)
Potency	5-count HDPE	R54046	72	72
		R54047	72	
		R54049	72	65
	100-count HDPE	R54046	72	
		R54047	72	72
		R54049	72	72
	Blister-Alusuisse	R54046	72	40
		R54047	72	
		R54049	72	38
30-Minute Dissolution	5-count HDPE	R54046	72	61
		R54047	72	
		R54049	72	72
	100-count HDPE	R54046	72	
		R54047	72	72
		R54049	72	72

	Blister-	R54046	72	42
	Alusuisse	R54047	72	
		R54049	72	72
Moisture	5-count	R54046	64	0
	HDPE	R54047	64	
		R54049	64	30
	100-count	R54046	72	
	HDPE	R54047	72	29
		R54049	72	58
	Blister-	R54046	62	0
	Alusuisse	R54047	62	
		R54049	62	44

As seen above, the estimated expiration dating periods resulting from the non-substitution data are varied from batch to batch and from variable to variable. Especially, for moisture, batch R54046 has 0 month estimated expiration dating period. For moisture, there were only three to four observed timepoints between 0 to 18 months (6, 12, and 18 or 3, 9, 12, and 18 month) in each batch. About 33%(2/6) to 50% (3/6) of required timepoints (0, 3, 6, 9, 12, and 18 month) are missing. There are just insufficient timepoints observed to provide enough information about degradation pattern of batches R54046, R54047, and R54049.

The original review stands. There were insufficient observed data to support a shelf-life at least 24 months in all three packages.

D. **Comments to be conveyed to the Sponsor**

The contents of Section of C may be conveyed to the sponsor.

/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 7 pages of text and 33 pages of table.

concur: Dr. Huque /S/ 10/31/96
Dr. Smith /S/ 11/1/96

cc:
Archival NDA 20-623
HFD-180
HFD-180/Mr. Adams
HFD-180/Dr. Duffy
HFD-180/Ms. Johnson
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/10/31/96

Redacted 33

pages of trade

secret and/or

confidential

commercial

information

STATISTICAL REVIEW AND EVALUATION --- NDA
(ADDENDUM)

Date: JUL 28 1997

NDA #: 20-623, 20-624

Applicant: Hoechst Marion Roussel, Inc.

Name of Drug: Anzemet (Dolasetron mesylate) Tablet
Anzemet (Dolasetron mesylate) Injection

Indication: Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy, Including Initial and Repeat courses.
Prevention of PONV (Postoperative Nausea and Vomiting)
Treatment of PONV (Postoperative Nausea and Vomiting)

Documents Reviewed: NDA Suppl. dated June 6, 1997

Medical Reviewer: This review has been discussed with the medical Officer, Hugo Gallo-Torres, M.D., Ph.D.

Key Words: Pooling studies

A. **Background**

Reviewer's evaluation and comments on sponsor's results of pooling data from dolasetron controlled clinical trials were given in the statistical review and evaluation dated July 16, 1997.

Per request, for iv dolasetron for the prevention of PONV, this reviewer re-analyzed the proportion of complete responder from the pooled data which included studies MCPR0084 and 73147-2-S-080 and females in study MCPR0045.

For oral dolasetron for the prevention of CONV, the dose response profile for the pooled data and for individual dose response trials are attached as figures 1a and 1b.

B. **Reviewer's Evaluation and Comments**

1. **Intravenous Dolasetron for the Prevention of PONV**

If studies MCPR0084, 73147-2-S-080 and MCPR0045 were pooled for females, the estimate differences and 95% confidence intervals for the differences in the proportion of complete responders for

all comparisons are:

IV Dolasetron for the Prevention of PONV --- Studies MCPR0045, MCPR0084 and 73147-2-S-080 for Females
Comparison of 12.5 mg and Higher Active Dose Groups
Difference in Proportions (Dose Group - 12.5 mg)

Dose Comparison	Estimate	95% Conf. Interval
12.5 mg vs. 25 mg	-0.02%	(-7.8%, 7.4%)
12.5 mg vs. 50 mg	0.02%	(-7.4%, 7.8%)
12.5 mg vs. 100 mg	4.0%	(-4.6%, 13.1%)

Estimates and 95% confidence intervals were obtained using Exact method.

As seen in the above table, the analysis of proportion of complete responder from the pooled data for females shows that there were no differences among 12.5 mg, 25 mg and 50 mg. Therefore, 12.5 mg seems to be the minimal effective dose with maximum response in the pooled analysis for females.

2. Oral Dolasetron for the Prevention of CCNV

The dose response profile for the pooled data and for individual dose response trials are given in Figures 1a and 1b, respectively.

The statistical review and evaluation dated May 20, 1996 stated "antiemetic efficacy of dolasetron for prevention of CCNV was linear related to dose. The maximal effectiveness seems to be achieved with a single dose of 200 mg."

C. Overall Summary and Recommendation

1. Intravenous Dolasetron for the Prevention of PONV

The analysis of proportion of complete responder from the pooled data for females shows that there were no differences among 12.5 mg, 25 mg and 50 mg. Therefore, 12.5 mg seems to be the minimal effective dose with maximum response in the pooled analysis for females.

2. Oral Dolasetron for the Prevention of CCNV

The maximal effectiveness seems to be achieved with a single dose of 200 mg.

/S/

/Milton C. Fan, Ph.D.
Mathematical Statistician

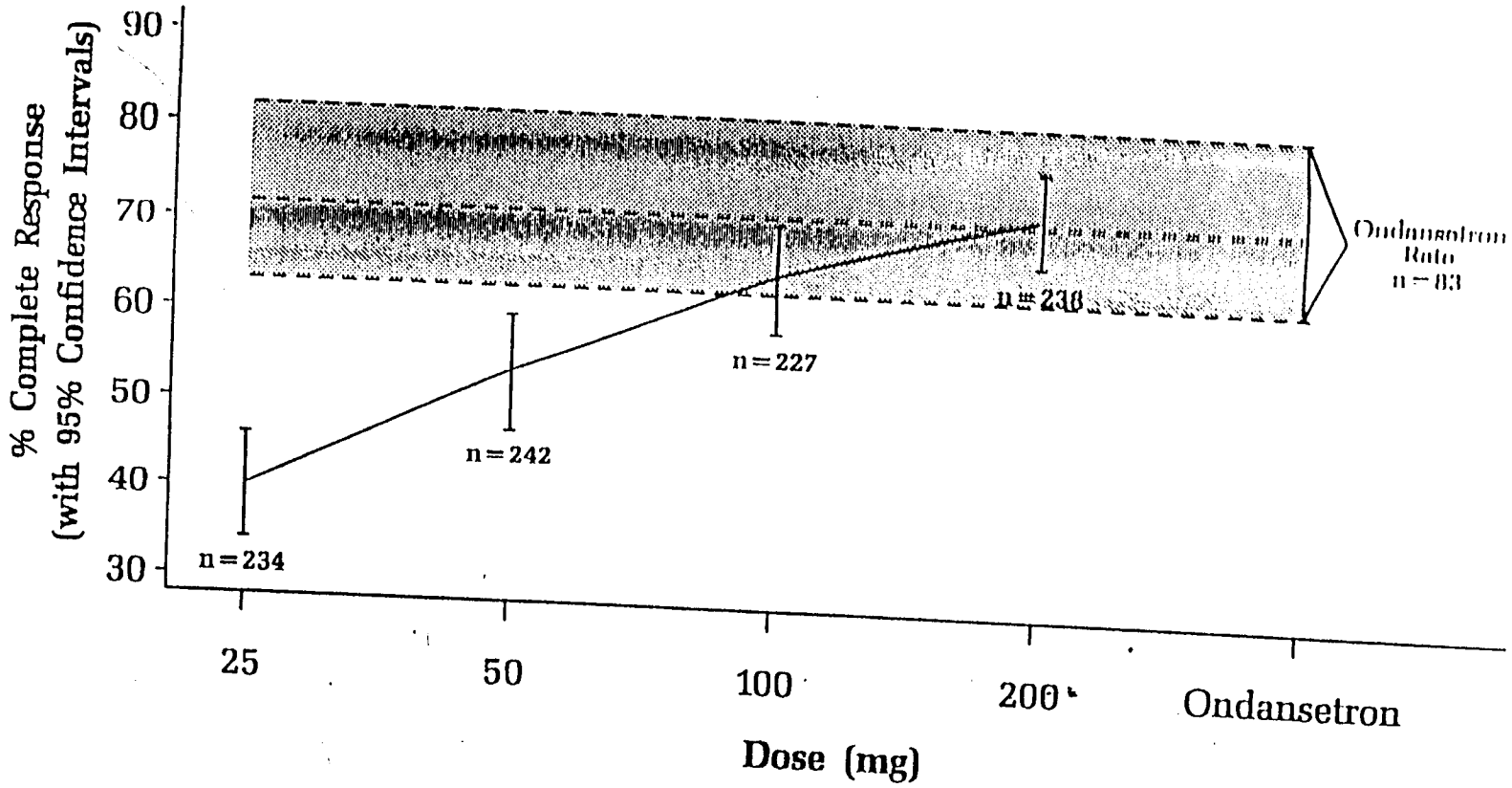
This review consists of 3 pages of text and 2 pages of tables.

Concur: Dr. Huque /S/ 7/22/97
Dr. Smith /S/ 7/28/97

cc:
Archival NDA 20-623, 20-624
HFD-180
HFD-180/Dr. Talarico
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-344/Dr. Lisook
HFD-720
HFD-720/Chron. Copy
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/07/22/97

Figure 1a

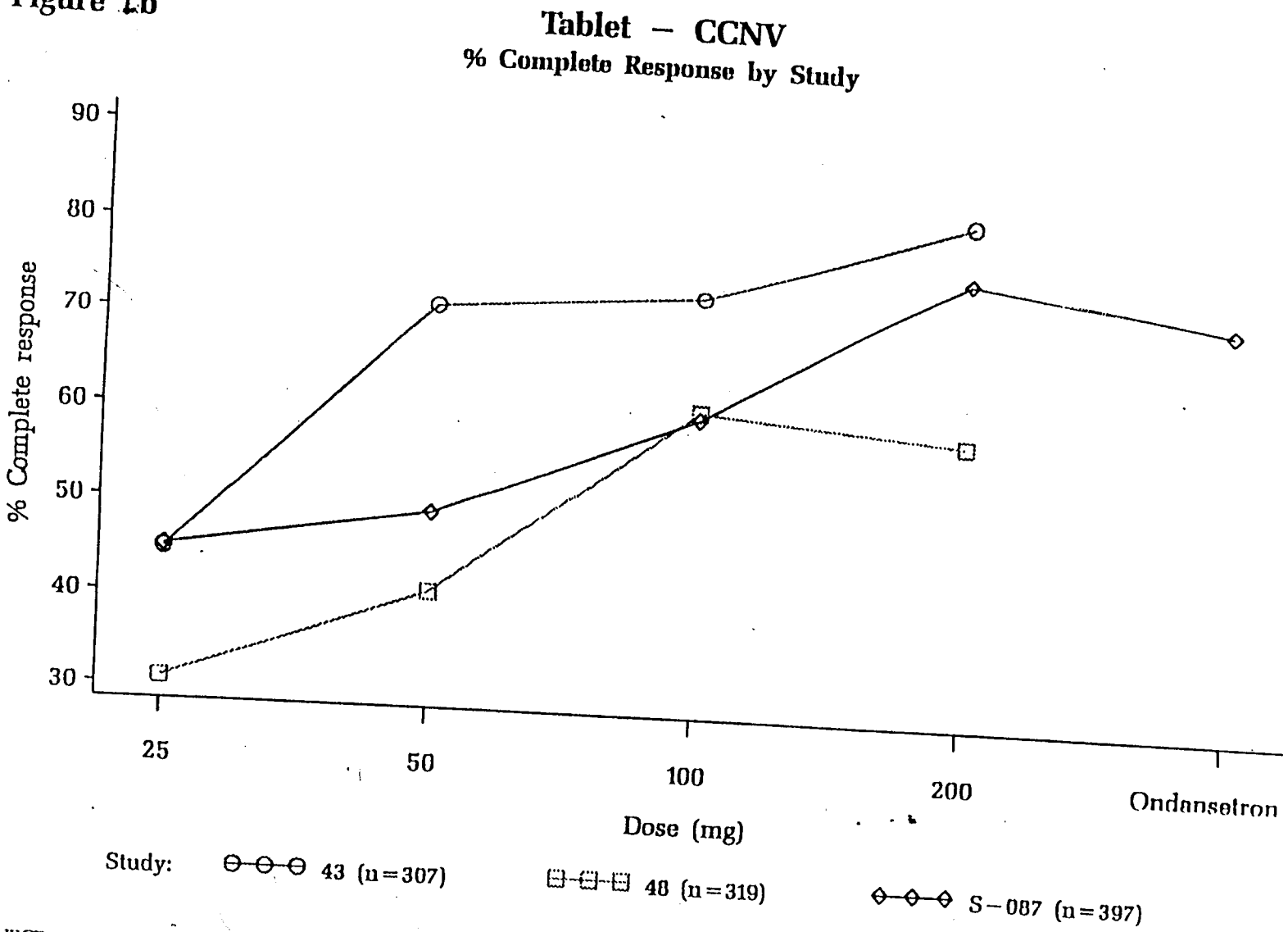
Oral Dolasetron/Chemotherapy
Randomized, Double Blind Trials
Complete Response by Dose
(Linear dose response, p < .0001)
(200 vs 25, p < .0001)



Includes studies MCPR0043, MCPR0048, 2-S-087

Source: MMD NM00274 - DOLCHEMO.SAS - (04JUN97, 16:04)

Figure 1b



SOURCE: MMD STAT_CDM NM08274 -OCHEM_EFF_4.SAS- (05JUN07, 16:05)

STATISTICAL REVIEW AND EVALUATION --- NDA

Date: JUL 16 1997

NDA #: 20-623, 20-624

Applicant: Hoechst Marion Roussel, Inc.

Name of Drug: Anzemet(Dolasetron mesylate) Tablet
Anzemet(Dolasetron mesylate) Injection

Indication: Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy, Including Initial and Repeat Courses.
Prevention of PONV (Postoperative Nausea and Vomiting)
Treatment of PONV (Postoperative Nausea and Vomiting)

Documents Reviewed: NDA Suppl. dated June 6, 1997

Medical Reviewer: This review has been discussed with the medical officer, Hugo Gallo-Torres, M.D., Ph.D.

Key Words: Pooling studies, logistic regression

A. Background

The sponsor formally submitted this NDA supplemental to document results of pooling of data from Dolasetron controlled clinical trials.

This document outlines the justification for pooling the efficacy data from pivotal dose response trials of dolasetron that were presented in the Integrated Summary of Efficacy (ISE) for the original NDA. This document describes data analytic approaches for analyzing the pooled data for each indication for which the sponsor and FDA currently having differing dose recommendations. Those indications are:

- * intravenous dolasetron for treatment and prevention of PONV
- * oral dolasetron for prevention of PONV, and
- * oral dolasetron for prevention of CCNV.

Some of rationales for FDA dose recommendations were given in the

statistical review and evaluation dated May 20, 1996, Jan 17, 1997, respectively for the above 3 indications.

For oral dolasetron for the prevention of CCNV, the statistical review and evaluation dated May 20, 1996 stated "antiemetic efficacy of dolasetron mesylate tablets in prevention of CCNV was linear related to dose. The maximal effectiveness seems to be achieved with a single dose of 200 mg."

This review will not discuss the issues of dose selection for the indications of oral dolasetron for prevention of CCNV. Instead, this review will discuss mainly the issues of dose selection for the indications of 1) oral dolasetron for prevention of PONV, and 2) intravenous dolasetron for treatment and prevention of PONV.

B. **Sponsor's Analysis**

1. **Pooling Data for Dosage Selection**

a). **Clinical and Scientific Rationale**

There were two considerations about pooling of data from independent studies. First, one must assess whether studies are sufficiently compatible to permit pooling of data. Issues regarding study design, patient population, dosing regiments, duration of follow-up etc must be reviewed to answer this question. Second, if the decision is made that studies are suitable for pooling, then one must decide how the pooling will be done, i.e., what statistical methodology is useful for answering the questions at hand.

In the case of the dolasetron program, the primary interest is to characterize the dose response profile in order to select the optimal dose of dolasetron in each indication. The sponsor's intent was to select the minimum dose with the maximal effect, i.e., the lowest dose on the plateau of the dose response curve.

The sponsor's intent for pooling of data was considered prospectively by the consistency of individual study designs and the multiple dose response studies that were conducted for each indication. The Phase III programs for the various indications were designed by a common Global Project Team. While slight variations were allowed to meet some regional needs or

accommodate the distinct indications, the essential elements of trial design and conduct were the same across all studies. Some of those major elements are:

all studies use a placebo, active control or low dose control;
inclusion/exclusion criteria were harmonized across studies;
medical procedures were similar;
the primary response variable were identically defined;
a common 24-hour evaluation window was used.

In addition to these design elements, studies were done concurrently in time to minimize potential bias due to changing medical practice over time. As noted in the sponsor's clinical study report, patients characteristics, medical histories and important prognostic factors were well-balanced across control and dose groups.

In order to increase the precision of the overall estimates of the dose effect, the sponsor believes that the data from these studies are appropriate for pooling.

b). **Statistical Consideration**

The definite dose response studies in the ISE were evaluated using a separate logistic regression analysis for each indication. For the present analysis, the model included a study identifier, dose group and a term for study-by-dose group interaction. The interaction term was used to assess the parallelism of the dose response curves across studies. The model may be written as:

logit=study dosegroup study*dosegroup

The outcomes of the tests for parallelism from the logistic model were summarized below.

Assessing Parallelism of Dose Response Across Studies Using Logistic Regression

Indication	Number of Studies	Logistic Regression Study*dose Group Interaction P-value
IV PONV Treatment	2	0.3859
IV PONV Prevention	3	0.4103
Oral PONV Prevention	2	0.2350

Copied from Table 1, page 4 of NDA supplemental dated 6/6/97.

Each of these p-values is large enough to indicate that the dose response profiles are parallel across the dose studies. In considering the power of these tests to detect meaningful differences in the parallelism of the dose response profiles. It is difficult to define an alternative hypothesis of interest since there are many patterns of dose response that could be evaluated. However, these p-values are sufficient large and are based on 2 or 3 studies each involving 300 to 1000 patients for each indication.

Estimation of the dose effect and the difference between selected doses is of interest for the pooled data. At the request of FDA Biometric Division, exact estimation of the odds ratio and confidence intervals (Mantel-Haenzsel test) was used since it is not model dependent as is the case of logistic regression. Also, exact estimates of the odds ratio and confidence intervals were computed for the difference in proportions. To assess the consistency of the results, the logistic regression model given above without the interaction term was used to estimate the odds ratio and its confidence intervals.

For the dolasetron injections (treatment and prevention) for PONV, the dose comparisons of greatest interest were:

12.5 mg versus 25 mg
12.5 mg versus 50 mg, and
12.5 mg versus 100 mg.

Small differences between the proportion of responders with narrow confidence intervals indicates similarity of response

across this broad dose range (i.e. 12.5 mg to 100 mg) and the existence of a dose response plateau beginning at 12.5 mg.

For the oral dolasetron indications for the prevention of PONV, the dose comparisons of greatest interest were

50 mg versus 100 mg, and
50 mg versus 200 mg.

Again, small differences between the proportion of responders with narrow confidence intervals indicate a dose response plateau at the 50 mg oral dose.

2. Intravenous Dolasetron for the Treatment of PONV

The dose response profile for the pooled data and for individual dose response trials are given in Figures 1a and 1b, respectively.

The estimated differences and 95% confidence intervals for the differences in the proportion of complete responders for all comparisons are given below.

IV Dolasetron for the Treatment of PONV--- Pooled Comparison of 12.5 mg and Higher Active Dose Groups Difference in Proportions (Dose Group - 12.5 mg)

Dose Comparison	Estimate	95% Conf. Interval
12.5 mg vs. 25 mg	-3.9%	(-14.1%, 5.9%)
12.5 mg vs. 50 mg	0.3%	(-9.5%, 10.5%)
12.5 mg vs. 100 mg	-3.8%	(-14.1%, 5.7%)

Estimates and 95% confidence intervals were obtained using Exact method.
Copied from Table 2, page 7, NDA Supplemental dated 6/6/97.

3. Intravenous Dolasetron for the Prevention of PONV

The dose response profile for the pooled data and for individual dose response trials are given in Figures 2a and 2b, respectively.

The estimated differences and 95% confidence intervals for the

differences in the proportion of complete responders for all comparisons are given below.

IV Dolasetron for the Prevention of PONV--- Pooled Comparison of 12.5 mg and Higher Active Dose Groups Difference in Proportions (Dose Group - 12.5 mg)

Dose Comparison	Estimate	95% Conf. Interval
12.5 mg vs. 25 mg	-0.1%	(-7.3%, 6.7%)
12.5 mg vs. 50 mg	1.9%	(-5.0%, 8.9%)
12.5 mg vs. 100 mg	3.1%	(-4.7%, 11.1%)

Estimates and 95% confidence intervals were obtained using Exact method.
Copied from Table 3, page 11, NDA Supplemental dated 6/6/97.

4. Oral Dolasetron for the Prevention of PONV

The dose response profile for the pooled data and for individual dose response trials are given in Figures 3a and 3b, respectively.

The estimated differences and 95% confidence intervals for the differences in the proportion of complete responders for all comparisons are given below.

Oral Dolasetron for the Prevention of PONV--- Pooled Comparison of 50 mg and Higher Active Dose Groups Difference in Proportions (Dose Group - 50 mg)

Dose Comparison	Estimate	95% Conf. Interval
50 mg vs. 100 mg	-0.1%	(-7.3%, 6.7%)
50 mg vs. 200 mg	1.9%	(-5.0%, 8.9%)

Estimates and 95% confidence intervals were obtained using Exact method.
Copied from Table 3, page 11, NDA Supplemental dated 6/6/97.

C. Reviewer's Evaluation and Comments

In all these studies, there is not enough power to detect the differences among dose groups (e.g. oral 50 mg vs. 100 mg for prevention of PONV and intravenous 12.5 mg vs. 25 mg for treatment and prevention of PONV) due to insufficient sample

size.

Sponsor's additional analyses are post-hoc and exploratory analyses and hypothesis generating. Efficacy of test drug should be mainly based on the results from individual study not from the results of pooling studies.

1. **Pooling Data for Dosage Selection**

a). **Reviewer's Comments on Sponsor's Clinical and Scientific Rationale**

For each indication, there were one or two U.S. studies and one European study conducted. The protocols used in these studies were not identical. These studies were not designed to be pooled. In general, these studies are not sufficiently compatible in terms of sample size determination, patient population, inclusion and exclusion criteria, and concurrent medications.

For IV PONV prevention, the sponsor included three clinical trials (MCPR0084, MCPR0045 and 73147-2-S-80). Both studies MCPR0084 and 73147-2-S-80 included only female patients. Studies MCPR0045 included both male and female patients. Statistically significant gender by treatment interaction was observed in Study MCPR0045. So, the study population for study MCPR0045 was different from those for other two studies. Because of this reason, the study MCPR0045 should be not pooled with the other two studies.

If one intends to pool studies, one should consider only to pool studies MCPR0084 and 73147-2-S-80.

b). **Reviewer's Comments on Sponsor's Statistical Consideration**

The sponsor evaluated definite dose response studies in the ISE using a separate logistic regression analysis for each indication. For the analysis, the model included a study identifier, dose group and a term for study-by-dose group interaction. The interaction term was used to assess the parallelism of the dose response curves across studies.

The power of testing study-by-dose group interaction is very low. The significance level of 0.25 is highly recommended (see pages

86 and 108, Hosmer, D. W. and Lemeshow, S. (1989) "Applied Logistic Regression"). P-values for IV PONV treatment and IV PONV prevention seems large enough to indicate that the dose response profiles are parallel across the dose studies. However, p-values for the oral PONV prevention might be not sufficient large to indicate that the dose response profiles are parallel across the dose studies.

2. **Intravenous Dolasetron for the Treatment of PONV**

As seen in Figure 1b, the dose response profile for individual dose response trials shows as following:

1) Study MCPR0044 showed 12.5 mg is the minimal dose with maximum response.

2) Study 73147-2-S-0084 showed 12.5 mg and 25 mg results are about the same with a slightly numerical advantage for the 25 mg.

The p-value for interaction between dose and study in the pooled analysis was large enough ($p>0.25$) to indicate that the dose response profiles are parallel across the dose studies.

In the view of 95% confidence interval for the difference in the proportion of complete responders for comparisons between 25 mg and 12.5 mg in the pooled analysis, it indicates that the confidence interval (-14.1%, 5.9%) was not symmetric and the lower limit is lower than 10.0%. In the worst case, 25 mg would be inferior to 12.5 mg by 14.1%. So, 12.5 mg seems to be minimal effective dose with maximum response in the pooled analysis.

3. **Intravenous Dolasetron for the Prevention of PONV**

As seen in Figure 2b, the dose response profile for for individual dose response trials showed that dose response curves were different and reached the plateau at 12.5 mg and 25 mg, respectively for study MCPR0084 and study 73147-2-S-80.

As stated in Section C.1.a), the study population for study MCPR0045 was different from those for other two studies (MCPR0084 and 73147-2-S-080). The study MCPR0045 should be not pooled with the other two studies.

If studies MCPR0084 and 73147-2-S-080 were pooled, the estimated differences and 95% confidence intervals for the differences in the proportion of complete responders for all comparisons are:

IV Dolasetron for the Prevention of PONV --- Studies MCPR0084 and 73147-2-S-080
Comparison of 12.5 mg and Higher Active Dose Groups
Difference in Proportions (Dose Group - 12.5 mg)

Dose Comparison	Estimate	95% Conf. Interval
12.5 mg vs. 25 mg	4.6%	(-5.1%, 14.6%)
12.5 mg vs. 50 mg	5.3%	(-4.4%, 15.3%)
12.5 mg vs. 100 mg	8.2%	(-6.4%, 24.1%)

Estimates and 95% confidence intervals were obtained using Exact method.

As seen in the above table, all of upper confidence limits are large in magnitude, so there is therapeutic gain by using the higher dose (e.g. 25 mg).

In the view of 95% confidence interval for the difference in the proportion of complete responders for comparisons between 25 mg and 12.5 mg in the pooled analysis, it indicates that the confidence interval (-5.1%, 14.6%) was not symmetric and the upper limit is higher than 10.0% in favor of the 25 mg dose. Therefore, 25 mg seems to be the minimal effective dose with maximum response in the pooled analysis.

Furthermore, as stated in the Statistical Review and Evaluation for the prevention of PONV for IV Dolasetron dated January 17,

"Two studies (MCPR0084 and 73147-2-S-80) showed that there was a significant overall effect for the "complete response" endpoint. For this endpoint, the highest observed complete response rates were achieved for the 50 mg dose in Study MCPR0084 and for the 25 mg dose in Study 73147-2-S-80.

Study MCPR0084 showed the 12.5 mg, 25 mg, and 50 mg dose groups were statistically significantly more effective than placebo. Study 73147-2-S-80 showed that only 25 mg dose group was statistically significantly better than the placebo."

Furthermore, study MCPR0045 showed that the linear dose trend was not significant.

Hence, the 25 mg comes out to be the optimal effective dose which was supported by both studies (MCPR0084 and 73147-2-S-080).

4. Oral Dolasetron for the Prevention of PONV

As seen in Figure 3b, the dose response profile for individual dose response trials showed that dose response curves were different and reached the plateau at 50 mg and 100 mg, respectively for study 73147-2-S-095 and study AN-PO-0292.

The p-value for interaction between dose and study in the pooled analysis was not sufficient large enough ($p<0.25$) to indicate that the dose response profiles are parallel across the dose studies. Hence, pooling of two studies is statistically not convincing.

Furthermore, all two studies (AN-PO-0292 and 73147-2-S-095) had highly significant trend with dose. Both studies showed that the 100 mg was significantly more effectively than placebo. But only study 73147-2-S-095 showed that the 50 mg was significantly more effectively than placebo.

In the comparison between 50 mg and 100 mg, there was a numerical difference of about 13% in favor of 100 mg group in complete response in the study AN-PO-0292. But, in the study 73147-2-S-095, there is a slight difference of about 6% in favor of 50 mg group in complete response.

Hence, the 100 mg seems to be the optimal effective dose which was supported by both studies (AN-PO-0292 and 73147-2-S-095).

D. Overall Summary and Recommendation

1. Pooling Data for Dosage Selection

Sponsor's additional analyses are post-hoc and exploratory analyses. Efficacy of test drug should be mainly based on the results from individual study not from the results of pooling studies.

P-values of study-by-dose group interaction for IV PONV treatment and IV PONV prevention seem large enough to indicate that the dose response profiles are parallel across the dose studies. However, p-values for oral PONV prevention might not not sufficient large enough to indicate that the dose response profiles are parallel across the studies.

For IV PONV prevention, both studies MCPR0084 and 73147-2-S-80 included only female patients. Studies MCPR0045 included both male and female patients. Statistically significant gender by treatment interaction was observed in Study MCPR0045. So, the study population for study MCPR0045 was different from those for other two studies. Therefore, the study MCPR0045 should be not pooled with the other two studies.

2. **Intravenous Dolasetron for the Treatment of PONV**

Study MCPR0044 showed 12.5 mg is the minimal dose with maximum response. Study 73147-2-S-0084 showed 12.5 mg and 25 mg results are about the same with a slightly numerical advantage for the 25 mg.

The 95% confidence interval (for the difference in the proportion of complete responders for comparisons between 25 mg and 12.5 mg in the pooled analysis) indicates that the confidence interval of (-14.1%, 5.9%) was not symmetric and the lower limit is lower than 10.0%. In the worst case, 25 mg would be inferior to 12.5 mg by 14.1%. Therefore, 12.5 mg seems to be minimal effective dose with maximum response in the pooled analysis.

3. **Intravenous Dolasetron for the Prevention of PONV**

The 25 mg is recommended as the optimal effective dose which was supported by both studies (MCPR0084 and 73147-2-S-080).

4. **Oral Dolasetron for the Prevention of PONV**

The 100 mg is recommended as the optimal effective dose which was supported by both studies (AN-PO-0292 and 73147-2-S-095).

/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

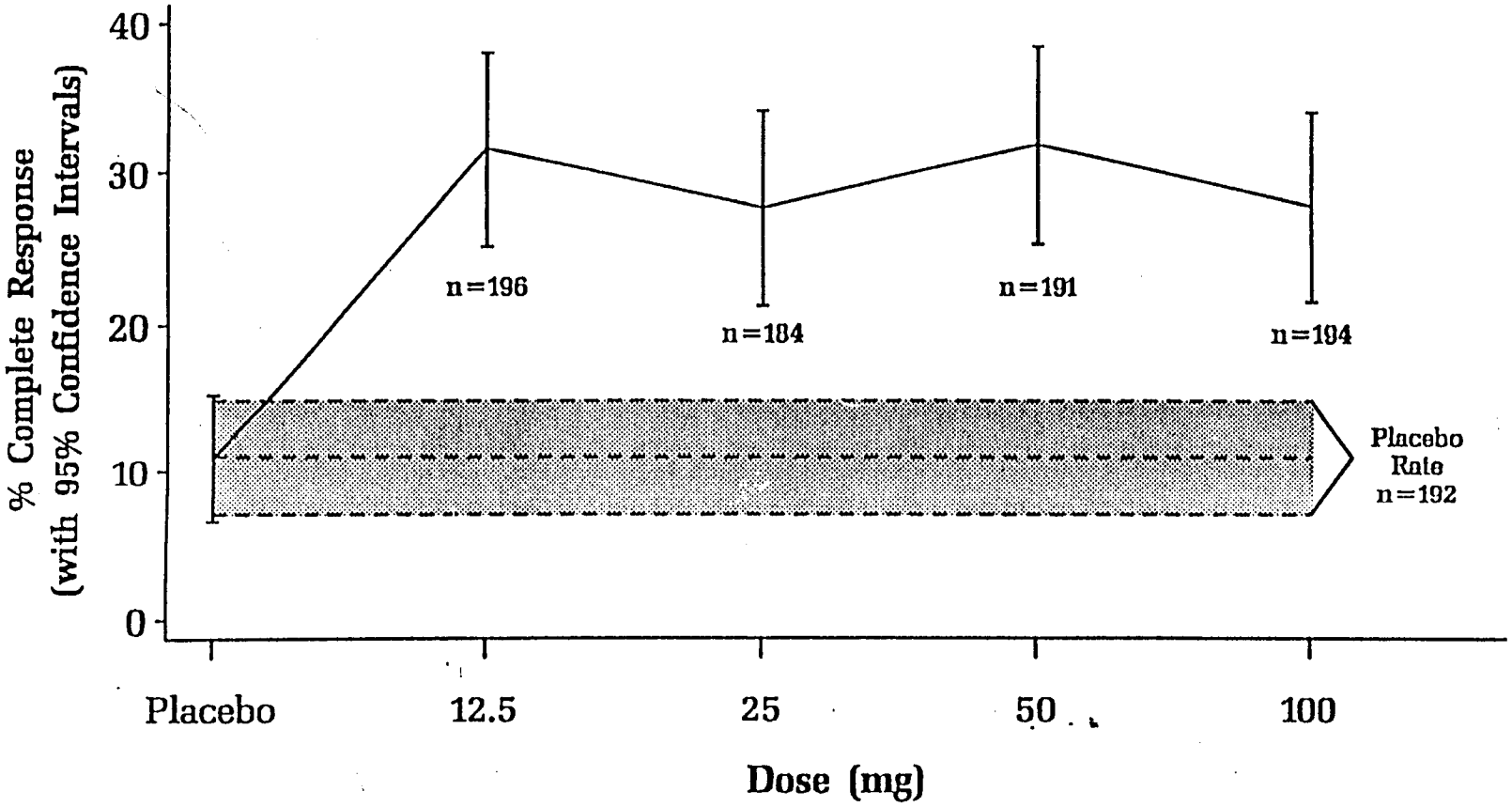
This review consists of 12 pages of text and 6 pages of tables.

concur: Dr. Huque /S/ 1/8/97
Dr. Smith /S/ 7/15/97

cc:
Archival NDA 20-623, 20-624
HFD-180
HFD-180/Dr. Talarico
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-344/Dr. Lisook
HFD-720
HFD-720/Chron. Copy
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/07/08/97

Figure 1a

IV Dolasetron/PONV (Treatment)
Randomized, Double Blind Trials
Complete Response by Dose
(12.5 vs Placebo, P<.0001)



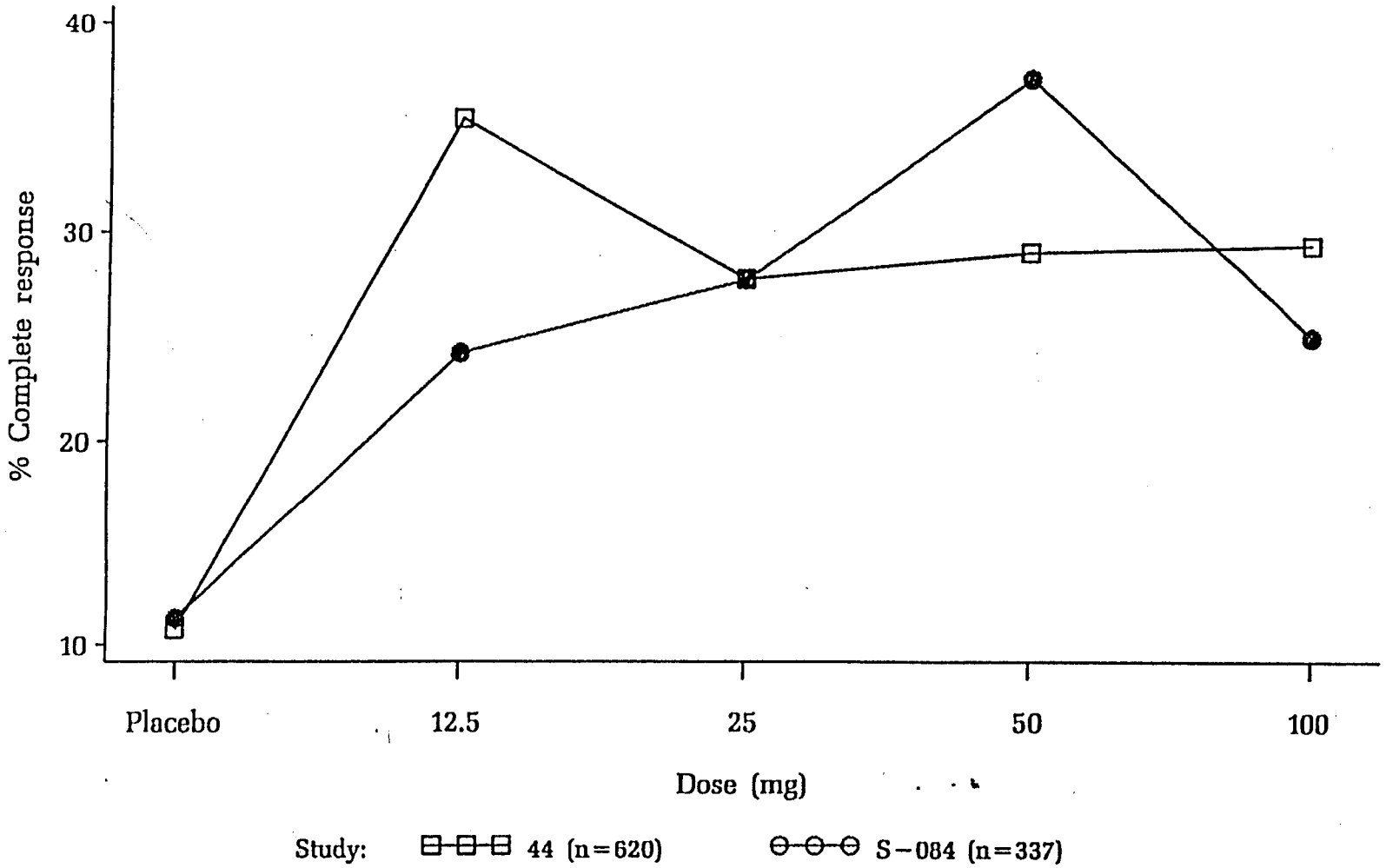
Includes studies MCPR0044, 73147-2-S-084

rce: MMD NM08274 - IVPONV.SAS - (04JUN97, 16:20)

Figure 1b

IV PONV Treatment

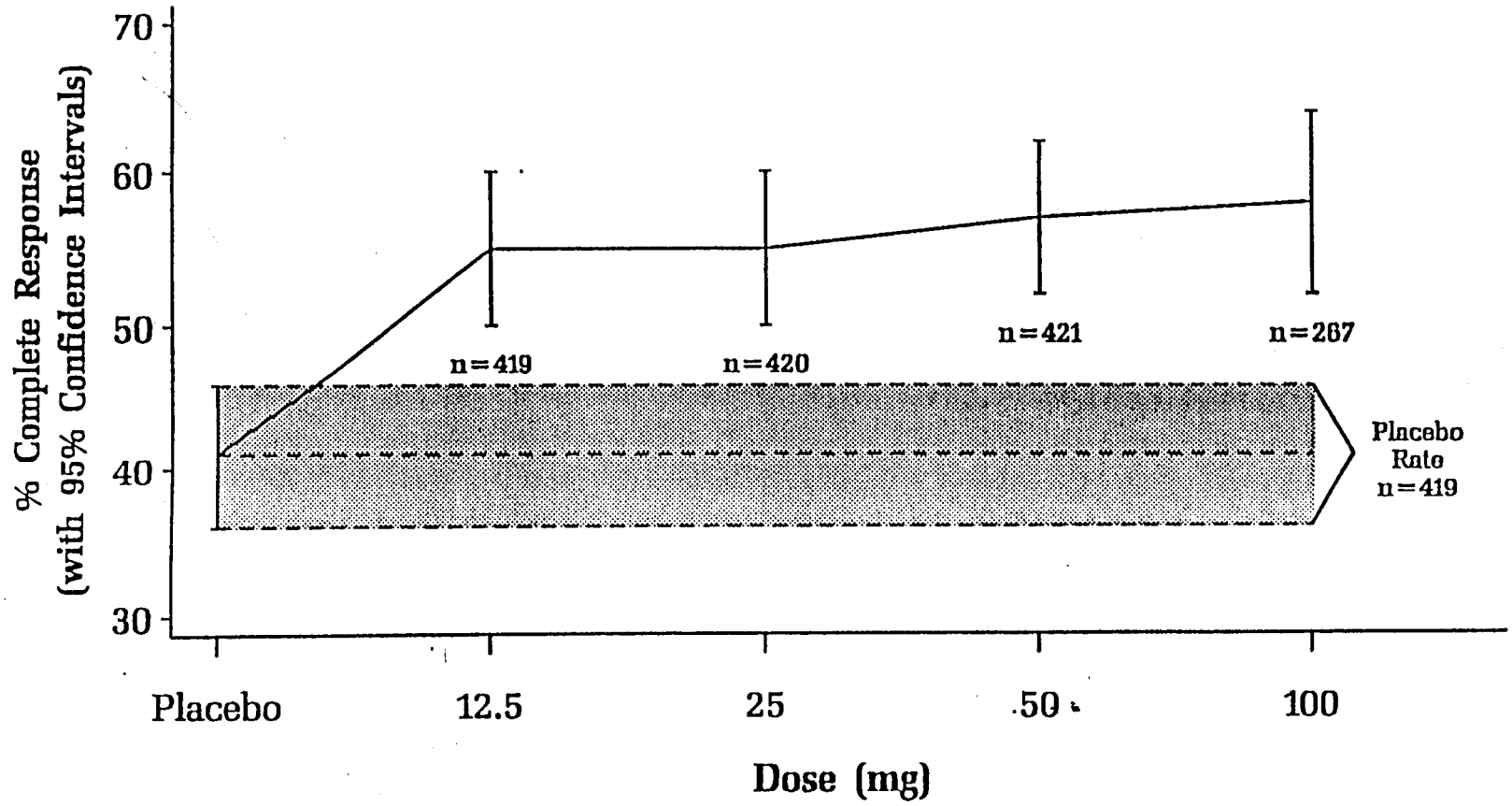
% Complete Response by Study



SOURCE: MMD STAT_CDM NM08274 -IPONVT_EFF_2.SAS- (05JUN97, 16:01)

Figure 2a

IV Dolasetron/PONV (Prevention)
Randomized, Double Blind Trials
Complete Response by Dose
(12.5 vs Placebo, p=.0003)



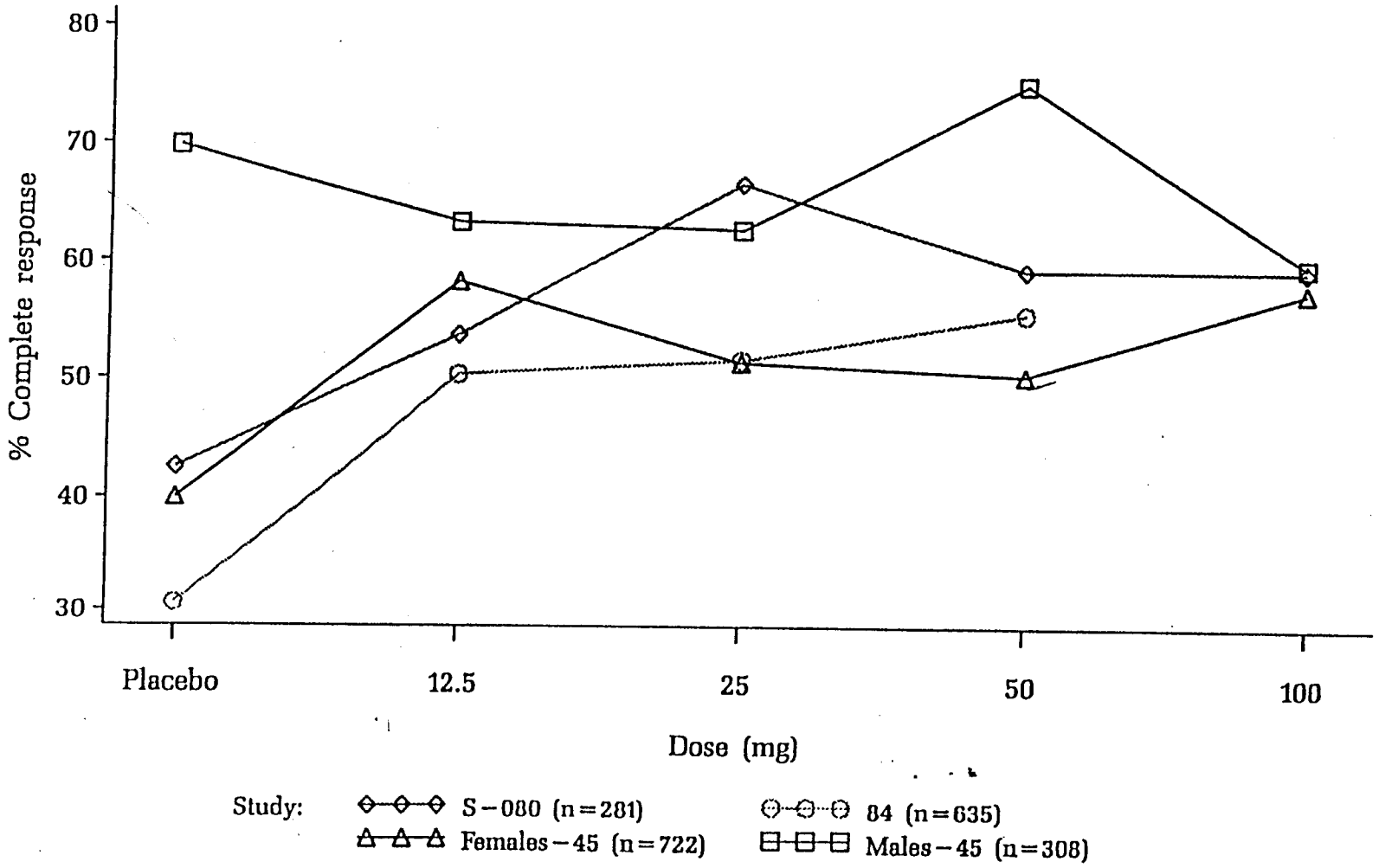
Includes studies MCPR0045, MCPR0084, 2-S-080

Source: MMD NM08274 - IVPONV_P.SAS - (04JUN97, 16:21)

Figure 2b

IV PONV Prevention

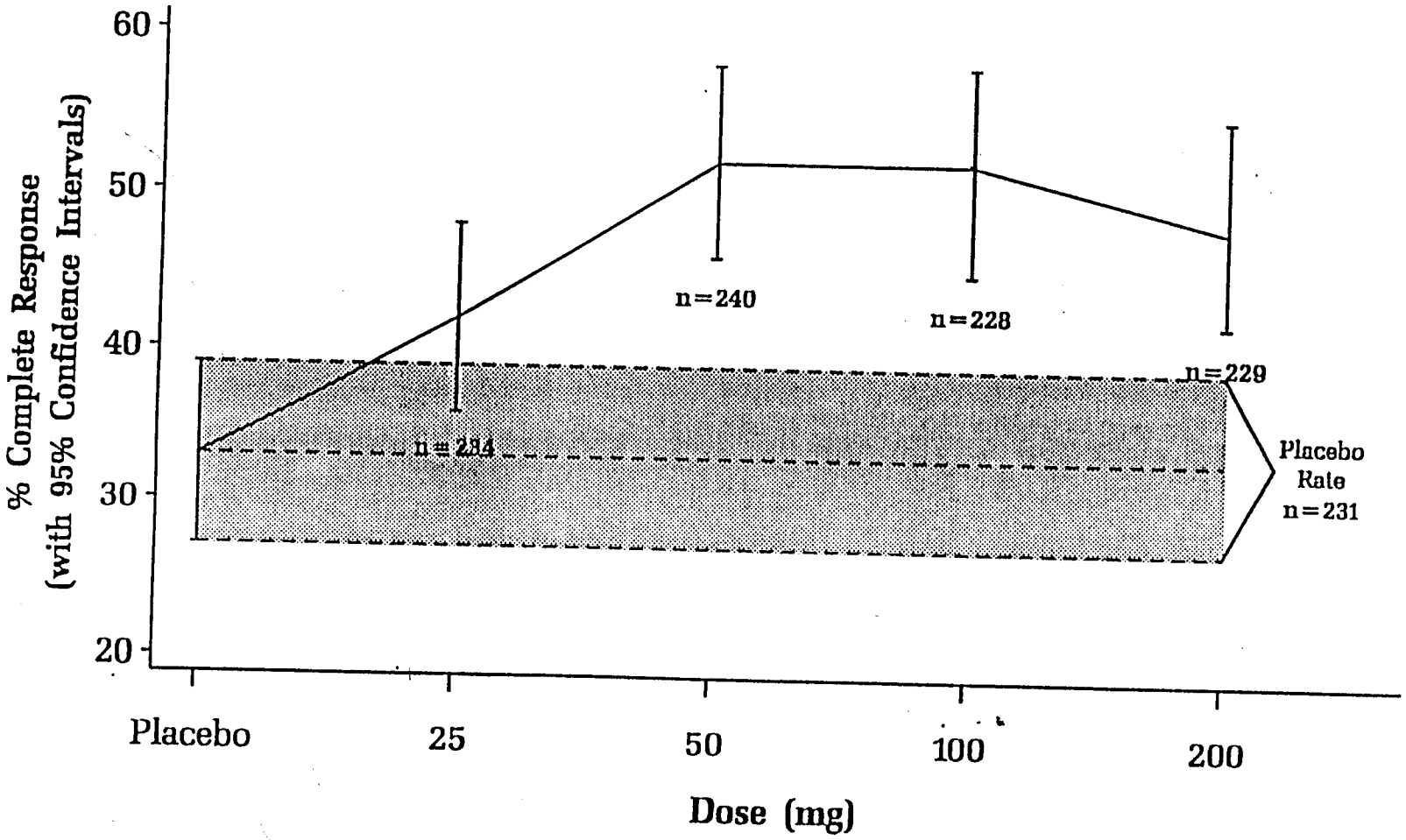
% Complete Response by Study



SOURCE: MMD STAT_CDM NM08274 -IPONVP_EFF_1.SAS- (05JUN97, 16:03)

Figure 3a

Oral Dolasetron/PONV (Prevention)
Randomized, Double Blind Trials
Complete Response by Dose

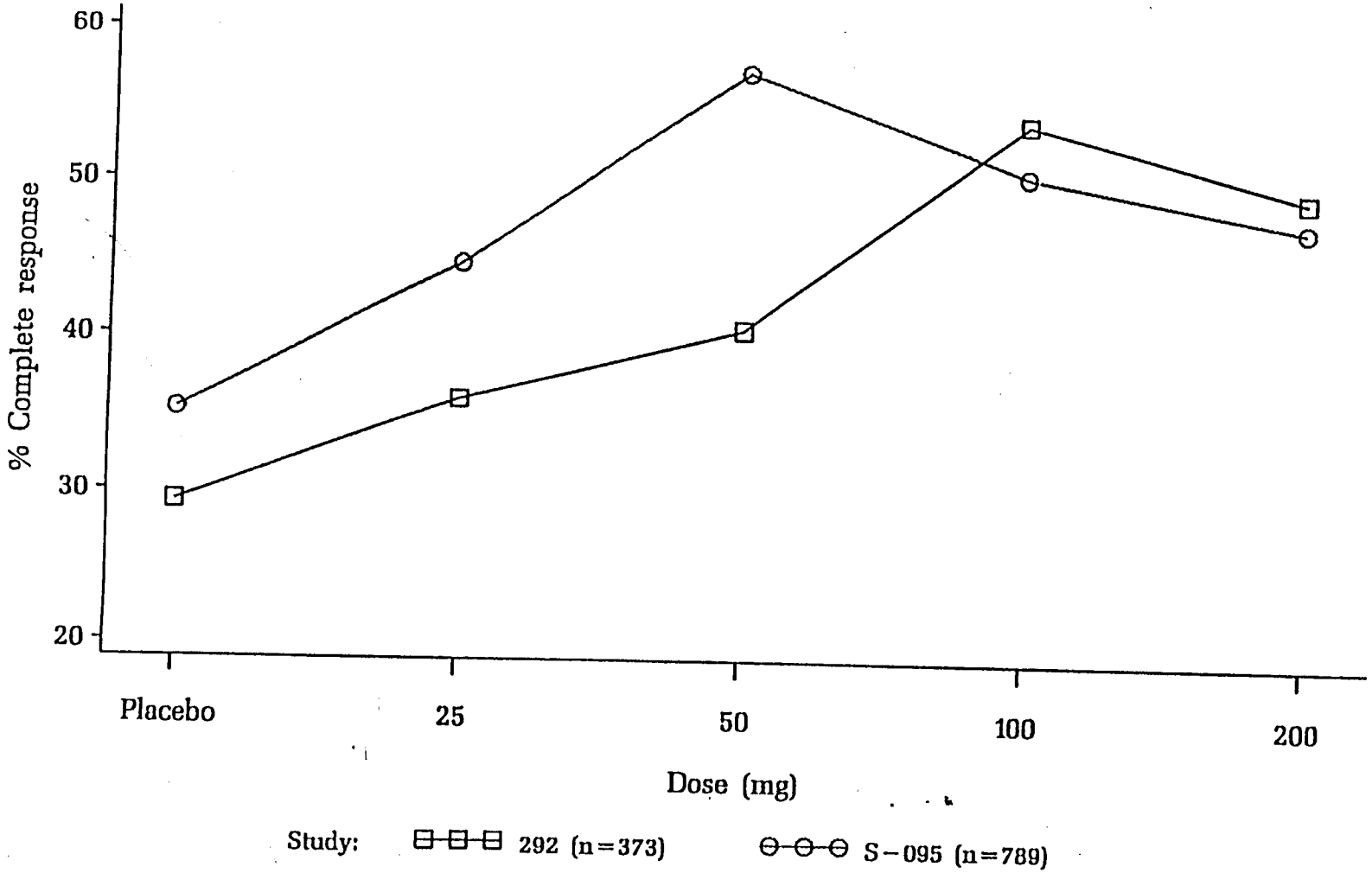


Source: MMD NM08274 – ORALPONV.SAS – (04JUN97, 16:21)

Figure 3b

Tablet – PONV

% Complete Response by Study



SOURCE: MMD STAT_CDM NM08274 -OPONVP_EFF_3.SAS- (05JUN97, 16:04)

Statistical Review and Evaluation --- Stability

Date: JUN 11 1996

NDA #: 20-623

Applicant: Hoechst Marion Roussel, Inc.

Name of Drug: Anzemet (dolasetron mesylate) Tablet

Documents Reviewed: NDA Vol. 1.4 Dated September 28, 1995
Supplements Dated February 6, 1996
Supplements Dated March 1, 1996

A. Background

The sponsor submitted the results of an analysis of 18-month stability data for dolasetron mesylate tablets made from five NDA lots (R54046, R54047, R54048, R54049, R53677) and packaged in 5-, 100, or 500-count bottles or blisters with either Data are presented for three tablet lots of 25, 50, and 200 mg tablets and for four tablet lots of 100 mg tablet.

Self-life is assessed using 30°C storage stability data for the variables: potency of dolasetron mesylate, 30-minute dissolution of dolasetron mesylate, and moisture.

The sponsor's protocol for the stability study has been reviewed and documented in the Statistical Review and Evaluation dated October 12, 1994 and July 5, 1995.

The Statistical Review and Evaluation dated October 12, 1994 suggested that the design shown in Table 1 was not acceptable because, for a given package-strength combination, the matrix design provided stability data from two rather than three granulation lots.

Due to the sponsor's reliance on the matrix stability plan, the sponsor does not have data from all time points (3,6,9,12,18,24,36 mos.) for all stability batches of each strength in each package proposed for marketing. The sponsor proposed an alternate protocol to sacrifice the 48 and 60 month stability stations and use the 12 month data from these to fill

the missing stations for the other package. It was determined that proposed alternate protocol was acceptable for filing of the NDA for the reasons listed in Memorandum of Telephone dated June 20, 1995 between Dr. Dhiren Shad of HMR and Kati Johnson of FDA. The proposed alternate protocol would, in principle, provide data for each package-strength combination from three granulation lots for those packages in the original design that were intended for commercialization, namely the 5- and 100-count bottles, and the

A summary of the data proposed in the alternate protocol is provided in Table 2. The alternate protocol was created from the original matrix design as follows:

1) The sets of testing time point T1 and T2 were changed, primarily to augment testing beyond the time point already reached (13 months). Thus, testing at 13 and 24 months was added to T1 and testing at 18 and 36 months was added to T2.

2) Data was provided for earlier time points at 3, 6, 9 months (if no measurement were made according to the original matrix design) by making these data equal to data observed 12 (T2) or 13 (T1) months.

3) Data from the 500-count was substituted as the third lot for the 5-count or 100-count bottle, as needed (superscripts 3 and 4 in Table 2). This was possible in principle because the sponsor no longer planned to commercialize the 500-count bottle.

4) Data from the was substituted as the third lot for the in Table 2). This was possible in principle because the sponsor no longer planned to commercialize the

The alternate protocol thus provided data from three lots for each package-strength combination for the three packages indicated for all of the time points, 3, 6, 9, 12 or 13, and 18 months. This data is used in the first and second statistical analyses given later in this review.

The sponsor requests a 24 month expiration dating period for the drug product.

Mr. Adams (HFD-180) has requested this Division to perform a statistical evaluation of the stability data.

This review will only address on potency and 30-minute dissolution data in the 30°C storage.

B. **Sponsor's Results**

The reported measurements for potency are typically means of two individual measurements. The measurements are typically means of six measurements.

Three tablet lots were compressed from each lot R54046, R54047, R54058 and R54059. This resulted in a total of twelve tablets lots (three per tablet strength). The 200 mg tablet lot from granulation R54057 was not used in these stability studies due to film-coating problems experienced during manufacture. Instead, a 200 mg tablet lot made earlier from granulation lot R53677 was used. Four tablet lots were compressed from granulation lot R53677 (one per tablet strength). Only two of four tablet lots were used in these stability studies.

Dolasetron mesylate tablets were packaged in 5-, 100-, or 500-count bottles, with and blisters with

1. **First Analysis**

The first analysis was based on the data summarized in Table 2. It included the three packages 5-count bottle, 100-count , and with

1.1 **Test of Appropriateness of Substitution**

An ANCOVA was performed to test the appropriateness of the Table 2 substitution of 500-count data as 5- or 100-count bottle data and the substitution of data as Alusuisse blister data.

Using the ANCOVA model allowed different slopes for every lot, package, and strength, and different intercepts for every lot and strength, the appropriateness of package substitution was tested

by 0.05 P value testing of three one-degree-of-freedom contrasts examining package slope differences between the 5- and 500-count bottle, between the 100- and 500-count bottle, and between the

Table 3 shows that the p-values for slope comparisons between the 5- and 500-count bottle , the 100- and 500-count HDPE bottle , and the were all well above 0.05 for all three variables analyzed. This confirmed the appropriateness of the substitution of 500-count bottle data as 5- or 100-count HDPE bottle data and the substitution of

1.2 **Shelf-Life Analysis**

If the appropriateness of the package substitutions was supported, the second step in the first analysis was to use the data with substitution for three packages to estimate slopes and intercepts, and lower and/or upper one-sided 95% confidence limits for 24-month and 36-month means in an ANCOVA model which allowed different slopes for every lot and every strength-package combination, and allowed different intercepts for every lot-strength combination.

The regression estimates from a model were used to calculate shelf-life estimates. A shelf-life estimate was calculated as the point at which the lower (or upper) one-sided 95% confidence limit for the mean stability profile intersected the allowable lower (upper) limit of the variable's specification as described in the FDA guidelines for analyzing stability studies.

1.2.1 **5-Count HDPE Bottle Shelf-Life Analysis**

Table 4 summarizes the selected model estimated slopes and intercepts, lower and/or upper one-sided 95% confidence limits for 24-month and 36-month means, and expected shelf-life for the 5-count bottle stored at 30°C.

The potency data support at least 36-month shelf-life for all strengths. None of the slope estimates are significantly different from zero. The 36-month confidence limits are well within the specification in all cases.

The 30-minute dissolution data support at least a 36-month shelf-life for all strengths. The only slope estimate that is significantly different from zero is a positive 1.04% per year, the implied change actually being movement away from the Q=75% specification. The 36-month lower confidence limit is well above the Q=75% specification in all cases.

1.2.2 **100-Count Bottle Shelf-Life Analysis**

Table 5 summarizes the selected model results for the 100-count bottle stored at 30°C.

The potency data support at least 36-month shelf-life for all strengths. None of the slope estimates are significantly different from zero. The 36-month confidence limits are well within the specification in all cases.

The 30-minute dissolution data support at least a 36-month shelf-life for all strengths. There were no negative slope estimates that are significantly different from zero. The 36-month lower confidence limit is well above the Q=75% specification in all cases.

1.2.3 **Blister with Shelf-Life Analysis**

Table 6 summarizes the selected model results for the blister with stored at 30°C.

The potency data support at least 36-month shelf-life for all strengths. None of the slope estimates are significantly different from zero. The 36-month confidence limits are well within the 90.0% to 110.0% specification in all cases.

The 30-minute dissolution data support at least a 36-month shelf-life for all strengths. There were no negative slope estimates that are significantly different from zero. The 36-month lower confidence limit is well above the Q=75% specification in all cases.

2. **Second Analysis**

It repeated the first analysis using only Table 2 data that were

not substituted from one package to another and/or copied from a later time point to an earlier time point. The second analysis was a supporting analysis to the first analysis providing an opportunity to determine if the data manipulations involved in arriving at the Table 2 data might have caused any substantial bias or unexpected impact in the first analysis.

2.1 **Potency**

Thinking of potency degrading toward a lower specification of NLT 90.0%, the most negative slope estimate is -0.59% per year, but there are no negative slope estimates that are significantly different from zero. The smallest intercept estimate is 100.3%. The smallest lower one-sided 95% confidence limit value is 98.2% at 24 months and 97.2% at 36 months. Thus, the results support a shelf-life of at least 36 months in all three packages.

2.2 **30-Minute Dissolution**

there are no negative slope estimates that are significantly different from zero. The smallest intercept estimate is 99.7%. The smallest lower one-sided 95% confidence limit value is 98.4% at 24 months and 97.4% at 36 months. Thus, the results support a shelf-life of at least 36 months in all three packages.

C. **Reviewer's Comments and Evaluation**

1. **Comments on Sponsor's Stability Analysis**

The matrix approach described by Earl Nordbrock (1992) in "Statistical Comparisons of Stability Study Designs", *Journal of Biopharmaceutical Statistics*, Volume 2, Pages 91-113, was used by the sponsor for the stability study. The matrixing stability approach is a new methodology. The FDA guideline for stability studies using matrixing approach is not finalized yet.

2. **P-values for Pooling Data**

The sponsor performed all preliminary tests and a final test of interaction using significance level of 0.05. However, due to

poor power to test interaction, significance level of 0.25 was suggested by Fairweather et. al. (Regulatory, Design, and Analysis Aspects of Complex Stability Studies, Journal of Pharmaceutical Sciences, Vol. 84, No. 11, 1995).

The paper stated "In order to increase the power of detecting meaningful difference, we have advocated performing the tests of interaction at significance level of 0.25. The use of a large significance level in a preliminary test is based on a recommendation of Bancroft, as cited in the FDA stability guideline."

The Bancroft's paper (Analysis of Inference for Incompletely Specified Models Involving the Use of Preliminary Tests of Significance, Biometrics, 1964) stated in order to keep the actual significance level achieved in the final F-test for the interesting hypotheses at 0.05, the significance level for the preliminary tests is recommended at least 25%.

Furthermore, as stated in Statistical Review and Evaluation dated July 5, 1996, the matrixing stability approach is a new methodology. The guideline for stability studies using matrixing approach is not finalized yet. Therefore, if the sponsor thinks that the 25% significance level for the preliminary test is too high, it should perform a statistical analysis to evaluate the bias effects on the accuracies of the 95% confidence intervals induced by the preliminary tests to justify its choice of the significance level of the preliminary tests.

3. **Reviewer's Comments on Sponsor's Test of Appropriateness of Substitution**

There was inconsistency about the model used for the test of appropriateness of substitution. The model described in Appendix A in the NDA submission was not used. But, after reviewing the SAS printouts, this reviewer found the model described in Appendix B was actually used to compute the p-value. The sponsor's actually used model included an additional term of "START".

The sponsor's test of appropriateness of substitution was run using data summarized in the Table 7. The added testing was placing a third granulation lot of each strength on stability

packaged in the 5- and 100-count bottles, and blisters with either (the T3's in Table 7). This required using a lot for the 100 mg strength (R53677). Whereas there are 18 month data available for the original studies started in April 1994, only 3-month data are available from these supplemental studies started in June and July 1995.

As stated in Statistical Review and Evaluation dated October 12, 1994, the model should include the other two interaction effects, YEARS*LOT*PACKAGE and YEARS*LOT*STRENGTH, since theses effects may affect the response variables.

4. **Power of Testing of Interaction**

The levels of power of testing the effects of multi-factor interactions based on the sponsor's selected model should be evaluated.

5. **Probabilities of Shelf-Life**

The probabilities of shelf-life for slope based on the sponsor's selected model should be evaluated.

6. **Reviewer's Comments on Sponsor's Analysis I**

6.1 **Alternative Protocol**

Sponsor's stability analysis was based on an alternative protocol which allowed for the substitution of data from 500-count bottles as data from 5 and 100-count HDPE bottles and of data from blister with as data from blisters with

With substitution the design is still not a proper factorial design, since the lot R53677 was used for 200 mg only. The effect of this imbalance on the test of substitution and the final model used to estimate shelf-life is not clear.

6.2 Substitution

The sponsor tried to salvage the stability analysis based on the original protocol by substitutions. There were two kinds of substitutions made to fill in missing time points and missing cells of matrixing. One of these is to substitute the missing time point by later real time data, e.g., for 6-month time point, use the 13-month real time data; for 3- and 9-month time points, use the 12-month real time point data. Other is to substitute the missing time points in the matrix by substituting data from other package, e.g., data from 500-count bottle for 5-count bottle and 100-count bottle.

The effects on the accuracies of the 95% confidence intervals due to substituting the missing time points (3, 6 or 9 months) by later real time data (e.g., 12 month or 13 month) were not clear. This kind substitution needs to be justified.

Using the data from 500-count bottle to substitute the missing cells for 5-count and 100-count bottle assumed that there are not differences among 5-, 100- and 500-count bottle in terms of potency, dissolution and moisture.

It was also assumed that there is no difference between

However, as seen from Table 3, the p-value for slope comparisons between the 5- and 500-count was significant at 0.25 level of significance for moisture. This casts doubt about the assumption of there are not differences among 5-, 100- and 500-count bottle in terms of potency, dissolution and moisture.

Furthermore, there were lots of substitutions made; 8 of 21 (38%) for bottle packages and 8/15 (53%) for blister package. With data with substitution rates ranging this casts doubt about the accuracy of estimated shelf-life.

6.3 **P-value for Test of Appropriateness of Substitution**

Using the ANCOVA model allowed different slopes for every lot, package, and strength, and different intercepts for every lot and strength, the appropriateness of package substitution was tested by sponsor using 0.05 P value testing of three one-degree-of-freedom contrasts examining package slope differences between the-

5- and 500-count bottle, between the 100- and 500-count bottle, and between the

Since the test of appropriateness of substitution is a preliminary test, the significance level for the preliminary tests is recommended at least 25%.

The sponsor should redo analyses using 0.25 as significance level in preliminary tests.

6.4 **Adequacy of the Model**

As stated in Statistical Review and Evaluation dated July 5, 1996, the model should include the other two interaction effects, YEARS*LOT*PACKAGE and YEARS*LOT*STRENGTH, since theses effects may affect the response variables. The sponsor should evaluate the levels of power and probabilities of shelf-life of the new model.

The sponsor's final reduced model used for estimating the shelf-life did not include main effects STRENGTH, LOT, and YEARS. It included only interaction terms STRENGTH*LOT, YEARS*LOT, and YEARS*PACKAGE*STRENGTH. The sponsor did not go through any analysis seeking to estimate common slopes and intercepts across lots, packages, and strengths. The sponsor needs to justify the final reduced model.

7. **Reviewer's Comments on Sponsor's Analysis II**

The reviewer's comments on adequacy of the model made to the sponsor's analysis I also applies to the sponsor's analysis II.

Without substitution for the missing cells, for each strength there were only 13 data points for 100-count bottle, 10 data points for 5-count bottle, and 7 data points for blister. In the combination of packages and strength of 25 mg, there were only two data points from two lots from 18.1 months, one data point from three lots from time points 4.4, 6.2, 9.9, 12.2 and 14.5, and 3 to 6 data points from one or two lots from 0 months (see Table 8).

There were no data from all time points (3,6,9,12,18,24,36 mos.) for all stability batches of each strength in each package

proposed for marketing.

There are insufficient data to yield reasonably precise estimates of shelf-life.

D. **Summary and Conclusion**

In the sponsor's stability analysis based on an alternative protocol, there were lots of substitutions; 8 of 21 (38%) for 100-count HDPE bottle, 8 of 18 (44%) for 5-count bottle, and 8/15 (53%) for blister package. Using data with high substitution rates ranging from this casts doubt about the accuracy of estimated shelf-life.

The p-value for slope comparisons between the 5- and 500-count bottle was significant at 0.25 level of significance for moisture. This casts doubt about the assumption of there are not differences among 5-, 100- and 500-count bottle in terms of potency, dissolution and moisture.

The effects on the accuracy of the 95% confidence interval due to substituting the missing time points (3, 6 or 9 months) by later real time data (e.g., 12 month or 13 month) were not clear.

The sponsor performed all preliminary tests and the final test of interaction using significance level of 0.05. However, due to poor power to test interaction, significance level of 0.25 was suggested.

The sponsor's final reduced model used for estimating the shelf-life did not include main effects STRENGTH, LOT, and YEARS. It included only interaction terms STRENGTH*LOT, YEARS*LOT, and YEARS*PACKAGE*STRENGTH. The sponsor did not go through any analysis seeking to estimate common slopes and intercepts across lots, packages, and strengths. The sponsor's final reduced model needs justification.

In conclusion, there were insufficient observed data to support a shelf-life of at least 24 months in all three packages.

/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 12 pages of text and 12 pages of tables.

concur: Dr. Huque /S/ 7/29/96
Dr. Smith /S/ 7/29/96

cc:
Archival NDA 20-623
HFD-180
HFD-180/Mr. Adams
HFD-180/Dr. Gibbs
HFD-180/Ms. Johnson
HFD-720/Dr. Smith
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