Table A- 9: Study 77 Primary & Secondary Endpoints 7 AM Reflective Scores

Reflective 7 AM Symptom Assessment	Timepoint	Placebo n=105 MEAN	15 mg BID n=105 MEAN	15 mg BID n=105 DIFF	15 mg BID n=105 P-VAL	30 mg BID n=101 MEAN	30 mg BID n=101 DIFF	30 mg BID n=101 P-VAL	60 mg BID n=101 MEAN	60 mg BID n=101 DIFF	60 mg BID n=101 P-VAL
TSS	Baseline	7.32	6.79			6.93			6.94		
	Change	-0.46	-0.98	**0.79**	0.0105	-0.87	**0.70**	0.0249	-1.04	**0.78**	0.0125
Sneezing	Baseline	1.56	1.48			1.49			1.48		
	Change	0.01	-0.24	**0.30**	0.0019	-0.16	**0.22**	0.0211	-0.17	**0.23**	0.0161
Rhinorrhea	Baseline	2.10	1.93			2.02			1.96		
	Change	-0.10	-0.13	**0.11**	0.2539	-0.07	**0.04**	0.6756	-0.20	**0.18**	0.0722
Itchy Watery,	Baseline	1.70	1.54			1.48			1.63		
Red Eyes	Change	-0.19	-0.23	**0.12**	0.2159	-0.24	**0.17**	0.0883	-0.34	**0.18**	0.0665
Itchy Nose, Mouth,	Baseline	1.96	1.84			1.94			1.87		
Throat &/or Ears	Change	-0.18	-0.38	**0.26**	0.0076	-0.40	**0.26**	0.0078	-0.33	**0.19**	0.0525
Nasal	Baseline	2.32	2.25			2.25			2.32		
Congestion	Change	-0.15	-0.18	**0.05**	0.6020	-0.17	**0.07**	0.4467	-0.16	**0.02**	0.8726

Table 10: Sponsor's Summary of Additional Statistical Analyses for Possible Explanation of Difference between Efficacy Outcomes of Studies 066 and 077

Analysis	Objective	Method	Comment
Subgroup analyses (age category*, weight category*, gender, race, baseline symptom category*) using all patients (pooled protocols)	To identify factors which could explain differing levels of treatment effect.	ANCOVA with site, treatment, subgroup factor, and treatment-by-subgroup factor (if significant).	Only baseline symptom category had significant interaction at the .10 level (p=.0629). The main effect for **age** category is close to statistical significance at the .05 level (p=.0852), and the **baseline category** is highly statistically significant with p-value=.0001. Younger children responded better than older children. Patients with more severe symptoms had larger treatment effect
Baseline comparisons (age, gender, race, weight, baseline symptom category) of all patients (pooled and individual protocols)	To identify unbalanced baseline characteristics across treatment groups and across protocols.	Chi-square test for gender, race (white vs non-white), and categorized age, weight and baseline symptom severity.	Only race showed unbalance for the pooled protocol (p= .038). But subgroup analysis indicated race had no impact on the treatment effect.
Age subgroup analysis for both pooled and individual protocols	To determine if age accounts for some of the large placebo effect in Protocol 066 and/or different efficacy results in Protocol 066 and Protocol 077.	Examine the correlation between age composition in both pooled and individual studies and treatment effect observed in pooled and individual studies.	There was no consistent trend in the age subgroup analysis, which could adequately explain the large placebo effect and overall smaller fexofenadine effect of Protocol 066 compared to Protocol 077. The unexpectedly large placebo effect of Protocol 066 appears to be unrelated to age.
Baseline symptom subgroup analysis for both pooled and individual protocols	To determine if level of baseline symptoms accounts for some of the large placebo effect in Protocol 066 and/or different efficacy results in Protocol 066 and Protocol 077.	Examine the correlation between level of baseline symptoms of patients in both pooled and individual studies and treatment effect observed in pooled and individual studies.	Overall, there is no consistent evidence to support that the high placebo effect in Protocol 066 was caused by baseline symptom severity imbalance. In both the low and high baseline severity categories, the placebo group in Protocol 066 outperformed (or nearly) the fexofenadine groups, while in Protocol 077, placebo performed worse (or nearly) than all the fexofenadine groups. When comparing the proportions of low and high baseline patients in the placebo groups of the two studies, there is very little difference. Despite this, differences in change from baseline were seen between the two protocols.
Randomization failure rate at each investigative site	To compare the randomization rate and assess its correlation with treatment difference (fex-placebo).	T-test for comparing failure rate between Protocol 066 and Protocol 077. Regression model to assess the correlation between failure rate and treatment difference (Fex-placebo) for both pooled and individual protocols.	The test for the difference in randomization failure rate of the two protocols had p=.0612, indicating marginally significant difference (22% and 30% for Protocol 066 and Protocol 077 respectively). However, there was no statistical dependence of treatment difference on the randomization failure rate (p-value for dependence=.3609, .8186 and .7892 for pooled protocol, Protocol 066 and Protocol 077 respectively).
Pollen Count	To assess the correlation between level of pollen count and treatment difference (Fex-placebo).	Study duration was split into onset, peak and end allergy seasons based on local pollen count. The duration of each patient's treatment during each of these seasons was examined.	It was speculated that patients in Protocol 066 had stayed longer during the weak allergy seasons (onset or end season) than in Protocol 077. If so, the treatment effect may have been biased because of the lack of adequate allergy symptoms to discriminate the active treatment from placebo in Protocol 066. Nevertheless, regression analysis results showed patients duration in weak season was not correlated to treatment effect (slope=-0.025 with p-value=.2269).

Tabl continued: Sponsor's Summary Table

Additional treatment comparison, using multiple covariate adjustments.	To compare the treatment effect adjusted for all baseline characteristics and randomization failure rate.	ANCOVA model with all baseline characteristics (age, weight, gender, race, baseline TSS) and randomization failure rate of individual investigators site for both pooled and individual protocols.	Results were largely consistent with those in the final report. Thus the baseline characteristics and randomization failure rate could not explain the large placebo effect in Protocol 066 and the different treatment effects between the individual protocols.
Major protocol violations	To examine whether level of protocol violations differed between Protocol 066 and Protocol 077.	Major protocol violations were compared, and additional protocol correct analysis of the primary efficacy variable using ANCOVA was performed for the individual protocols.	Overall, the major protocol violation rates were comparable between the two protocols. The protocol correct analysis of the individual protocols was largely consistent with the intent-to-treat analysis of the individual protocols.
Additional treatment comparison, eliminating one outlier site.	To evaluate the impact of a site which reported an unusually large placebo response (mean reduction from baseline =-6.1).	Treatment comparison was performed using ANCOVA for both pooled protocol and Protocol 066 without one site (site 875 of Protocol 066) of extremely large placebo effect.	Site 875 enrolled ten patients, three of which were in the placebo group. The impact of these few outliers on the overall treatment comparison was minimal.
Non-parametric robust analysis	To moderate the impact of outliers and potential wrong model assumption.	Rank ANCOVA for both pooled and individual protocols.	The rank ANCOVA model moderated the impact of outliers and did not require normality assumption as in the usual ANCOVA model, and thus gave more robust treatment comparison. Overall, the rank ANCOVA results were very consistent with those in the report, and therefore potential outliers and model assumption violations did not explain the differing results.
Study drug testing	To determine if study drug was packaged correctly.	Retained samples tested. Plasma samples from placebo patients tested for presence of drug.	Retained samples indicated study drug was correctly packaged. No fexofenadine was found in plasma samples from placebo patients.
Treatment comparison for US sites only (without Canadian sites)	To examine if treatment effect was consistent between Canadian and US study sites.	ANCOVA models for rank transferred and raw data for US sites only, Canadian sites only and all study sites for pooled and individual protocols.	For Canadian sites, placebo effect was twice of that for fexofenadine in Protocol 066 (placebo: -2.65, Fex: –1.63, -1.15, and –0.96 for 15, 30 and 60 mg, respectively). For the US sites, although the placebo effect in Protocol 066 was still relatively larger than expected, fexofenadine effect in Protocol 066 was only slightly smaller than that in Protocol 077. Without Canadian sites, fexofenadine 30 mg and 60 mg were statistically significantly and 15 mg was marginally superior to placebo (p=.0814, .0276 and .0364 for 15, 30 and 60 mg respectively) in the pooled dataset. It is clear that the overall treatment comparison was largely weakened by the large placebo effect in Canadian sites of Protocol 066.

* Age categories are defined as <9 and ≥9 years of age; weight categories as <15, 15-<30, 30-<45 and ≥45 kgs, baseline category as ≤ or > median of baseline TSS of the primary efficacy variable (7PM 12-hour reflective TSS).

6.4 Chronic Idiopathic Urticaria Adult

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Figure A- 3: CIU Study 39 M Symptom Scores Over Time (LOCF)

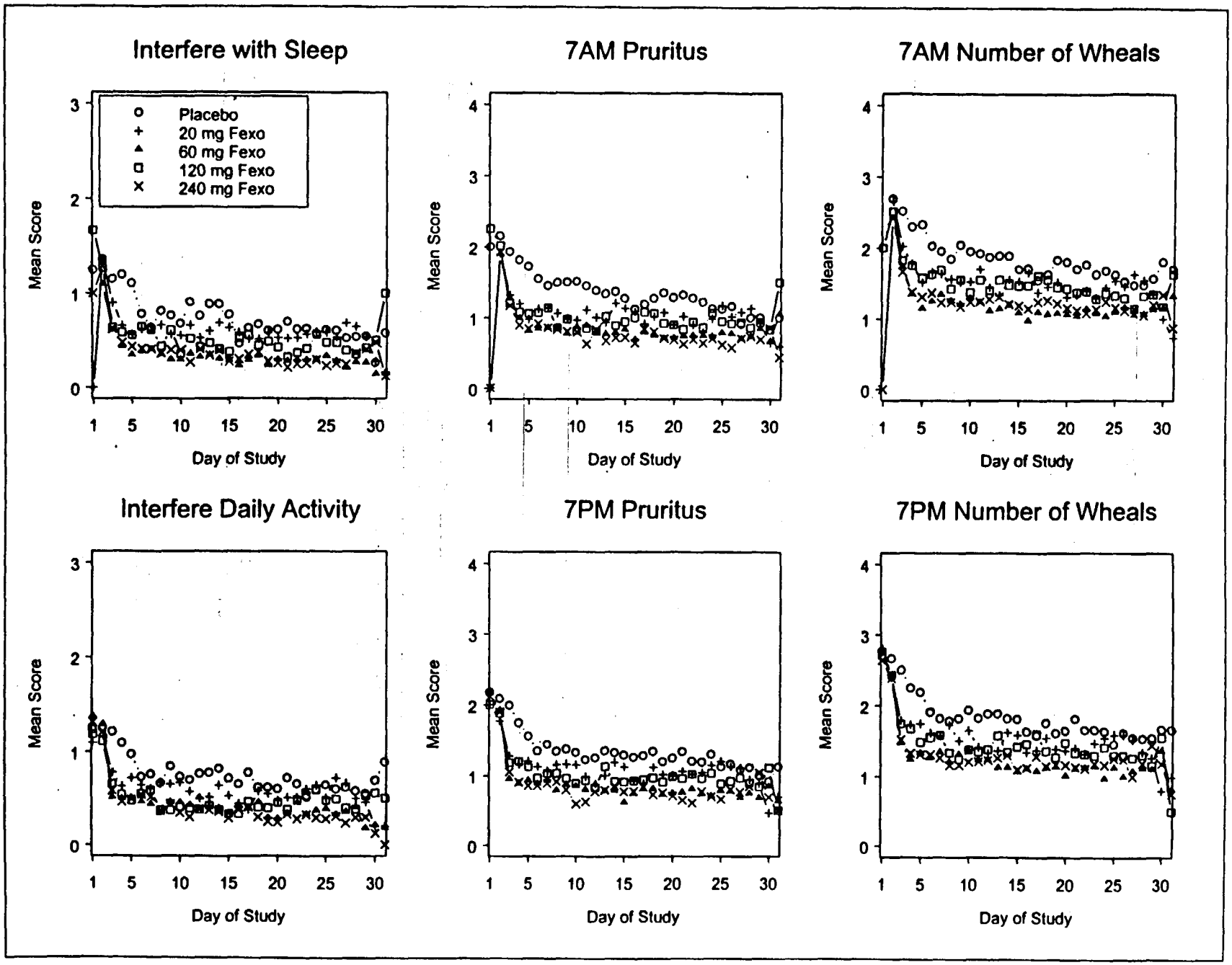

Figure A- 4: CIU Study 39 Mean Symptom Scores Over Time (LOCF)

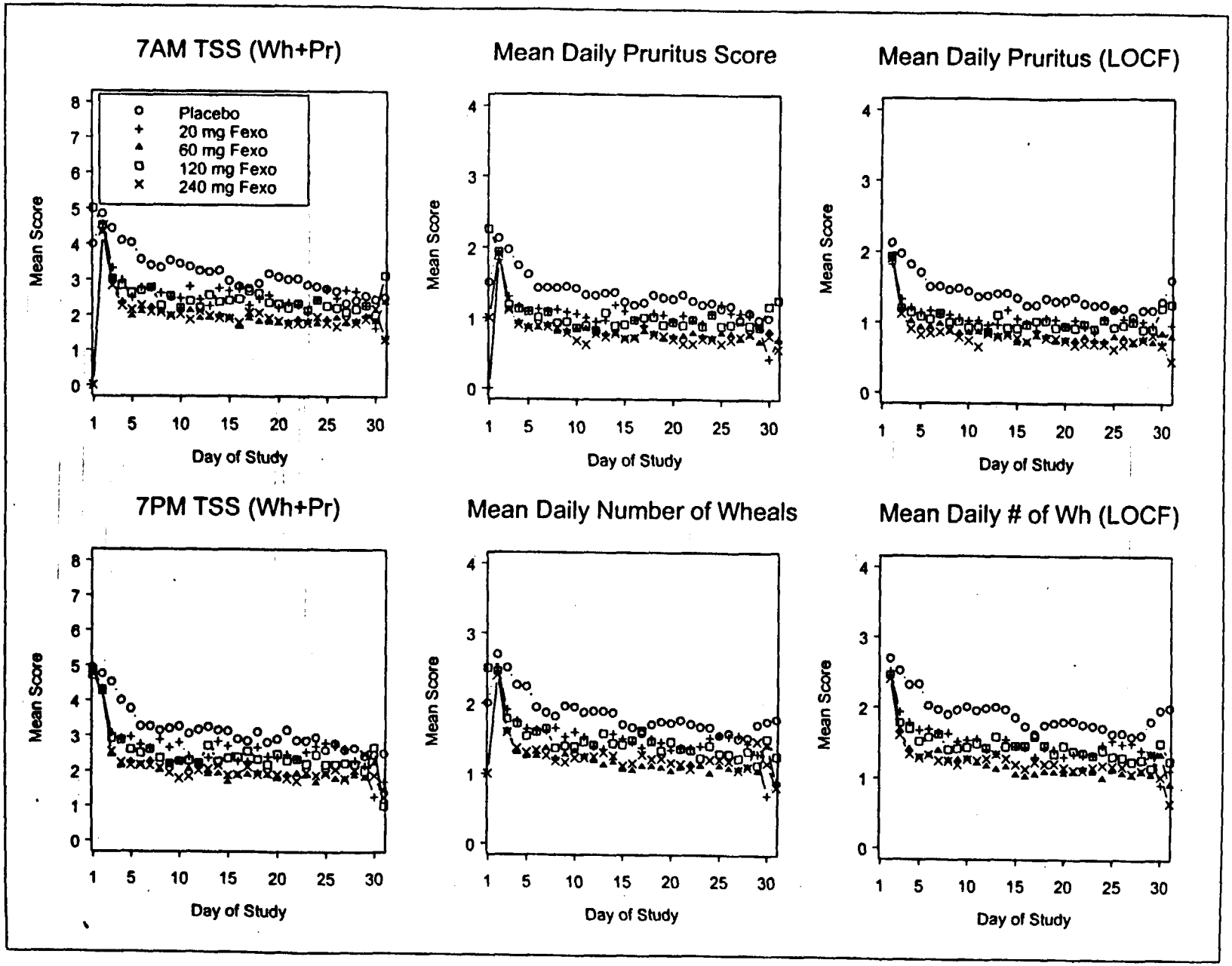

Table A- 11: CIU Study 39 Primary & Secondary Efficacy Variables

Symptom (LOCF)		Week	Placebo MEAN	20 mg BID MEAN	20 mg BID DIFF	20 mg BID P-VAL	60 mg BID MEAN	60 mg BID DIFF	60 mg BID P-VAL	120 mg BID MEAN	120 mg BID DIFF	120 mg BID P-VAL	240 mg BID MEAN	240 mg BID DIFF	240 mg BID P-VAL
		n	82	90			90			79			83		
Mean # Wheals		Baseline	2.69	2.51			2.43			2.46			2.40		
	Change	1	-0.39	-0.78	**0.46**	0.0030	-0.99	**0.74**	<0.0001	-0.85	**0.56**	0.0005	-1.08	**0.84**	<0.0001
	from	2	-0.65	-0.97	**0.41**	0.0197	-1.13	**0.69**	0.0001	-0.92	**0.39**	0.0310	-1.15	**0.66**	0.0002
	Baseline	3	-0.80	-1.09	**0.36**	0.0509	-1.23	**0.62**	0.0007	-0.94	**0.25**	0.1825	-1.17	**0.48**	0.0100
		4	-0.93	-0.96	**0.06**	0.7533	-1.28	**0.50**	0.0098	-1.06	**0.23**	0.2460	-1.25	**0.43**	0.0318
		Avge 1-4	-0.51	-0.89	**0.44**	0.0040	-1.07	**0.71**	<0.0001	-0.87	**0.47**	0.0030	-1.11	**0.76**	<0.0001
		n	82	91			93			79			83		
Mean Pruritus Score		Baseline	2.12	1.82			1.90			1.93			1.90		
	Change	1	-0.36	-0.61	**0.40**	0.0002	-0.88	**0.66**	<0.0001	-0.82	**0.55**	<0.0001	-1.01	**0.78**	<0.0001
	from	2	-0.60	-0.76	**0.29**	0.0179	-0.98	**0.53**	<0.0001	-0.93	**0.38**	0.0032	-1.13	**0.62**	<0.0001
	Baseline	3	-0.68	-0.78	**0.24**	0.0812	-1.03	**0.48**	0.0003	-0.96	**0.32**	0.0213	-1.11	**0.50**	0.0003
		4	-0.81	-0.67	**0.01**	0.9653	-1.05	**0.37**	0.0102	-0.95	**0.17**	0.2398	-1.18	**0.45**	0.0023
		Avge 1-4	-0.47	-0.66	**0.35**	0.0019	-0.93	**0.60**	<0.0001	-0.83	**0.47**	0.0001	-1.06	**0.73**	<0.0001
		n	79	89			87			77			82		
MTSS		Baseline	4.81	4.30			4.26			4.42			4.33		
	Change	Avge 1-4	-1.06	-1.56	**0.74**	0.0036	-2.07	**1.36**	<0.0001	-1.77	**0.94**	0.0004	-2.20	**1.44**	<0.0001
		n	82	91			89			80			84		
Wheals (AM)		Baseline	2.66	2.63			2.38			2.50			2.40		
	Change	Avge 1-4	-0.49	-1.02	**0.53**	0.0009	-1.08	**0.78**	<0.0001	-0.90	**0.50**	0.0025	-1.11	**0.77**	<0.0001
		n	82	89			90			77			82		
Wheals (PM)		Baseline	2.66	2.38			2.39			2.44			2.40		
	Change	Avge 1-4	-0.57	-0.77	**0.35**	0.0277	-1.15	**0.75**	<0.0001	-0.88	**0.45**	0.0059	-1.11	**0.72**	<0.0001
		n	82	91			91			80			84		
Pruritus (AM)		Baseline	2.15	1.86			1.86			1.99			1.90		
	Change	Avge 1-4	-0.49	-0.75	**0.42**	0.0003	-0.92	0.62	<0.0001	-0.92	**0.53**	<0.0001	-1.10	**0.77**	<0.0001
		n	82	90			93			77			82		
Pruritus (PM)		Baseline	2.09	1.74			1.87			1.88			1.89		
	Change	Avge 1-4	-0.47	-0.58	**0.33**	0.0043	-1.00	**0.68**	<0.0001	-0.80	**0.48**	0.0001	-1.04	**0.73**	<0.0001
		n	81	91			92			80			82		
Interfere w/Sleep		Baseline	1.35	1.31			1.07			1.26			1.29		
	Change	Avge 1-4	-0.30	-0.65	**0.34**	0.0007	-0.64	**0.50**	<0.0001	-0.69	**0.43**	<0.0001	-0.87	**0.58**	<0.0001
		n	84	90			93			78			83		
Interfere w/Daily Activities		Baseline	1.25	1.11			1.26			1.12			1.19		
	Change	Avge 1-4	-0.22	-0.48	**0.34**	0.0008	-0.78	**0.54**	<0.0001	-0.57	**0.44**	<0.0001	-0.76	**0.58**	<0.0001

Table A- 12: CIU Study 67 Primary & Secondary Efficacy Variables

Symptom (LOCF)		Week	Placeb	20 mg BID			60 mg BID			120 mg BID			240 mg BID		
				MEAN	DIFF	P-VAL	MEAN	DIFF	P-VAL	MEAN	DIFF	P-VAL	MEAN	DIFF	P-VAL
		n	89	93			84			89			83		
Mean #		Baseline	2.45	2.35			2.45			2.60			2.41		
Wheals	Change	1	-0.48	-0.78	0.35	0.0133	-1.05	0.59	0.0001	-1.30	0.77	<0.0001	-1.20	0.74	<0.0001
	from	2	-0.70	-0.88	0.28	0.0703	-1.22	0.56	0.0004	-1.45	0.69	<0.0001	-1.36	0.69	<0.0001
	Baseline	3	-0.80	-1.02	0.32	0.0587	-1.26	0.48	0.0054	-1.45	0.60	0.0003	-1.28	0.54	0.0015
		4	-0.81	-1.16	0.43	0.0159	-1.33	0.52	0.0034	-1.52	0.67	0.0001	-1.45	0.69	0.0001
		Avge 1-4	-0.62	-0.88	0.31	0.0299	-1.16	0.56	0.0001	-1.41	0.73	<0.0001	-1.30	0.70	<0.0001
		n	91	93			86			90			84		
Mean		Baseline	1.92	1.87			1.98			2.03			1.82		
Pruritus	Change	1	-0.39	-0.69	0.33	0.0011	-1.04	0.62	<0.0001	-1.07	0.62	<0.0001	-1.03	0.71	<0.0001
Score	from	2	-0.51	-0.81	0.32	0.0023	-1.17	0.61	<0.0001	-1.19	0.58	<0.0001	-1.13	0.68	<0.0001
	Baseline	3	-0.57	-1.01	0.43	0.0002	-1.14	0.48	<0.0001	-1.18	0.48	<0.0001	-1.10	0.56	<0.0001
		4	-0.61	-1.16	0.53	<0.0001	-1.20	0.48	0.0001	-1.20	0.46	0.0001	-1.21	0.64	<0.0001
		Avge 1-4	-0.47	-0.82	0.38	0.0001	-1.11	0.61	<0.0001	-1.14	0.61	<0.0001	-1.11	0.71	<0.0001
		n	88	91			84			88			82		
MTSS		Baseline	4.36	4.20			4.42			4.63			4.20		
	Change	Avge 1-4	-1.11	-1.75	0.75	0.0010	-2.28	1.17	<0.0001	-2.57	1.33	<0.0001	-2.43	1.41	<0.0001
		n	91	94			88			89			82		
Wheals		Baseline	2.49	2.40			2.44			2.60			2.43		
(AM)	Change	Avge 1-4	-0.70	-0.95	0.32	0.0270	-1.15	0.51	0.0006	-1.46	0.72	<0.0001	-1.41	0.77	<0.0001
		n	89	91			86			89			83		
Wheals		Baseline	2.43	2.32			2.40			2.51			2.40		
(PM)	Change	Avge 1-4	-0.62	-0.84	0.28	0.0543	-1.07	0.49	0.0011	-1.35	0.68	<0.0001	-1.25	0.64	<0.0001
		n	91	94			89			90			83		
Pruritus		Baseline	1.93	1.90			1.98			2.07			1.88		
(AM)	Change	Avge 1-4	-0.52	-0.87	0.39	0.0001	-1.13	0.60	<0.0001	-1.20	0.60	<0.0001	-1.21	0.74	<0.0001
		n	90	91			87			89			83		
Pruritus		Baseline	1.90	1.82			1.93			2.00			1.73		
(PM)	Change	Avge 1-4	-0.46	-0.81	0.40	0.0001	-1.04	0.57	<0.0001	-1.11	0.58	<0.0001	-1.02	0.69	<0.0001
		n	91	94			89			90			83		
Interfere		Baseline	1.20	1.18			1.27			1.43			1.16		
w/Sleep	Change	Avge 1-4	-0.38	-0.73	0.38	<0.0001	-0.87	0.46	<0.0001	-1.04	0.49	<0.0001	-0.82	0.49	<0.0001
Interfere		n	89	91			88			89			83		
w/Daily		Baseline	1.18	1.13			1.10			1.51			1.10		
Activities	Change	Avge 1-4	-0.34	-0.63	0.33	<0.0001	-0.67	0.40	<0.0001	-0.99	0.43	<0.0001	-0.77	0.49	<0.0001

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STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

Date: JUL 1 2 1999

NDA Number:	20-872
Applicant:	Hoechst Marion Roussel/ Quintiles
Name of Drug:	Allegra (fexofenadine HCl) (small tablets)
Statistical Reviewer:	Barbara Elashoff
Chemistry Reviewer:	Houssein Korshedi
Documents Reviewed:	5/21/99 Vol 20.2; 6/28/99 electronic data

Summary of Review

- The sponsor proposed an 18-month expiration date for the 30 mg tablets based on 18 months of data; and a 30-month expiration date for the 60, 120 and 180 mg tablets based on 24 months of data.

- The chemist requested a statistical review of the sponsor's stability data for the blister packages, and the 30- and 3000-count bottles.

- The data support an 18-month expiration date for the 30 mg tablets for all three package types and a 30-month expiration date for the 60 and 120 mg tablets for all three package types.

- The data support a 30 month expiration date for the 180 mg tablets for only two of the three package types: blister packages and 3000-count bottles. The data support a 25-month expiration date for the 180 mg tablets for the 30-count bottles.

- One interesting finding in these data was the fact that the slopes for the dissolution data at 15 and 45 minutes were slightly positive for the 30 mg tablets, flat for the 60 mg tablets, slightly negative for the 120 mg tablets and slightly more negative for the 180 mg tablets.

Introduction

Hoechst Marion Roussel has submitted 18- and 24-month stability data on 30- and 3000-count bottles and clear PVC/PE/PVDC blisters for Allegra small tablets at the following strengths: 30, 60, 120 and 180 mg. The sponsor has proposed an 18-month expiration period for the 30 mg tablets and a 30-month expiration period for the other strengths. The reviewing chemist has requested Division of Biometrics to perform a statistical review and evaluation of the sponsor's stability data for each of the following parameters in Table 1 using the specifications listed below:

Table 1: Factors Used to Estimate Expiration Dates
FDA Specifications
(Sponsor Specifications in Parentheses)

Test Factor	Minimum Specification	Maximum Specification
Degradation Products		
MDL 102,038		
MDL 46,016		
Total Other Degradents		
Total Degradents		
Moisture		
Dissolution in 15 minutes		

The chemist requested results using both FDA and sponsor proposed specifications. Since the FDA limits were either identical to or more conservative ("tighter") than the sponsors' limits, this review presents the results for the FDA limits. In cases where the data did not support the sponsor's proposed expiration dates using the FDA limits, the data were re-analyzed using the sponsor's limits.

Most of the data for the "Total Other Degradents" variable (93%) and about half the data for the MDL 46,016 degradent variable (49%) were measured and recorded as <0.05, because the data were below the limit of detection for the assay. These data were used in the analyses as "0.05". This resulted in a conservative, or "under-estimate" of the true expiration dating period. (None of the analyses for these two variables resulted in expiration dates shorter than those the sponsor proposed.)

The sponsor submitted electronic data for this review. In a teleconference on July 7, 1999, the sponsor answered questions about the electronic data for the dissolution variable. The sponsor stated that the dissolution data were generated from 3 stages of samples (S1, S2 and S3). If a sample of 6 observations of a batch failed the S1 criteria, another sample of 6 was taken. If this sample failed S2 criteria, a third sample of 6 was taken. The means in the electronic dataset the sponsor submitted were means of the first sample of 6. The S2 and S3 data were excluded from these means. The sponsor stated that the other variables had similar sampling schemes; the electronic data reflected the first samples of these variables as well. The details of the sampling schemes of these other variables were not fully understood by the team participating in the teleconference. In contrast to the electronic data, the sponsor stated that the means in the line listings provided in Volume 20.2 (response to FDA questions received April 26, 1999) included data from all three stages of sampling (S1, S2 and S3). This review is based on the data from the electronic datasets, not the line listings in Volume 20.2.

Reviewer's Analyses

The statistical procedures in the FDA Guidelines (February 1987) were applied to the stability data provided by the sponsor. For all the parameters with upper limit specifications only, the estimated expiration dates were calculated from the specifications limit and the upper one-sided 95% confidence interval of the regression lines. For the dissolution variable (lower limit specifications only), the estimated expiration dates were calculated from the specifications limit and the lower one-sided 95% confidence interval of the regression lines. The estimated expiration dating periods for the three package types are listed in Table 2.

Table 2: Summary Table of Expiration Dates
(Data were extrapolated 18 months beyond the range of available data.)

Strength	Package	Test	Intercepts	Slopes	Exp Date
30 mg	Clear Blisters	MDL 102,038	Pooled	Pooled	30
		MDL 46,016	Separate	Separate	≥36
		Total Other Degradents	Separate	Pooled	≥36
		Total Degradents	Separate	Pooled	≥36
		Moisture	Pooled	Pooled	32
		Dissolution in 15 minutes	Separate	Separate	≥36
	30-count	MDL 102,038	Separate	Separate	≥36
		MDL 46,016	Separate	Pooled	≥36
		Total Other Degradents	Separate	Pooled	≥36
		Total Degradents	Separate	Pooled	≥36
		Moisture	Pooled	Pooled	≥36
		Dissolution in 15 minutes	Separate	Separate	≥36
	3000-count	MDL 102,038	Pooled	Pooled	≥36
		MDL 46,016	Separate	Pooled	≥36
		Total Other Degradents	Separate	Pooled	≥36
		Total Degradents	Separate	Pooled	≥36
		Moisture	Pooled	Pooled	≥36
		Dissolution in 15 minutes	Separate	Pooled	≥36
60 mg	Clear Blisters	MDL 102,038	Separate	Separate	33
		MDL 46,016	Separate	Pooled	≥42
		Total Other Degradents	Separate	Pooled	≥42
		Total Degradents	Separate	Separate	≥42
		Moisture	Pooled	Pooled	≥42
		Dissolution in 15 minutes	Separate	Pooled	≥42
	30-count	MDL 102,038	Separate	Pooled	≥42
		MDL 46,016	Separate	Separate	≥42
		Total Other Degradents	Separate	Pooled	≥42
		Total Degradents	Separate	Pooled	≥42
		Moisture	Pooled	Pooled	≥42
		Dissolution in 15 minutes	Separate	Pooled	≥42
	3000-count	MDL 102,038	Separate	Pooled	≥40
		MDL 46,016	Separate	Pooled	≥42
		Total Other Degradents	Separate	Pooled	≥42
		Total Degradents	Separate	Pooled	≥42
		Moisture	Pooled	Pooled	≥42
		Dissolution in 15 minutes	Separate	Pooled	≥42

(Table 2 continued)

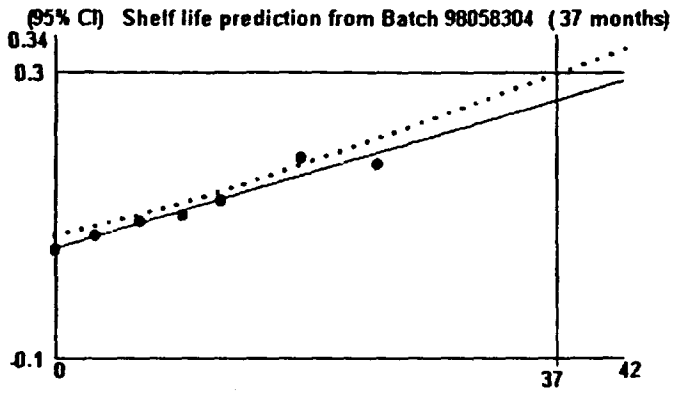
Strength	Package	Test	Intercepts	Slopes	Exp Date
120 mg	Clear Blisters	MDL 102,038	Separate	Pooled	≥42
		MDL 46,016	Separate	Separate	≥42
		Total Other Degradents	Pooled	Pooled	≥42
		Total Degradents	Separate	Pooled	≥42
		Moisture	Pooled	Pooled	≥42
		Dissolution in 15 minutes	Pooled	Pooled	≥42
	30-count	MDL 102,038	Separate	Pooled	≥43
		MDL 46,016	Separate	Pooled	≥42
		Total Other Degradents	Separate	Pooled	≥42
		Total Degradents	Separate	Pooled	≥43
		Moisture	Pooled	Pooled	≥43
		Dissolution in 15 minutes	Pooled	Pooled	≥43
	3000-count	MDL 102,038	Separate	Pooled	≥43
		MDL 46,016	Separate	Pooled	≥42
		Total Other Degradents	Separate	Pooled	≥42
		Total Degradents	Separate	Pooled	≥43
		Moisture	Pooled	Pooled	≥43
		Dissolution in 15 minutes	Pooled	Pooled	≥43
180 mg	Clear Blisters	MDL 102,038	Pooled	Pooled	≥42
		MDL 46,016	Separate	Pooled	≥42
		Total Other Degradents	Separate	Pooled	≥42
		Total Degradents	Pooled	Pooled	≥42
		Moisture	Pooled	Pooled	≥42
		Dissolution in 15 minutes	Separate	Separate	41
	30-count	MDL 102,038	Separate	Separate	25
		MDL 46,016	Separate	Pooled	≥42
		Total Other Degradents	Separate	Pooled	≥42
		Total Degradents	Separate	Separate	≥42
		Moisture	Pooled	Pooled	≥42
		Dissolution in 15 minutes	Pooled	Pooled	≥42
	3000-count	MDL 102,038	Pooled	Pooled	≥42
		MDL 46,016	Pooled	Pooled	≥42
		Total Other Degradents	Separate	Separate	≥42
		Total Degradents	Pooled	Pooled	≥42
		Moisture	Pooled	Pooled	≥42
		Dissolution in 15 minutes	Pooled	Pooled	≥42

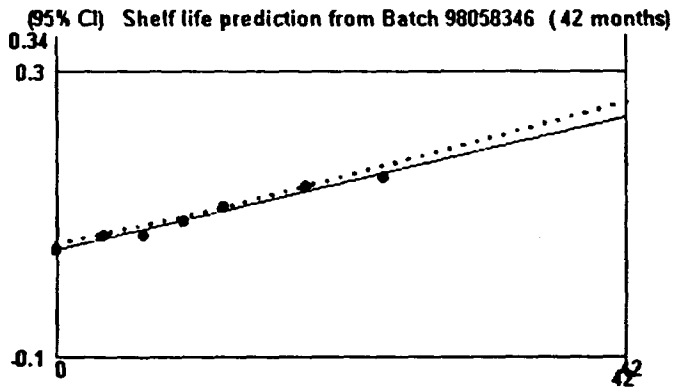
All the data for the 30 mg tablet support the proposed 18-month expiration date and all the data for the 60, 120 and 180 mg tablets, with one exception, support the proposed 30-month expiration date using FDA and sponsor proposed specifications. The exception is the Degradent MDL 102,038 data for the 180 mg tablet in 30-count bottles. The upper confidence limit for this tablet and variable from Batch #98058962 crosses the FDA specification line (0.3 units) at 25 months, as seen in Figure 1 on the next page. (Using the sponsor's specification of ~~0.5~~ 0.4 units, the confidence limit of this same batch crosses the line at 34 months, thus supporting the 30-month expiration date.)

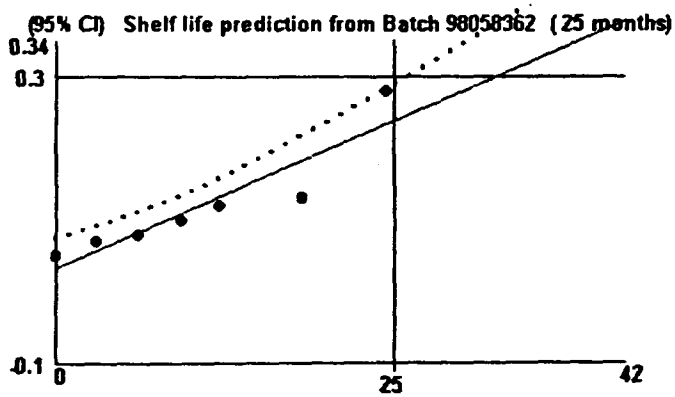
Figure 1: FDA Specifications
MDL 102,038
180 mg strength: 30-count Bottles

98058304	37	Max Spec:	0.30
98058346	42	Min Spec:	None
98058362	25		

Separate intercepts and separate slopes







The graphs of the MDL 102,038 data for all the batches, for all the strengths and package types, are presented in Appendix A.

Dissolution Data

One interesting finding in the dissolution at 15 minutes data was the fact that slopes were positive for the 30 mg tablets, flat for the 60 mg tablets, slightly negative for the 120 mg tablets and slightly more negative for the 180 mg tablets. The intercepts and slopes calculated from the analyses are presented in Table 3 below. For the batches in which the analyses did not allow for pooled slopes and/or intercepts, the results are presented separately. The graphs of these data are provided in Appendix B where the differences in slopes can be seen more easily. A similar pattern was seen in the data of Dissolution at 45 minutes (see Table 4 below and graphs in Appendix B).

Table 3: Dissolution (at 15 minutes) Intercepts and Slopes

Strength	Package	Batch	Intercept	Slope
30 mg	BLISTER	9713	85.2	**0.224**
		9714	77.7	**0.589**
		9715	85.8	**0.344**
	HDPE30	9713	85.4	**0.145**
		9714	77.1	**0.534**
		9715	86.4	**0.157**
	HDPE3000	9713	83.2	**0.087**
		9714	78.	**0.087**
		9715	83.8	**0.087**
60 mg	BLISTER	98057614	92.2	**0.074**
		98057617	93.1	**0.074**
		98057619	95.2	**0.074**
	HDPE30	98057614	91.2	**0.073**
		98057617	93.9	**0.073**
		98057619	95.1	**0.073**
	HDPE3000	98057614	90.9	**-0.001**
		98057617	94.3	**-0.001**
		98057619	96.3	**-0.001**
120 mg	BLISTER	All Batches	92.1	**-0.254**
	HDPE30	All Batches	91.9	**-0.238**
	HDPE3000	All Batches	91.4	**-0.176**
180 mg	BLISTER	98058304	85.2	**-0.133**
		98058346	89.2	**-0.570**
		98058362	87.	**-0.382**
	HDPE30	All Batches	85.6	**-0.139**
	HDPE3000	All Batches	87.4	**-0.331**

Table 4: Dissolution (at45 minutes) Intercepts and Slopes

Strength	Package	Batch	Intercept	Slope
30 mg	BLISTER	All Batches	98.5	**0.086**
	HDPE30	9713	98.1	**0.132**
		9714	97.9	**0.132**
		9715	98.9	**0.132**
	HDPE3000	9713	98.6	**0.024**
		9714	97.3	**0.024**
		9715	99.	**0.024**
60 mg	BLISTER	98057614	97.5	**0.006**
		98057617	98.2	**0.006**
		98057619	100.1	**0.006**
	HDPE30	98057614	97.5	**-0.076**
		98057617	98.1	**0.068**
		98057619	99.8	**0.060**
	HDPE3000	98057614	96.3	**-0.040**
		98057617	98.8	**-0.040**
		98057619	101.	**-0.040**
120 mg	BLISTER	98054478	101.1	**-0.297**
		98054529	99.2	**-0.123**
		98054530	100.4	**-0.269**
	HDPE30	All Batches	100.4	**-0.210**
	HDPE3000	All Batches	100.	**-0.173**
180 mg	BLISTER	98058304	95.4	**-0.140**
		98058346	98.	**-0.375**
		98058362	97.9	**-0.379**
	HDPE30	98058304	95.2	**-0.037**
		98058346	96.4	**-0.110**
		98058362	97.1	**-0.234**
	HDPE3000	98058304	96.	**-0.098**
		98058346	98.2	**-0.357**
		98058362	98.2	**-0.355**

Conclusions

The estimated expiration dating periods in this review are based on data extrapolation beyond the range of storage time actually observed, which is valid under the assumption that the pattern of deterioration does not change significantly over the extrapolation period.

The proposed 18-month expiration date for the 30 mg tablets for the clear blister packages and the 30- and 3000-count bottles are supported by the 18-month data the sponsor submitted. This is based on the specification limits of the degradation products (MDL 102,038; MDL 46,106; total other degradents and total degradents), moisture content, and dissolution at 15 minutes.

The proposed 30-month expiration date for the 60 and 120 mg tablets for the clear blister packages and the 30- and 3000-count bottles are supported by the 24-month data the sponsor submitted. This is based on the specification limits of the degradation products (MDL 102,038; MDL 46,106; total other degradents and total degradents), moisture content, dissolution at 15 minutes, and on extrapolation 6 months beyond the range of available data.

The proposed 30-month expiration date for the 180 mg tablets for the clear blister packages and the 3000-count bottles are supported by the 24-month data the sponsor submitted. This is based on the specification limits of the degradation products (MDL 102,038; MDL 46,106; total other degradents and total degradents), moisture content, dissolution at 15 minutes, and on extrapolation 6 months beyond the range of available data.

The proposed 30-month expiration date for the 180 mg tablets for the 30-count bottles is not supported by the 24-month MDL 102,038 degradation data. Using the FDA specification limits, the data yielded a 25-month expiration dating period for the 180 mg tablets in 30-count bottles. This is based on the specification limits of the degradation products (MDL 102,038; MDL 46,106; total other degradents and total degradents), moisture content, dissolution at 15 minutes, and on extrapolation 6 months beyond the range of available data.

/S/
Barbara Elashoff

Concur: Dr. Lin /S/ 7/12/99

cc:
Orig. NDA
HFD-570 / Division File
HFD-570 / LCobbs, HKorshedi, GPoochikian, Y-YChiu, AWorobec
HFD-715 / Division File, SWilson, KLin

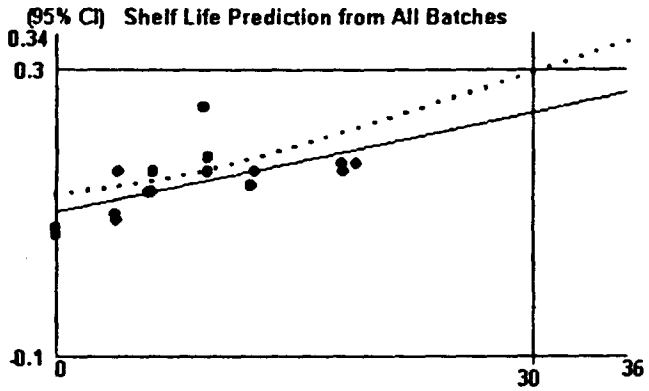
Appendix A

MDL 102,038

30 mg strength: Blister Packages

All Batches	30	Max Spec:	0.30
		Min Spec:	None

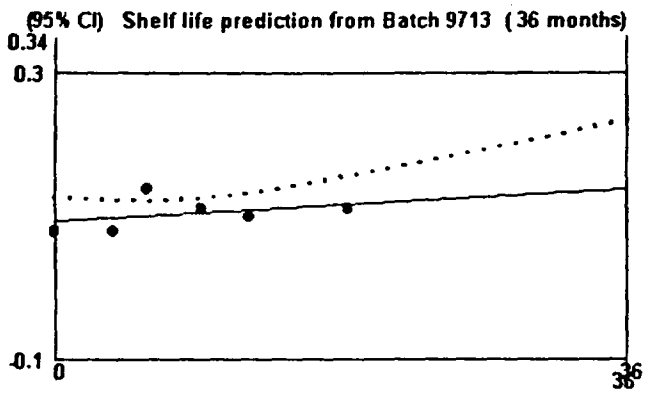
Common intercept and common slope therefore data are pooled

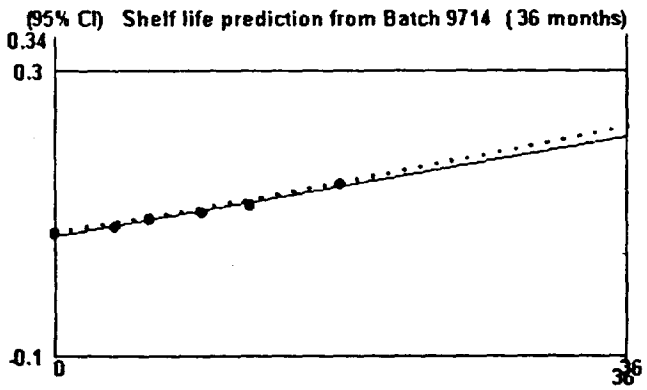


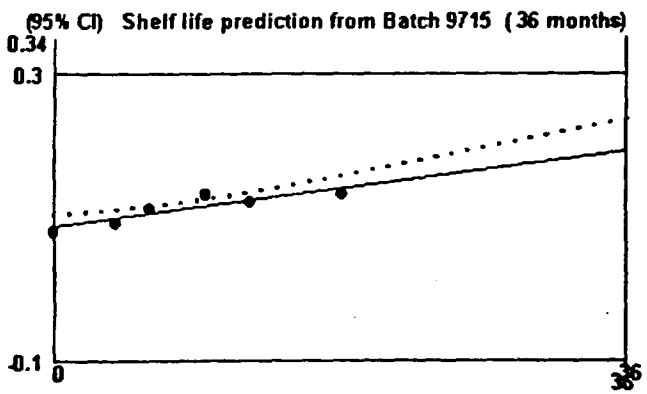
MDL 102,038
30 mg strength: 30-count Bottles

9713	36	Max Spec:	0.30
9714	36	Min Spec:	None
9715	36		

Separate intercepts and separate slopes





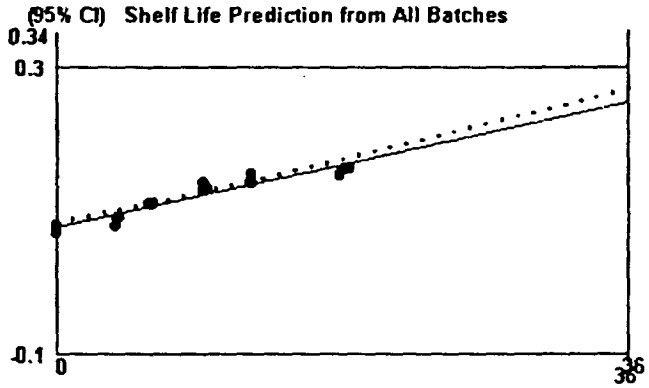


MDL 102,038

30 mg strength: 3000-count Bottles

All Batches	36	Max Spec:	0.30
		Min Spec:	None

Common intercept and common slope therefore data are pooled

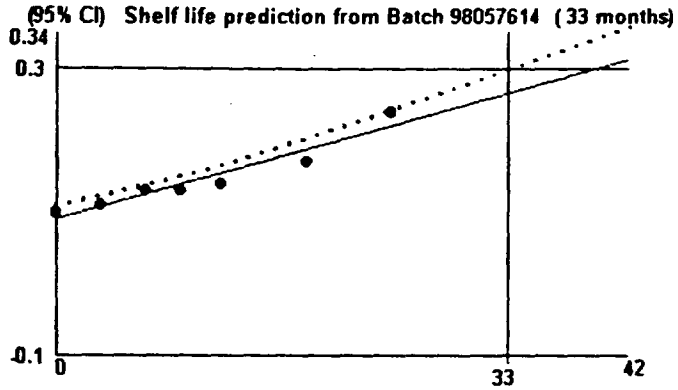


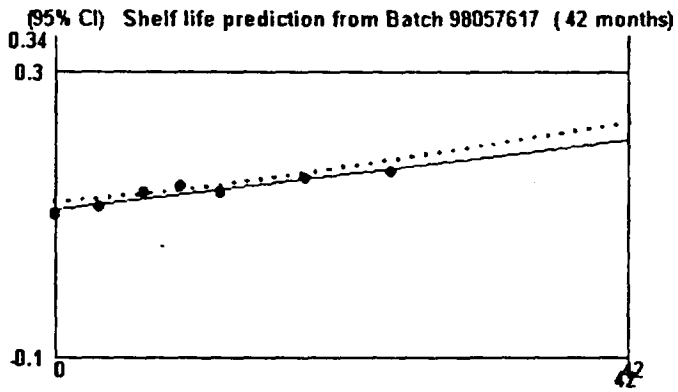
MDL 102,038

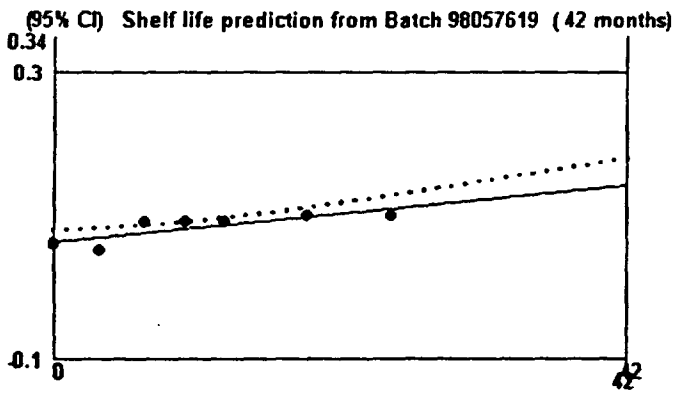
60 mg strength: Blister Packages

98057614	33	Max Spec:	0.30
98057617	42	Min Spec:	None
98057619	42		

Separate intercepts and separate slopes





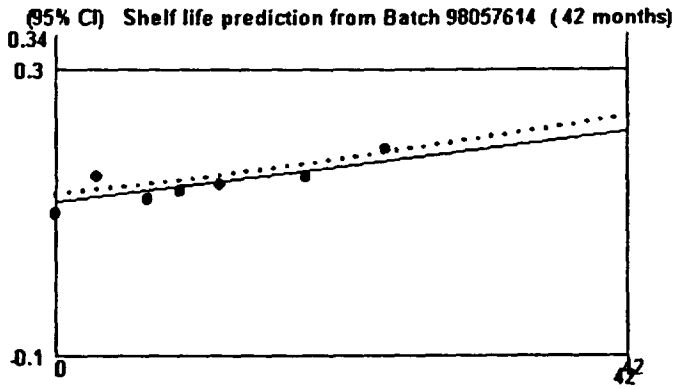


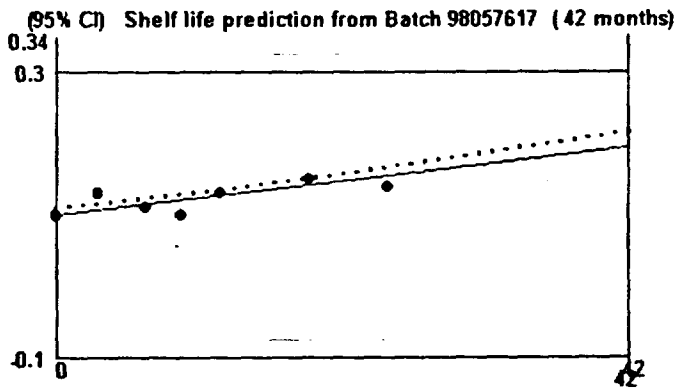
MDL 102,038

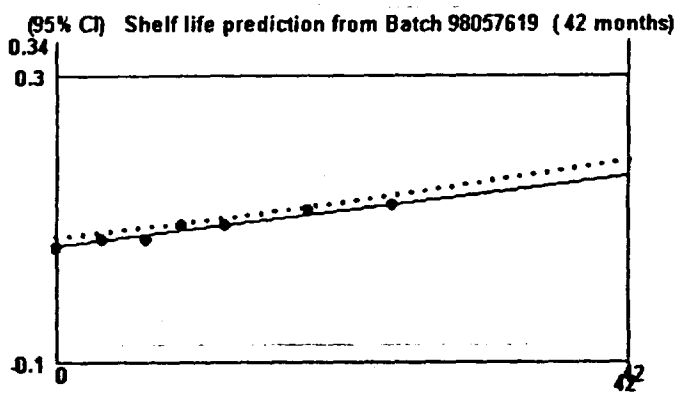
60 mg strength: 30-count Bottles

98057614	42	Max Spec:	0.30
98057617	42	Min Spec:	None
98057619	42		

Separate intercepts and common slope





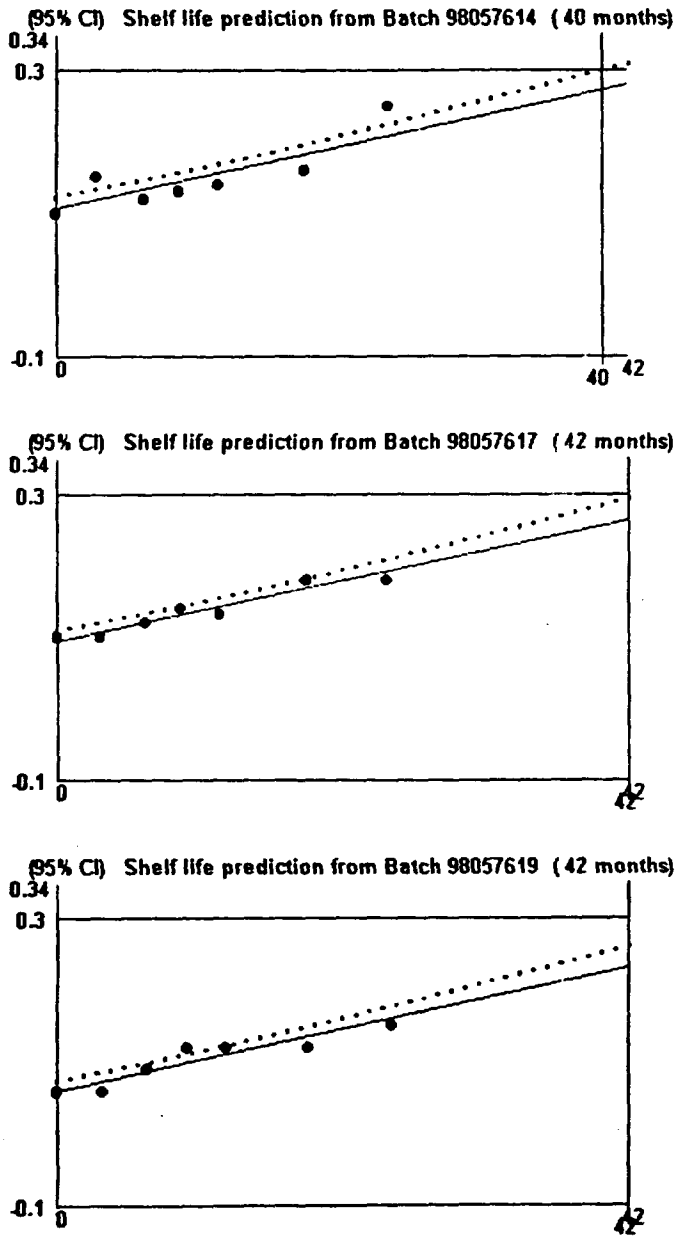


MDL 102,038

60 mg strength: 3000-count Bottles

98057614	40	Max Spec:	0.30
98057617	42	Min Spec:	None
98057619	42		

Separate intercepts and common slope

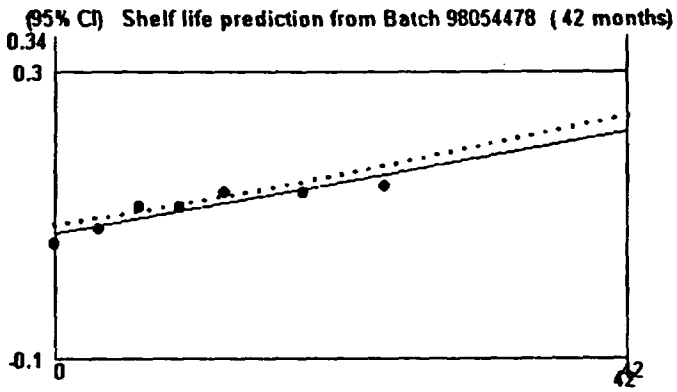


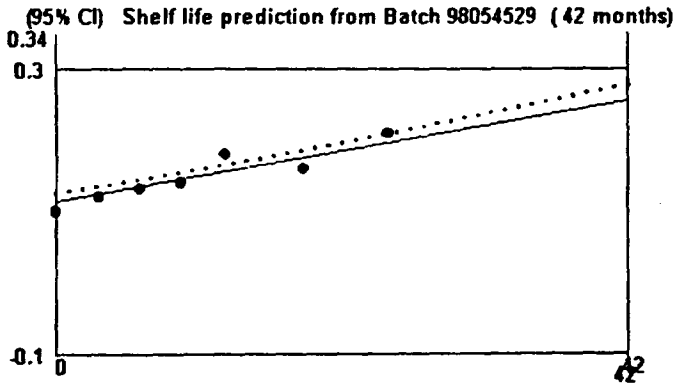
MDL 102,038

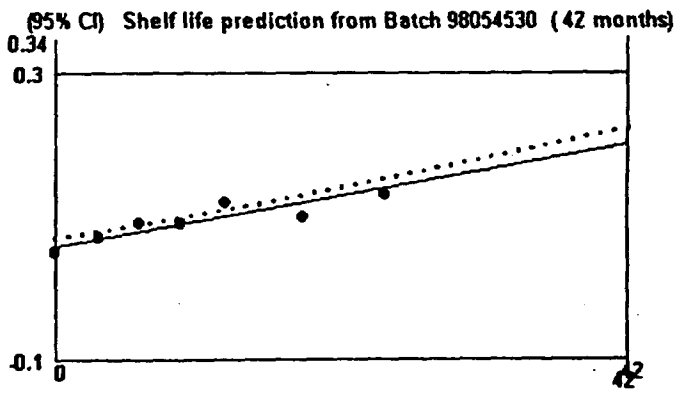
120 mg strength: Blister Packages

98054478	42	Max Spec:	0.30
98054529	42	Min Spec:	None
98054530	42		

Separate intercepts and common slope





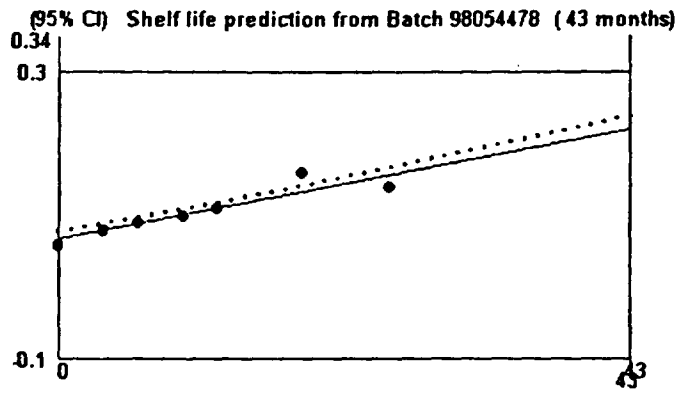


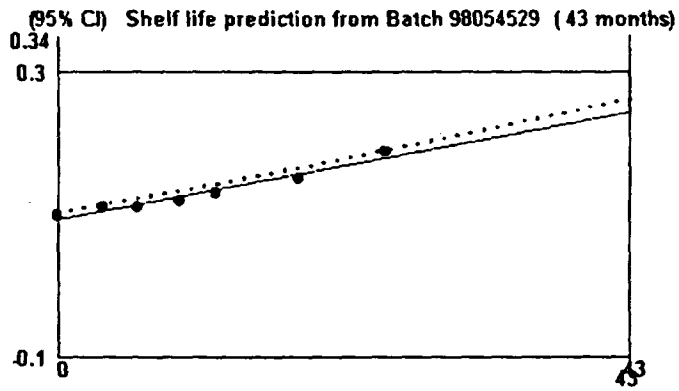
MDL 102,038

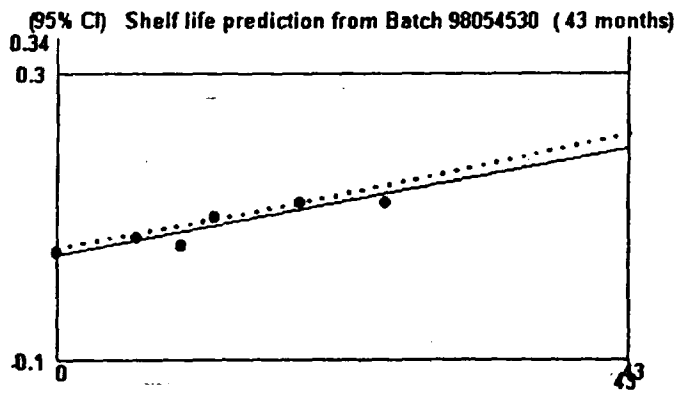
120 mg strength: 30-count Bottles

98054478	43	Max Spec:	0.30
98054529	43	Min Spec:	None
98054530	43		

Separate intercepts and common slope





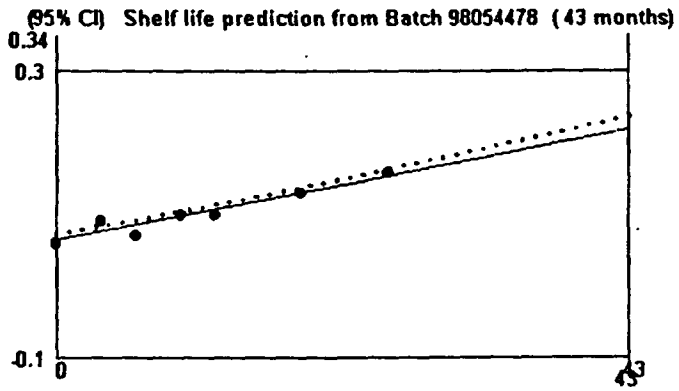


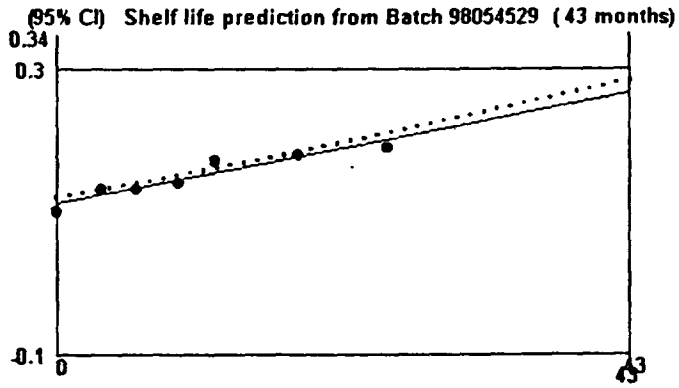
MDL 102,038

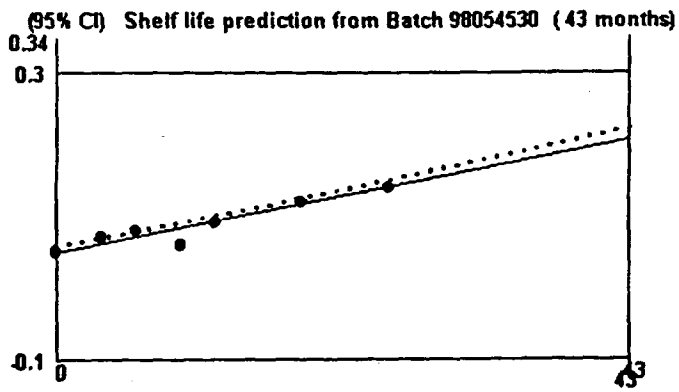
120 mg strength: 3000-count Bottles

98054478	43	Max Spec:	0.30
98054529	43	Min Spec:	None
98054530	43		

Separate intercepts and common slope





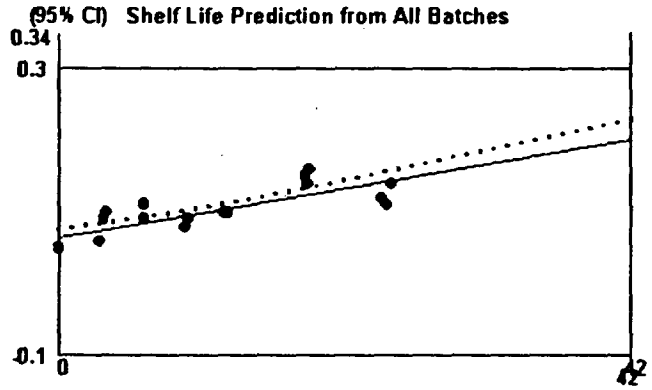


MDL 102,038

180 mg strength: Blister Packages

All Batches 42 Max Spec: 0.30
Min Spec: None

Common intercept and common slope therefore data are pooled

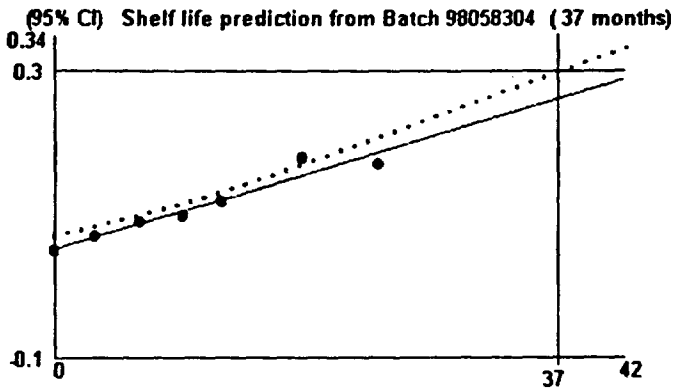


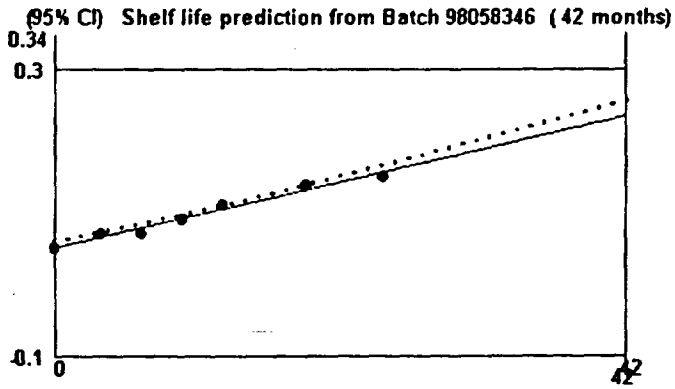
MDL 102,038

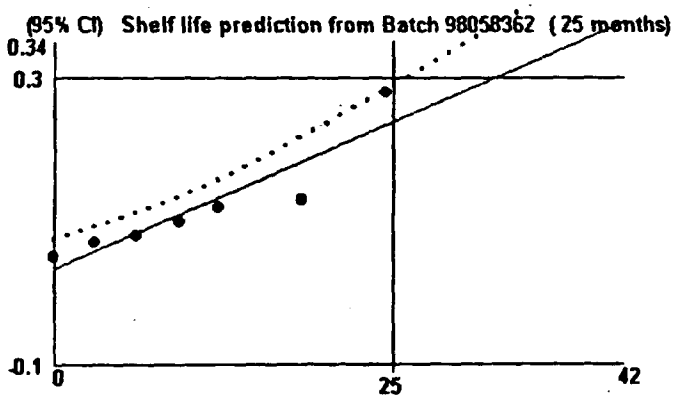
180 mg strength: 30-count Bottles

98058304	37	Max Spec:	0.30
98058346	42	Min Spec:	None
98058362	25		

Separate intercepts and separate slopes





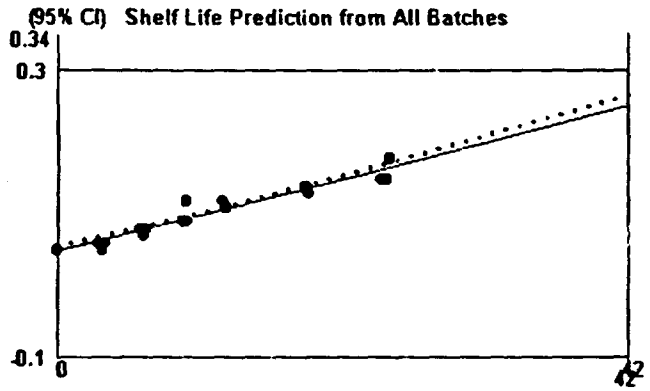


MDL 102,038

180 mg strength: 3000-count Bottles

All Batches 42 Max Spec: 0.30
Min Spec: None

Common intercept and common slope therefore data are pooled



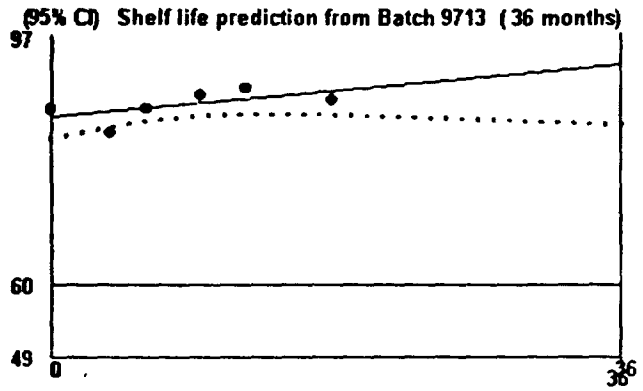
Appendix B

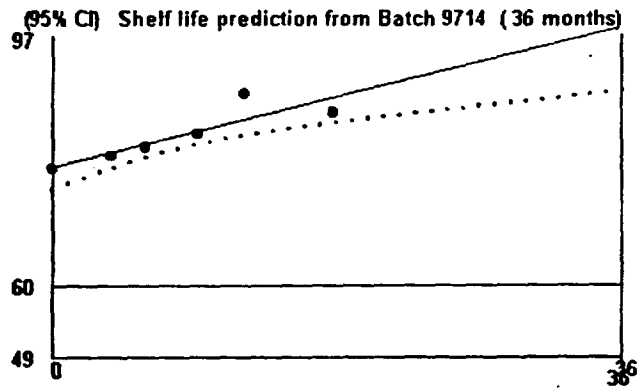
Dissolution in 15 minutes

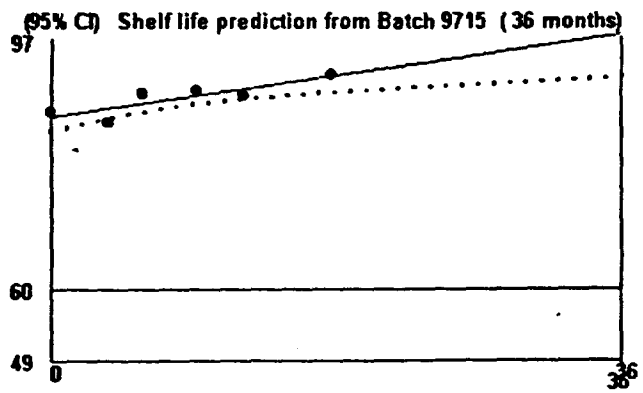
30 mg strength: Blister Packages

9713	36	Max Spec:	None
9714	36	Min Spec:	60
9715	36		

Separate intercepts and separate slopes





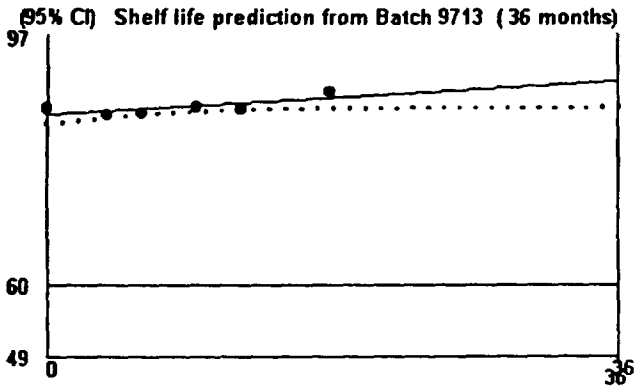


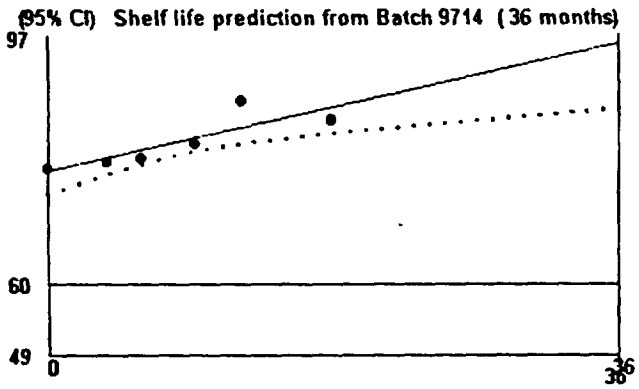
Dissolution in 15 minutes

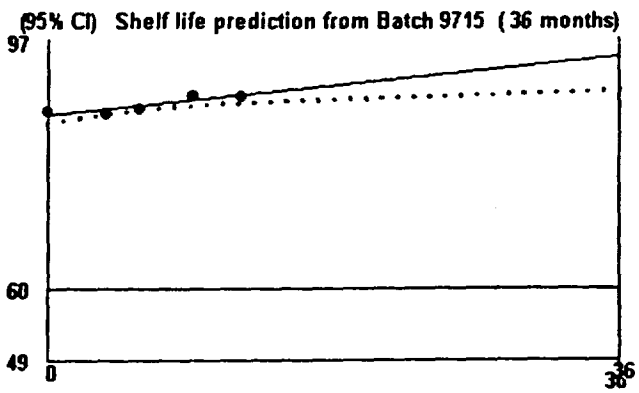
30 mg strength: 30-count Bottles

9713	36	Max Spec:	None
9714	36	Min Spec:	60
9715	36		

Separate intercepts and separate slopes





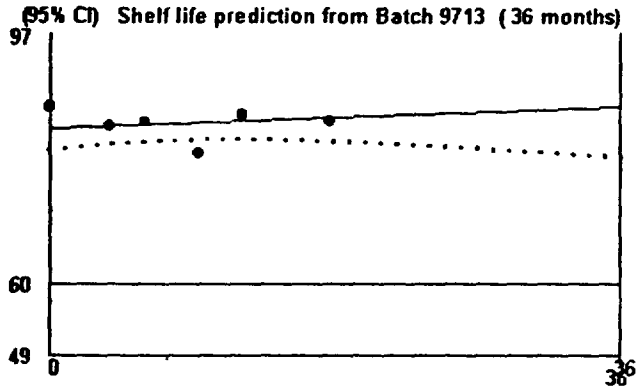


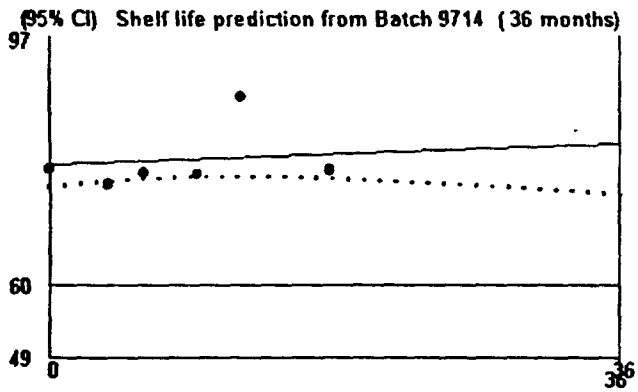
Dissolution in 15 minutes

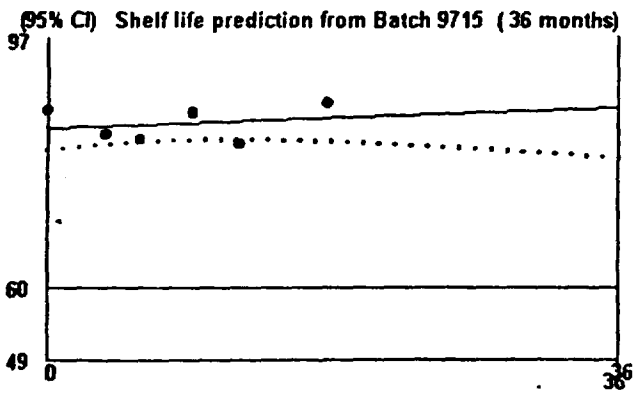
30 mg strength: 3000-count Bottles

9713	36	Max Spec:	None
9714	36	Min Spec:	60
9715	36		

Separate intercepts and common slope



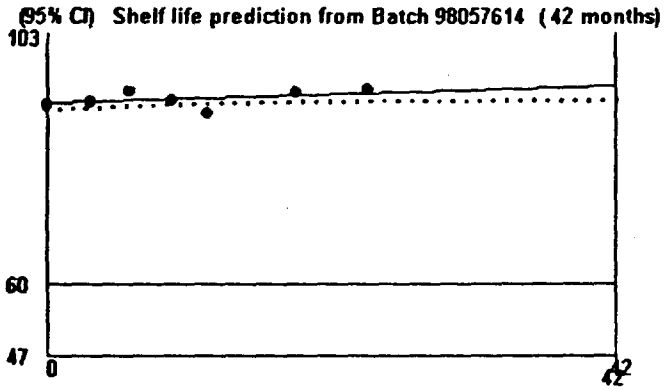


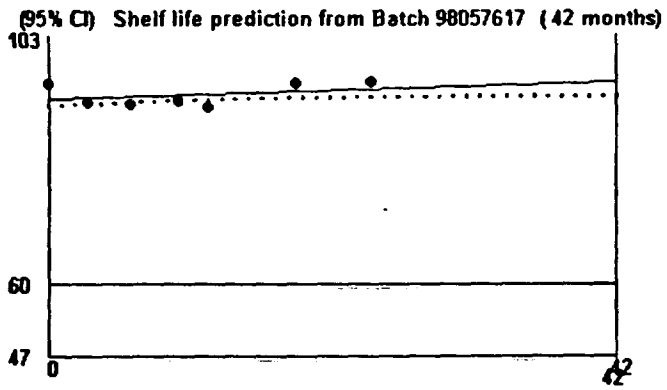


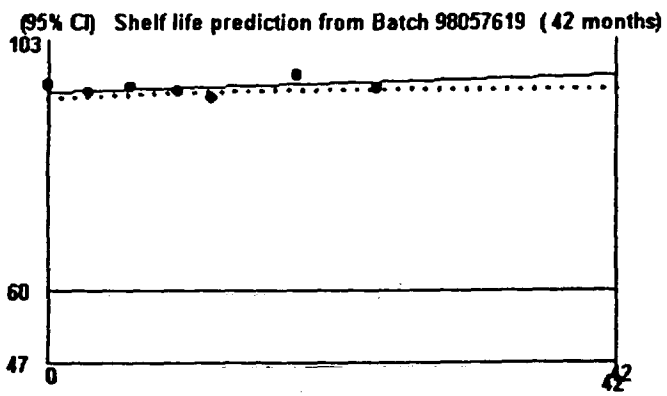
Dissolution in 15 minutes
60 mg strength: Blister Pacakges

98057614	42	Max Spec:	None
98057617	42	Min Spec:	60
98057619	42		

Separate intercepts and common slope



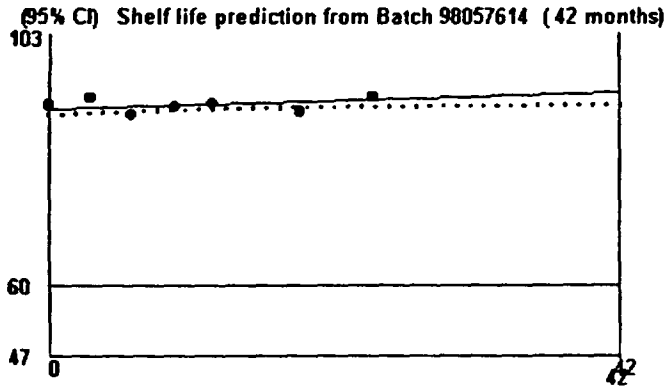


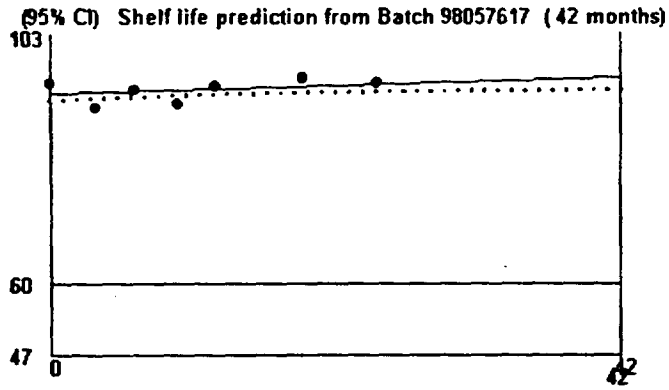


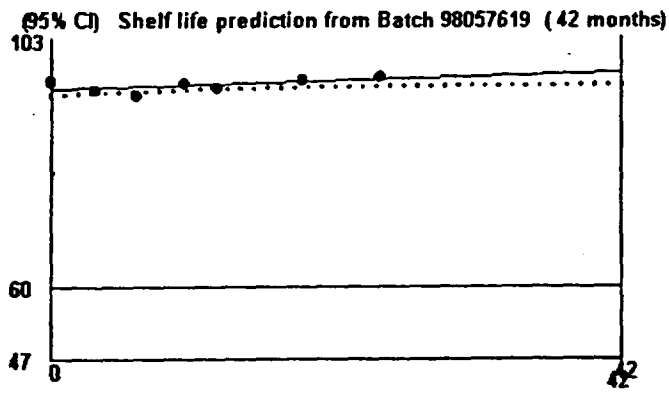
Dissolution in 15 minutes
60 mg strength: 30-count Bottles

98057614	42	Max Spec:	None
98057617	42	Min Spec:	60
98057619	42		

Separate intercepts and common slope



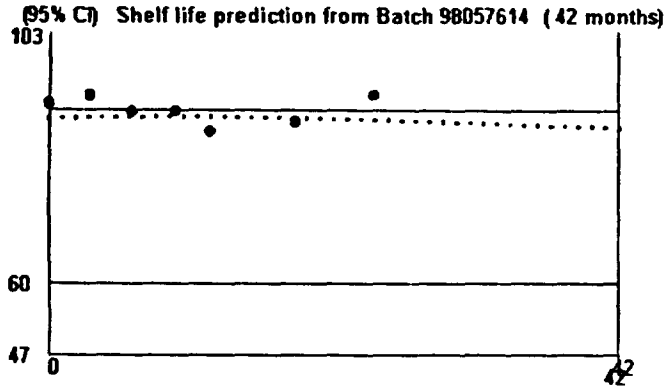


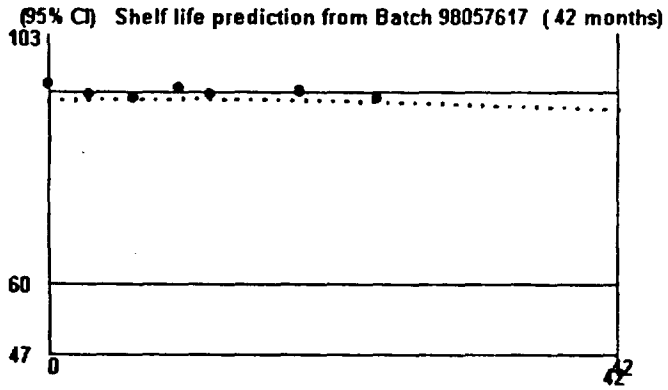


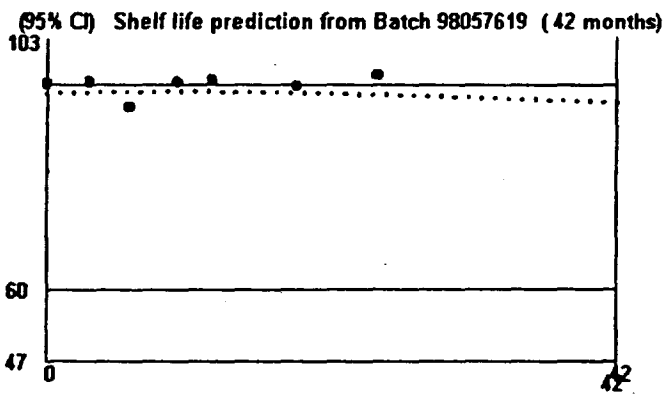
Dissolution in 15 minutes
60 mg strength: 3000-count Bottles

98057614	42	Max Spec:	None
98057617	42	Min Spec:	60
98057619	42		

Separate intercepts and common slope





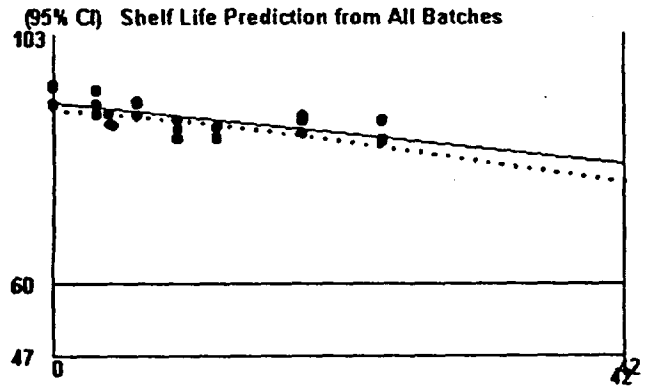


Dissolution in 15 minutes

120 mg strength: Blister Packages

All Batches	42	Max Spec:	None
		Min Spec:	60

Common intercept and common slope therefore data are pooled

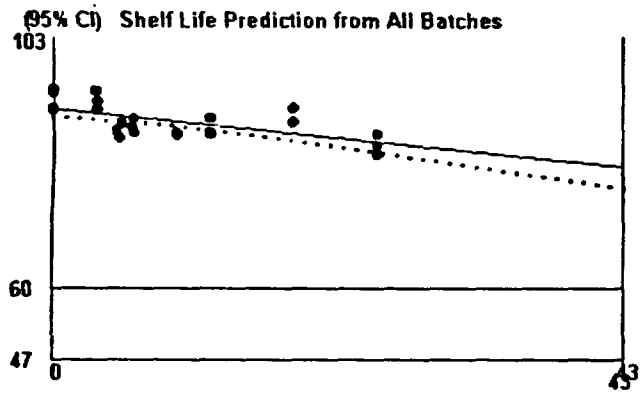


Dissolution in 15 minutes

120 mg strength: 30-count Bottles

All Batches	43	Max Spec:	None
		Min Spec:	60

Common intercept and common slope therefore data are pooled

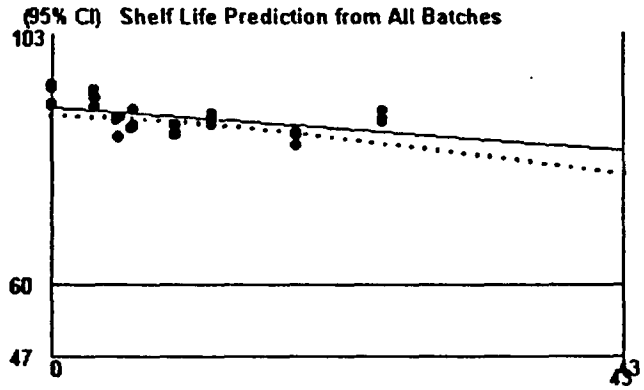


Dissolution in 15 minutes

120 mg strength: 3000-count Bottles

All Batches	43	Max Spec:	None
		Min Spec:	60

Common intercept and common slope therefore data are pooled

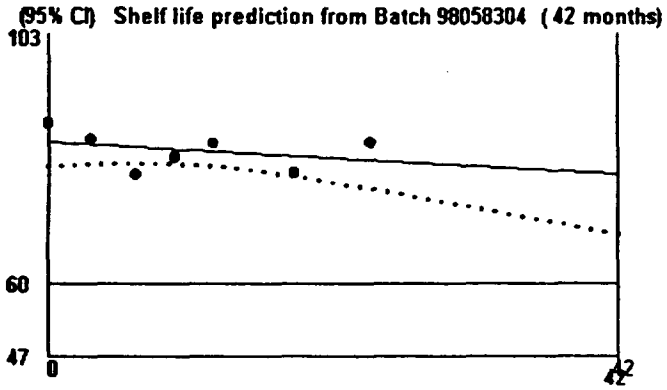


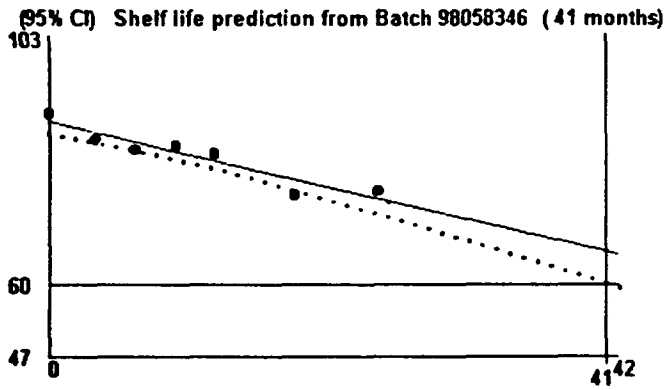
Dissolution in 15 minutes

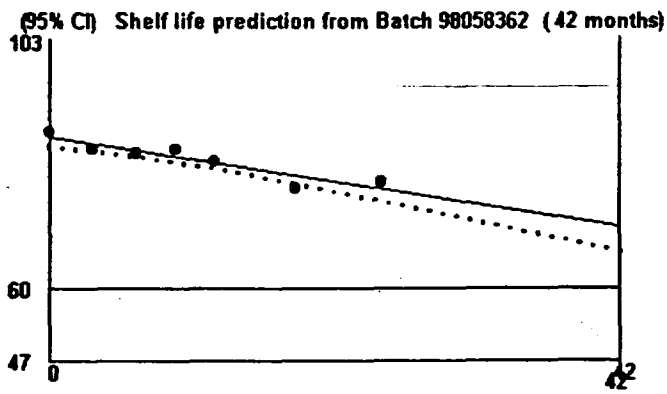
180 mg strength: Blister Packages

98058304	42	Max Spec:	None
98058346	41	Min Spec:	60
98058362	42		

Separate intercepts and separate slopes





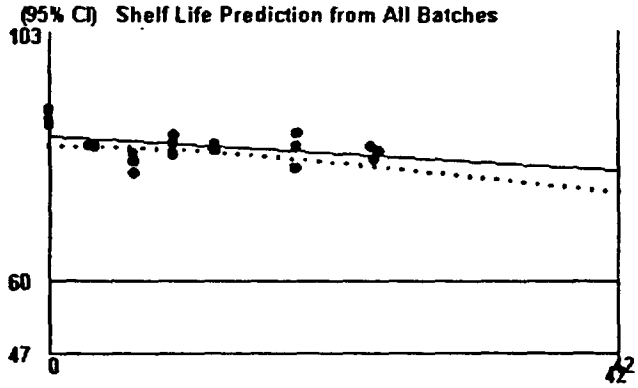


Dissolution in 15 minutes

180 mg strength: 30-count Bottles

All Batches	42	Max Spec:	None
		Min Spec:	60

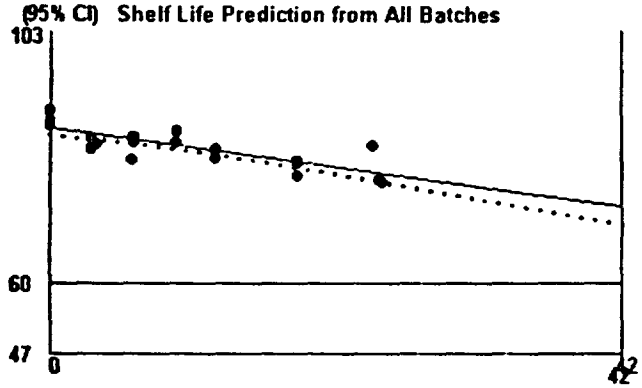
Common intercept and common slope therefore data are pooled



Dissolution in 15 minutes
180 mg strength: 3000-count Bottles

All Batches	42	Max Spec:	None
		Min Spec:	60

Common intercept and common slope therefore data are pooled

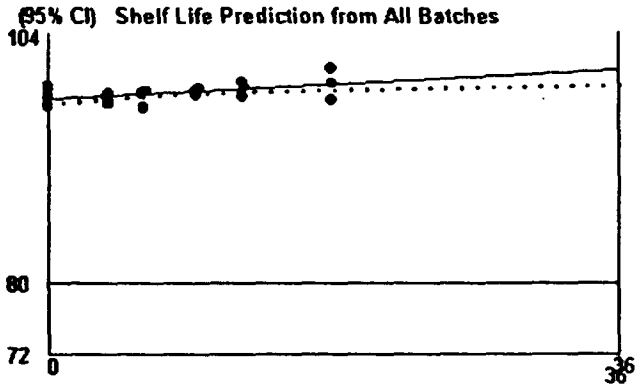


Dissolution in 45 Minutes

30 mg strength: Blister Packages

All Batches	36	Max Spec:	None
		Min Spec:	80

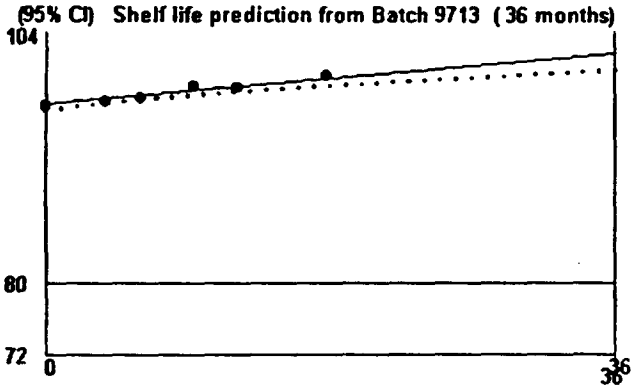
Common intercept and common slope therefore data are pooled

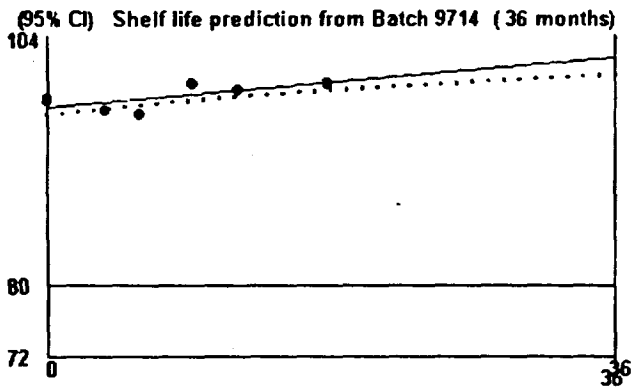


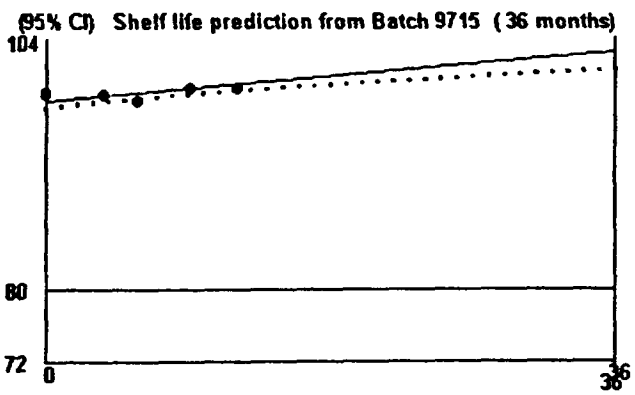
Dissolution in 45 Minutes
30 mg strength: 30-count Bottles

9713	36	Max Spec:	None
9714	36	Min Spec:	80
9715	36		

Separate intercepts and common slope





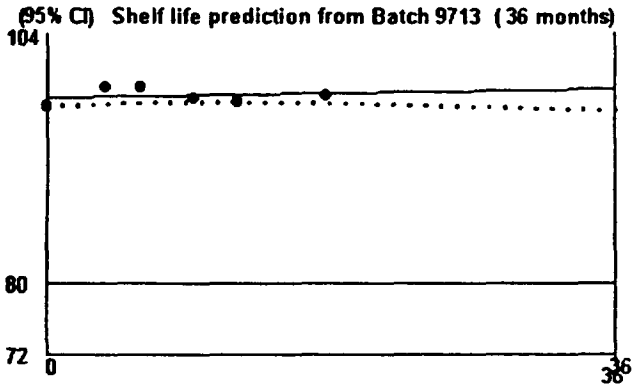


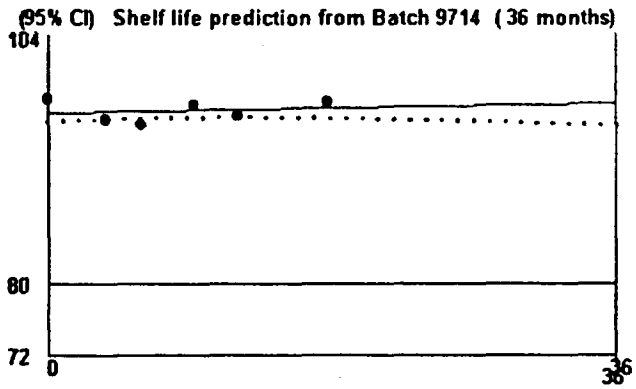
Dissolution in 45 Minutes

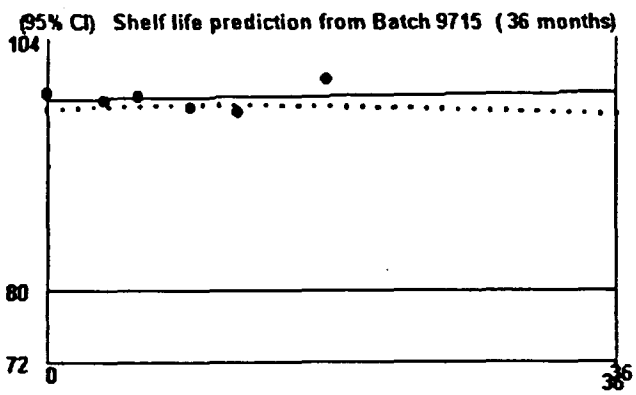
30 mg strength: 3000-count Bottles

9713	36	Max Spec:	None
9714	36	Min Spec:	80
9715	36		

Separate intercepts and common slope



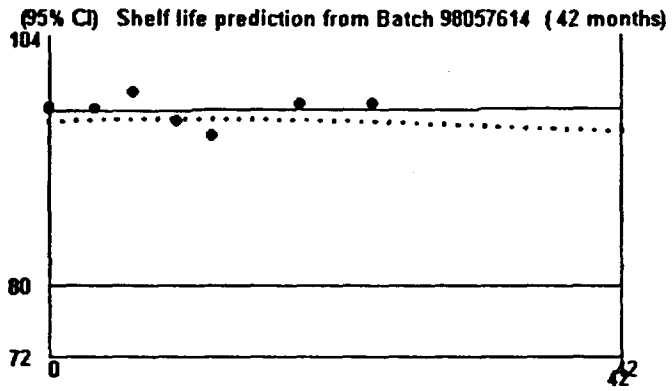


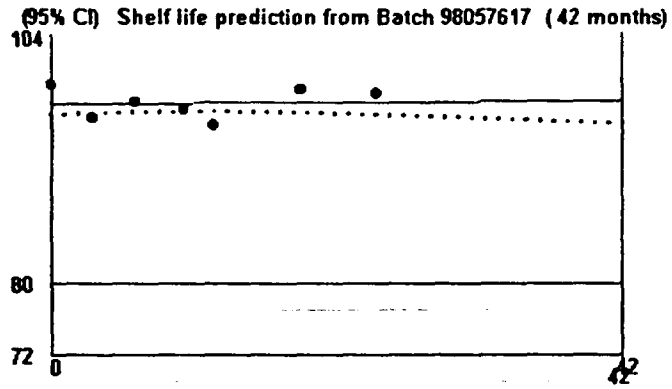


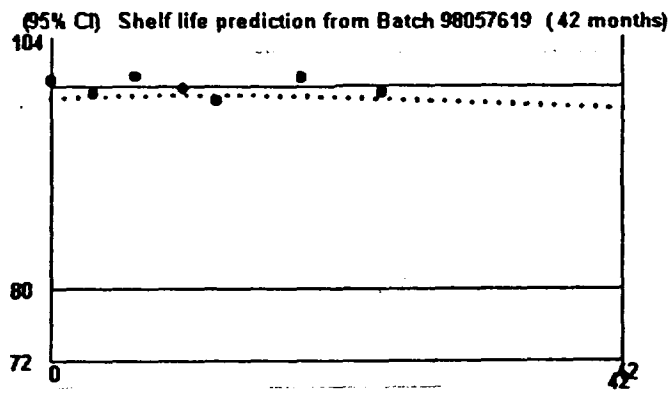
Dissolution in 45 Minutes
60 mg strength: Blister Packages

98057614	42	Max Spec:	None
98057617	42	Min Spec:	80
98057619	42		

Separate intercepts and common slope



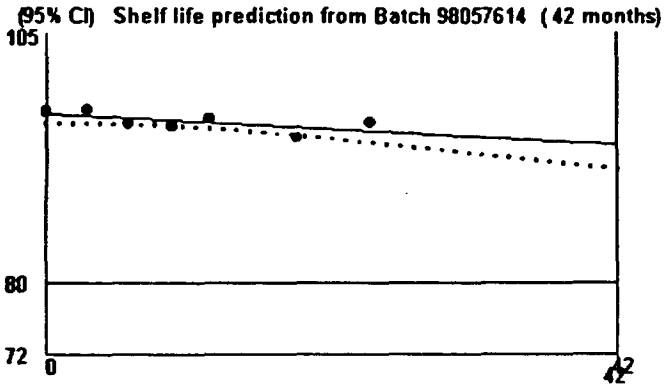


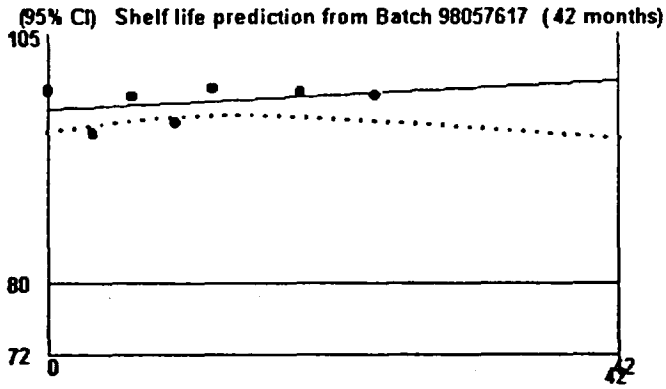


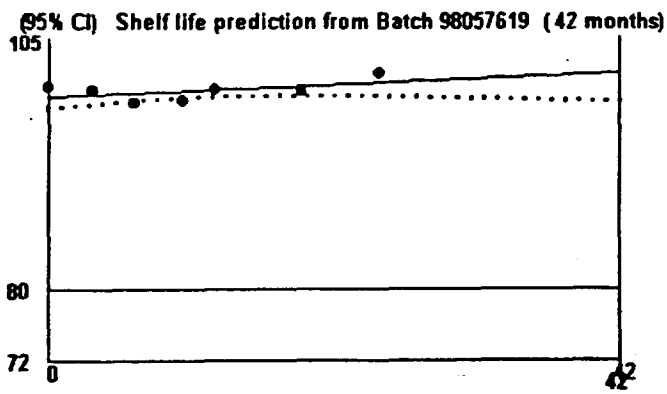
Dissolution in 45 Minutes
60 mg strength: 30-count Bottles

98057614	42	Max Spec:	None
98057617	42	Min Spec:	80
98057619	42		

Separate intercepts and separate slopes



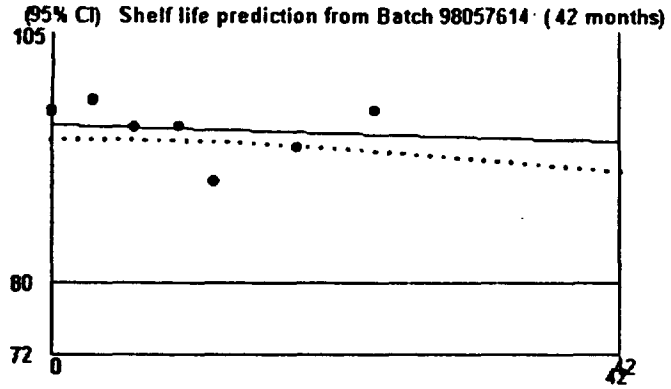


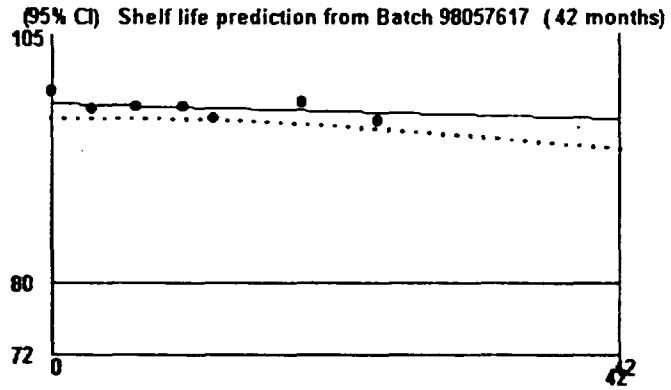


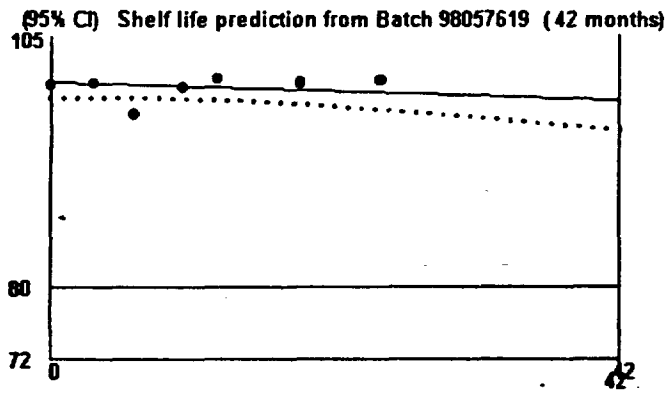
Dissolution in 45 Minutes
60 mg strength: 3000-count Bottles

98057614	42	Max Spec:	None
98057617	42	Min Spec:	80
98057619	42		

Separate intercepts and common slope



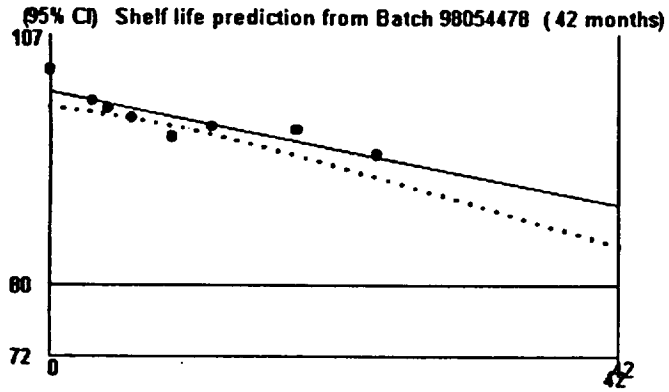


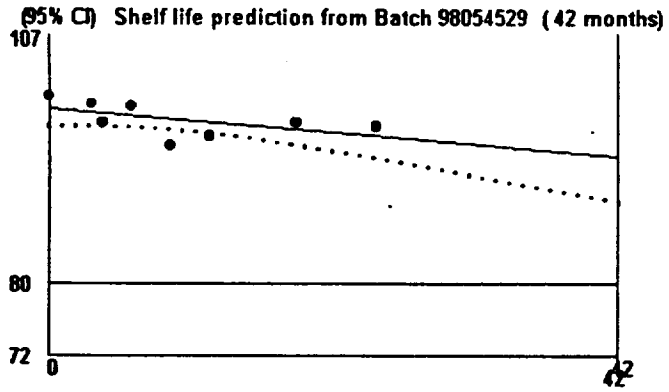


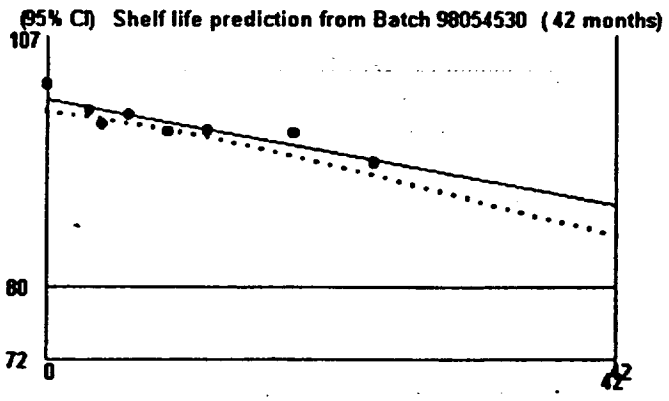
Dissolution in 45 Minutes
120 mg strength: Blister Packages

98054478	42	Max Spec:	None
98054529	42	Min Spec:	80
98054530	42		

Separate intercepts and separate slopes





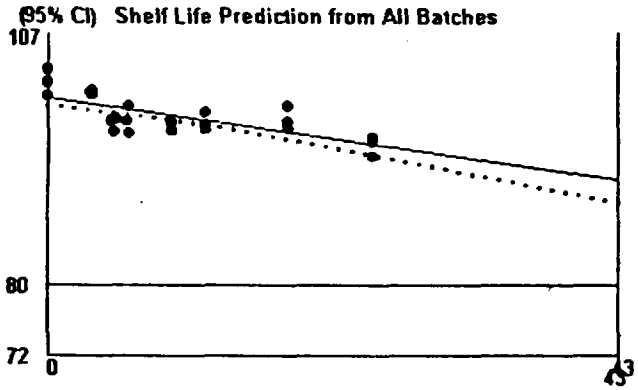


Dissolution in 45 Minutes

120 mg strength: 30-count Bottles

All Batches 43 Max Spec: None
Min Spec: 80

Common intercept and common slope therefore data are pooled

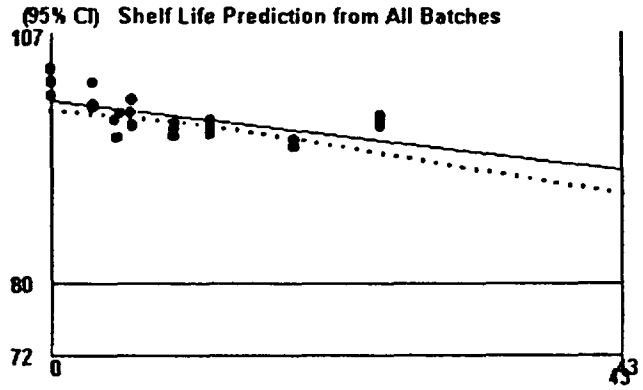


Dissolution in 45 Minutes

120 mg strength: 3000-count Bottles

All Batches	43	Max Spec:	None
		Min Spec:	80

Common intercept and common slope therefore data are pooled

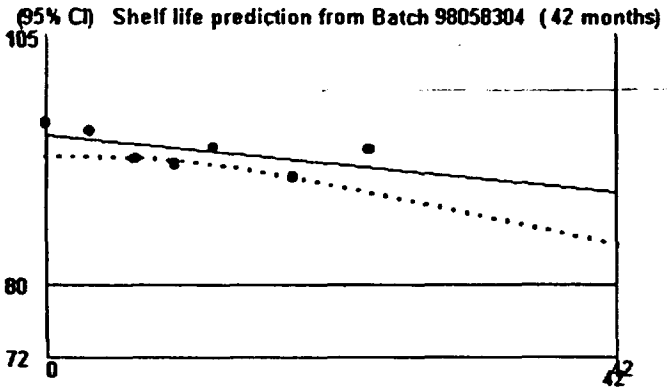


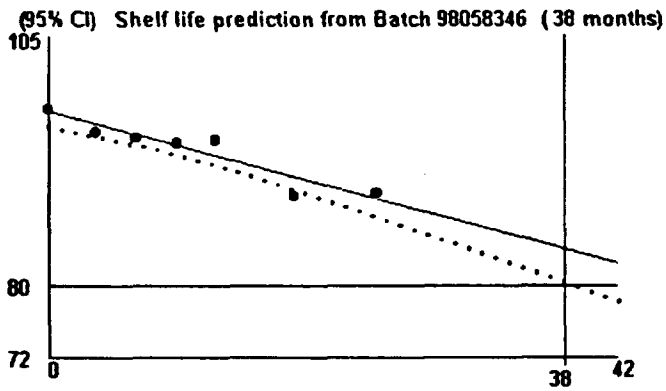
Dissolution in 45 Minutes

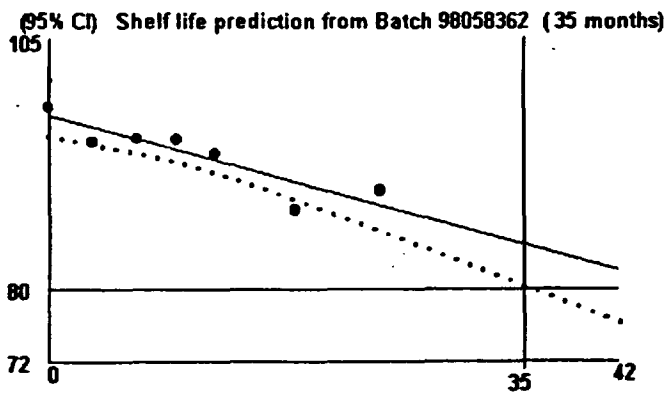
180 mg strength: Blister Packages

98058304	42	Max Spec:	None
98058346	38	Min Spec:	80
98058362	35		

Separate intercepts and separate slopes



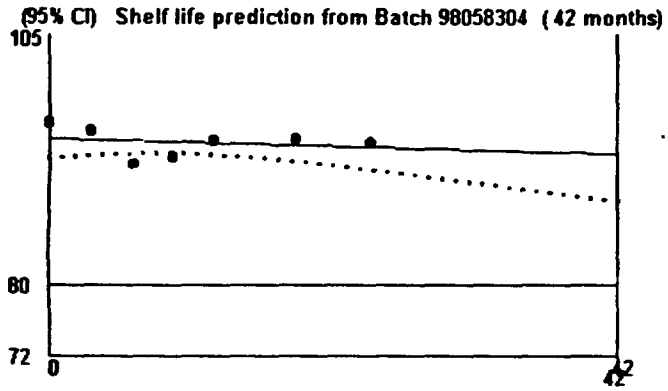


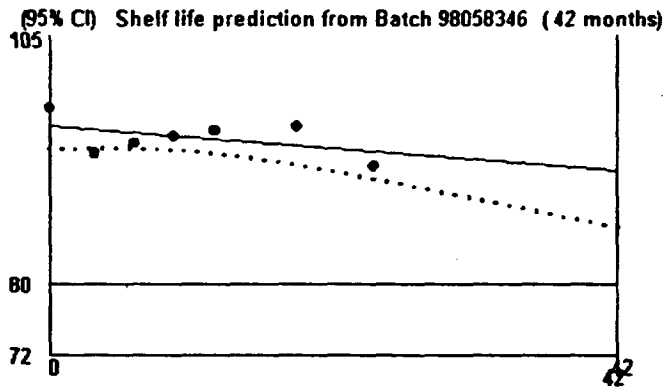


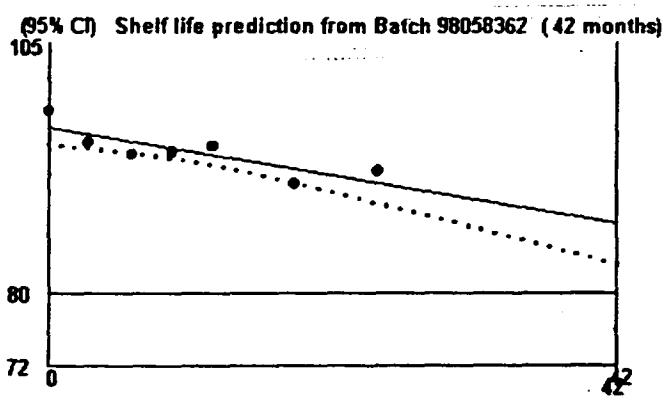
Dissolution in 45 Minutes
180 mg strength: 30-count Bottles

98058304	42	Max Spec:	None
98058346	42	Min Spec:	80
98058362	42		

Separate intercepts and separate slopes







STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY
ADDENDUM

Date: JUL 12 1999

NDA Number:	20-872
Applicant:	Hoechst Marion Roussel/ Quintiles
Name of Drug:	Allegra (fexofenadine HCl) (small tablets)
Statistical Reviewer:	Barbara Elashoff
Chemistry Reviewer:	Hossein Khorshidi
Documents Reviewed:	5/21/99 Vol 20.2

- Please refer to the original stability review for this NDA (dated July 12, 1999) regarding the method of analysis, specifications, test parameters and proposed expiry dates.

- The reviewing chemist requested additional analyses: dissolution at 30 minutes for the 180 mg tablets, 3000-count bottles using % as the lower specification limit.

- This reviewer entered the data from Volume 20.2. There were no occurrences of means of 12 timepoints. All means were calculated from 6 timepoints. See page 2 of the original stability review for further explanation.

- The results of the 24-month dissolution data at 30 minutes for the 180 mg strength tablets in the 3000-count bottles support the 30-month expiration date the sponsor proposed. These results are based on data extrapolation 6 months beyond the range of observed data.

APPEARS THIS WAY
ON ORIGINAL

Test of Batch Poolability (p-value cutpoint used: 0.25)

Variable Analyzed: 3000ct

Poolability	Pr(C)<0.25	Pr(C)>=0.25
Pr(B)<0.25	MODEL3	MODEL2
Pr(B)>=0.25	MODEL3	MODEL1

Model Determined: MODEL3

Poolability: The regression lines have separate slopes & intercepts.

11:15 Monday, July 12, 1999

SOURCE	SS	DF	MS	F	P
A	19.8224	4	4.9556	2.3831	0.0978
B	0.8600	2	0.4300	0.2068	0.8155
C	18.9624	2	9.4812	4.5595	0.0284
RESIDUAL	31.1917	15	2.0794		

C: Ho: sep. intercept com. slope, Ha: sep. intercept sep. slope
B: Ho: com. intercept com. slope, Ha: sep. intercept com. slope
A: Ho: com. intercept com. slope, Ha: sep. intercept sep. slope

Source: c:\elashoff\Poolable.sd2

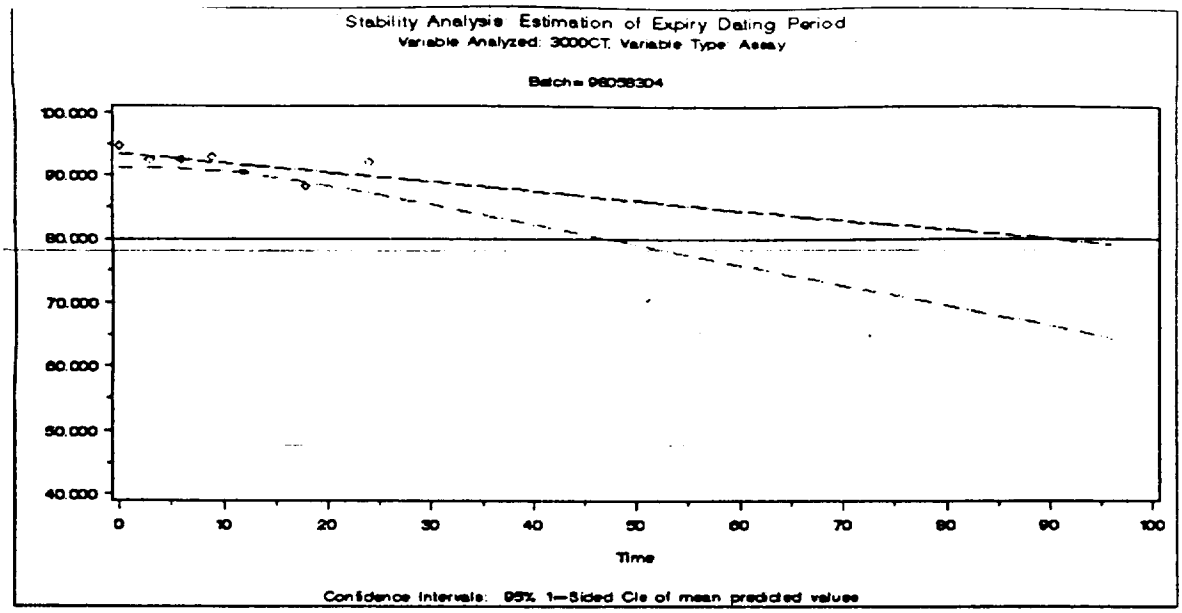
11:15 Monday, July 12, 1999

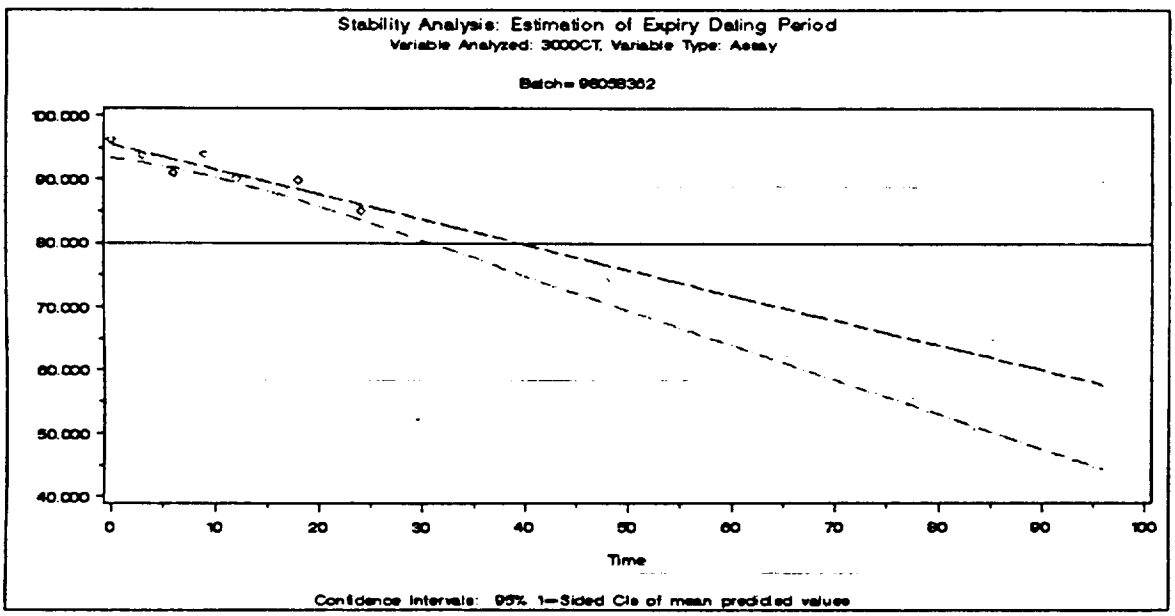
Analysis of Stability
Estimation of Expiry Dating Period
Variable Analyzed: 3000ct
Model Determined: MODEL3

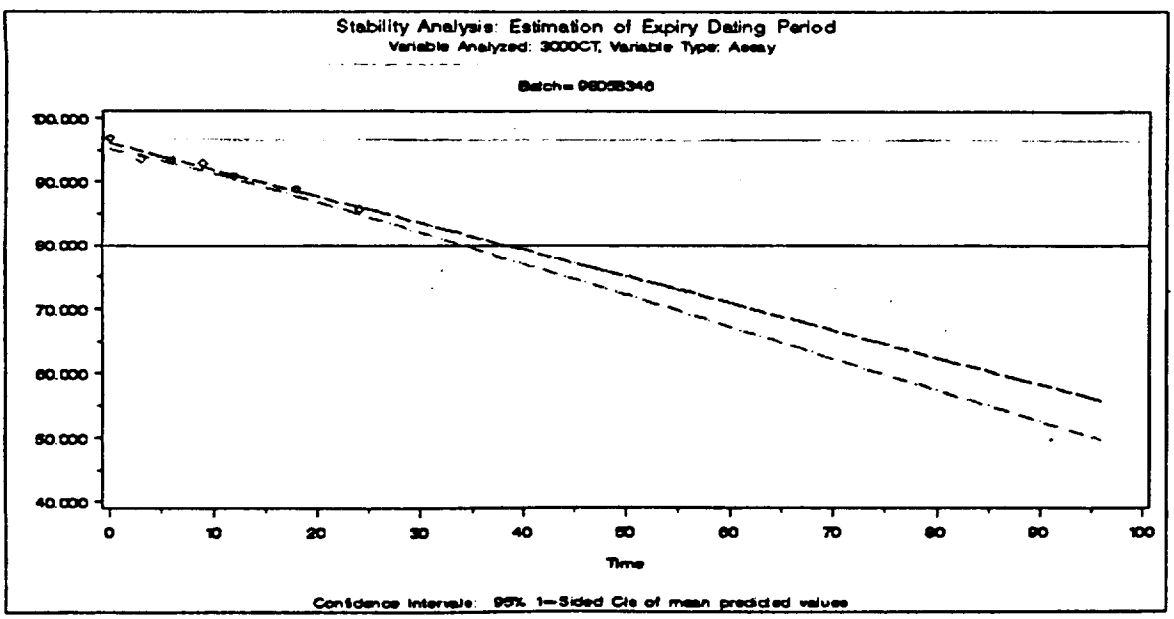
Poolability: The regression lines have separate slopes & intercepts.

------- Fitted Line -------	Batch	Estimated Expiry Period
Y=93.4725 + -0.1501 * Time	98058304	47
Y=96.0910 + -0.4200 * Time	98058346	34
Y=95.4832 + -0.3928 * Time	98058362	30
	-MIN. TIME-	30

Specification Limits: Confidence Intervals: 95% 1 - Sided CIs


Stability Analysis: Estimation of Expiry Dating Period
Variable Analyzed: 3000CT, Variable Type: Assay
Batch= 98038304
100.000
90.000
80.000
70.000
60.000
50.000
40.000
0
10
20
30
40
50
60
70
80
90
100
Time
Confidence Intervals: 95% 1-Sided CIs of mean predicted values


Stability Analysis: Estimation of Expiry Dating Period
Variable Analyzed: 3000CT, Variable Type: Assay
Batch= 98038302
100.000
90.000
80.000
70.000
60.000
50.000
40.000
0
10
20
30
40
50
60
70
80
90
100
Time
Confidence Intervals: 95% 1-Sided CIs of mean predicted values


Stability Analysis: Estimation of Expiry Dating Period
Variable Analyzed: 3000CT, Variable Type: Assay
Batch= 98038346
100.000
90.000
80.000
70.000
60.000
50.000
40.000
0
10
20
30
40
50
60
70
80
90
100
Time
Confidence Intervals: 95% 1-Sided CIs of mean predicted values

/S/

Barbara Elashoff

/S/ 8/12/99

Concur: Dr. Lin

cc:

Orig. NDA

HFD-570 / Division File

HFD-570 / LCobbs, HKhorshidi, GPoochikian, Y-YChiu, AWorobec

HFD-715 / Division File, SWilson, KLin