References

Huber, P.J. "The behavior of maximum likelihood estimates under nonstandard conditions," in *Proceedings of the Fifth Berkeley Symposium in Mathematical Statistics and Probability*, Berkeley: University of California Press, 221-233, 1967.

Lan, K.K.G. and Zucker, D.M. "Sequential monitoring of clinical trials: the role of information and Brownian motion," *Statistics in Medicine*, 12: 753-765, 1993.

Little, R.J.A. "Pattern-mixture models for multivariate incomplete data," *JASA*, 88: 125-134, 1993.

Little, R.J.A. "Modeling the drop-out mechanism in repeated-measures studies," *JASA*, 90: 1112-1121, 1995.

Liang, K.Y. and Zeger, S.L. "Longitudinal data analysis using generalized linear models," *Biometrika*, 73: 13-22, 1986.

White, H. "Maximum likelihood estimation of misspecified models," *Econometrica*, 50: 1-25, 1982.

Concur:

Dr. Chen

Dr. Chi

cc: Archival NDA 20-886

HFD-150 / Ms. A. Chapman, Project Manager

HFD-150 / Dr. R. White

HFD-150 / Dr. J. Johnson

HFD-344 / Dr. B. Barton

HFD-710 / Dr. G. Chi

HFD-710 / Dr. G. Chen

HFD-710 / Dr. D. Smith

HFD-710 / Chron

Smith / 17 November 1998 / Word / c:\data\wordfiles\20886.doc

This review consists of 15 pages of text.

Statistical Review and Evaluation
Stability Review of Panretin 0.1% Gel

(ADDENDUM)

DATE: DEC -7 1998

NDA #: 20-886

DATE CDER RECEIVED: September 24, 1998 (Sponsor's submitted date: 9/23/98).

DATE DATAT FOR ADDENDUM WAS AVAILABLE: December 01, 1998.

APPLICANT: Ligand Pharmaceuticals.

NAME OF DRUG: Panretin® (Alitretinoin) Gel 0.1%.

DOCUMENTS REVIEWED: Addendum Data in addition to Vol. 1 (Vol. 1 of 1).

INDICATION: First-Line Topical Treatment of Cutaneous Lesions in Patients With Acquired AIDS-Related Kaposi's Sarcoma.

This is an addendum to this reviewer's original stability review of Panretin 0.1% gel (NDA 20-886), completed on November 4, 1998.

I. BACKGROUND

This reviewer thinks that it is appropriate to give a brief explanation for the reason for this addendum. At the time of original review there was no sufficient amount of data available for Batches 9709003 and 9711005 to make any reliable estimation of expiry dating period. These two batches were stored under the condition of at 25^{0}C/60% RH, without 5% manufacturing overage. The available data at the time of original review was storage data of 6 month for Batch 9711005 and 9 month for Batch 9709003. Based on the given data, the estimated expiry dating period was **14 months** for Batch 9711005 and **23 month** for Batch 9709003. In this regard, as expressed by Dr. Sung Kim[1] to Dr. Gang Chen[2], the main concern is the stability of batches without 5% manufacturing overage. Therefore, based on the present stability results, Parnetin is not approvable.

1- Review chemist, from the Division of Oncology Drug Products (HFD-150).

2 - The Statistical Team Leader from the Division of Biometrics 1 (HFD-710), assigned to the Division of Oncology Drug Products (HFD-150).

In the original stability review, this reviewer commented that:

"The sponsor needs to provide, sufficiently, further stability data on batches (6 to 8 batches) without 5% manufacturing overage. Also, the time points at which the observations are collected should go beyond 24 months (24-30 months)."

The above view was conveyed to the sponsor, and in response the sponsor provided further potency data. The new data consist of extension to only ONE extra potency observation for each Batch 9711005 and 9709003. Namely, 1 observation at Month 9 Batch 9711005 (previously 6 months data) and 1 observation at Month 12 for Batch 9709003 (Previously 9 months data).

I. REVIEW OF NEW DATA SET

The stability analysis results for the new data for the Batch 9711005 and 9709003 are presented below. For the detail discussion the readers my consult this reviewer's original review (completed 11/4/98).

Poolability Analysis

The result of conducting a test for the following set of null and alternative hypothesis has produced the P-value of 0.0150.

Ho: Common Intercept and Common Slopes vs. Ha: Separate Intercept and Common Slopes.

Therefore, separate regression line for each batch with common slope but different intercept was fitted to the data of each batch, for the estimation of expiry dating period.

Estimation of Expiry Dating Period

The analysis for the estimation of the expiry dating period for each batch produced the following results. The readers may also consult the appendix for the graphical representation of the estimation procedures.

Batch	Specifications	Fitted Line	Expiry Dating Period (in month)
9711005	90% to 110%	Potency = 100.98 - 0.1675*Month	30
9709003	90% to 110%	Potency = 99.13 - 0.1675*Month	24

III. COCLUSION

The addition of **one data point** at Month **9** for Batch 9711005 and **one data point** at Month **12** for Batch 9709003 have produced the estimate of expiry dating period of 30 and 24 months respectively. It seems that the results have provided a support for the claimed expiry dating period of 24 month, however, due to lack of sufficient data this reviewer believes that the support is very marginal and the results should be interpreted with caution.

/S/

Kooros Mahjoob, Ph.D.
Mathematical Statistician

This review consists of 2 pages and one appendix consisting of 1 table and 2 figures.

Concur:

Dr. Chen /S/

Dr. Chi /S/ 12/07/98

CC:
Arch. NDA 20-886/Addendum Review

HFD-150
HFD-150/Dr. Kim
HFD-150/Dr. Wood
HFD-150/Mrs. Chapman, Project Manager
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Dr. Mahjoob
HFD-710/Chron.

K. Mahjoob: 4-5301; first draft 12/03/98.

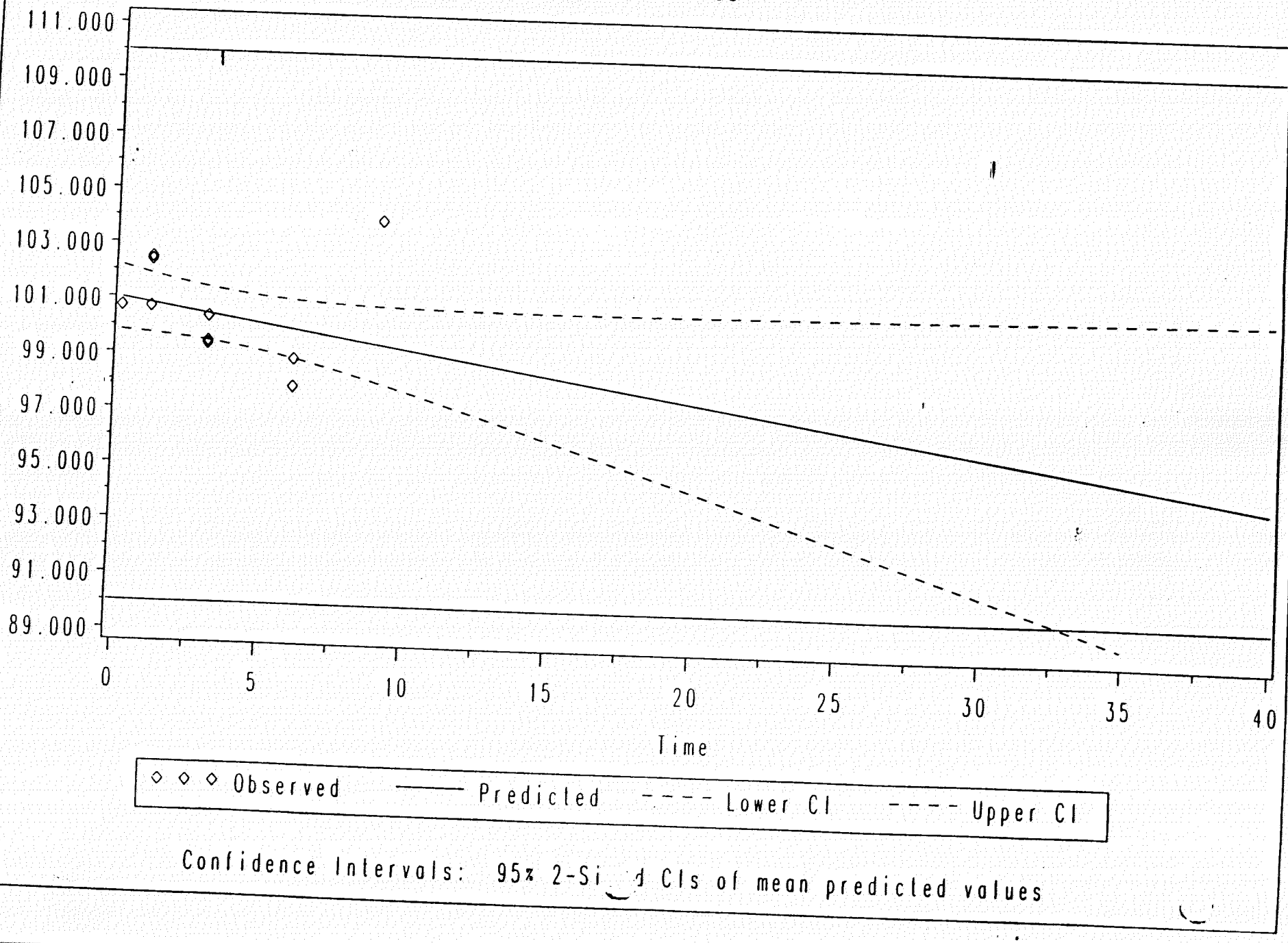
APPENDIX

Print of Data

Batch	Month	Assay
9711005	0	
9711005	1	
9711005	1	
9711005	1	
9711005	3	
9711005	3	
9711005	3	
9711005	6	
9711005	6	
9711005	6	
9711005	9	
9709003	0	
9709003	0.8	
9709003	0.8	
9709003	0.8	
9709003	1.8	
9709003	1.8	
9709003	1.8	
9709003	2.9	
9709003	2.9	
9709003	2.9	
9709003	4	
9709003	4	
9709003	4	
9709003	6	
9709003	6	
9709003	6	
9709003	9	
9709003	9	
9709003	9	
9709003	12	

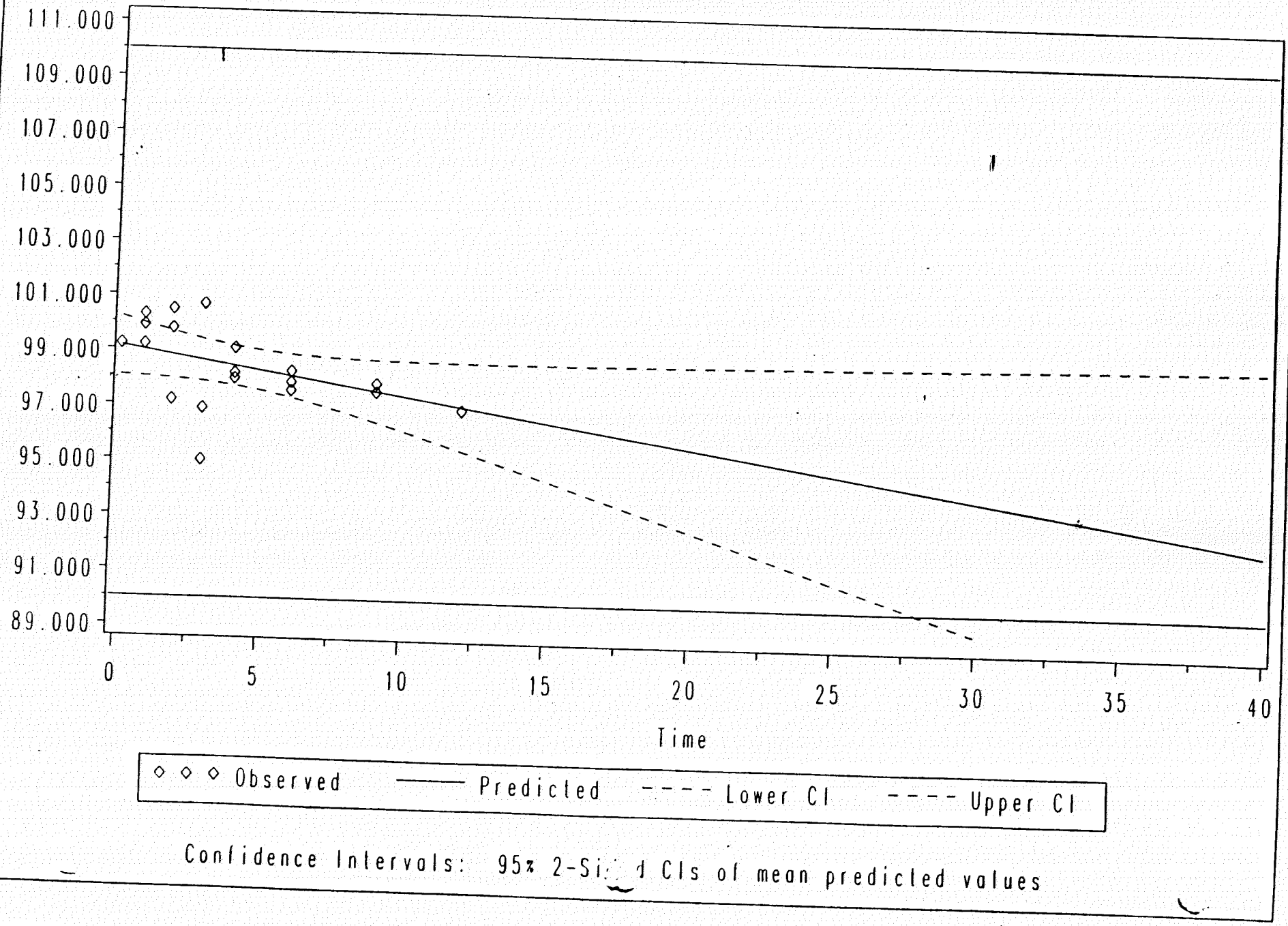
Stability Analysis: Estimation of Expiry Dating Period

Variable Analyzed: POTENCY
Variable Type: Assay
Batch=9711005



Stability Analysis: Estimation of Expiry Dating Period

Variable Analyzed: POTENCY
Variable Type: Assay
Batch=9709003



Confidence Intervals: 95% 2-Sided CIs of mean predicted values

A. Chapman

Statistical Review and Evaluation
Stability Review of Panretin 0.1% Gel

(ADDENDUM II)

DEC 21 1998

DATE:

NDA #: 20-886

DATE CDER RECEIVED: September 24, 1998 (Sponsor's submitted date: 9/23/98).

DATE DATA FOR ADDENDUM WAS AVAILABLE: December 01, 1998.

APPLICANT: Ligand Pharmaceuticals.

NAME OF DRUG: Panretin® (Alitretinoin) Gel 0.1%.

DOCUMENTS REVIEWED: Addendum Data in addition to Vol. 1 (Vol. 1 of 1).

INDICATION: First-Line Topical Treatment of Cutaneous Lesions in Patients With Acquired AIDS-Related Kaposi's Sarcoma.

This is the second addendum to this reviewer's original stability review of Panretin 0.1% gel (NDA 20-886), completed on November 4, 1998. The first addendum was completed on December 7, 1998.

I. BACKGROUND

As a background, this is the second to the original stability review of Panretin. This addendum is pertained to the estimation of the expiry dating period relative to "**Total Related Substance**" of Batches 9709003 and 9711005. The reason for this addendum is that, at the time of original review there was no sufficient amount of data available for these two batches to make a reliable estimation of expiry dating period. The expiry dating period, relative to the "LGD 1057 Assay" was assessed in the first addendum.

These two batches were stored under the condition of 25^0C/60% RH, without 5% manufacturing overage. The available data at the time of original review was storage data of 6 month for Batch 9711005 and 9 month for Batch 9709003. Based on the given data, the estimated expiry dating period, relative total related substance, with specification limits of ( )% was **58 months** for Batch 9711005 and **30 month** for Batch 9709003.

As was commented in the original review, the results from these two batches were not reliable, because of the lack of sufficient data.

The following comment was made in the original review.

The sponsor needs to provide, sufficiently, further stability data on batches (6 to 8 batches) without 5% manufacturing overage. Also, the time points at which the observations are collected should go beyond 24 months (24-30 months)."

As expressed by Dr. Sung Kim[1] to Dr. Gang Chen[2], the main concern is the stability of batches without 5% manufacturing overage (which included Batches 9711005 and 9709003). Therefore, based on the lack of strong support from the results of these two batches, Panretin may not be approvable.

As a conclusion, the sponsor, provided further total related substances data, which consist of extension to only **ONE** extra observation for each Batch 9711005 and 9709003. Namely, 1 observation at Month 9 for Batch 9711005 (previously 6 months data) and 1 observation at Month 12 for Batch 9709003 (Previously 9 months data).

Dr. Kim requested the stability evaluation of these two batches with specification limits of % as with specification limits of %.

I. REVIEW OF NEW DATA SET

The stability analysis results for the new data for Batches 9711005 and 9709003 are presented below. For the detailed discussion the readers my consult this reviewer's original review (completed 11/4/98).

Poolability Analysis

The result of conducting a test for the set of null and alternative hypotheses:

(1) Ho: Common Intercept and Common Slopes vs. Ha: Separate Intercept and Common Slopes

produced a P-value of 0.4402. Thus, the null hypothesis (1) was not rejected.

Also, the result of conducting a test for the set of null and alternative hypotheses:

(2) Ho: Common Intercept and Common Slopes vs. Ha: Separate Intercept and Separate Slopes

produced a P-value of 0.3633. Thus, the null hypothesis (2) was not rejected.

1- Review chemist, from the Division of Oncology Drug Products (HFD-150).

2 - The Statistical Team Leader from the Division of Biometrics 1 (HFD-710), assigned to the Division of Oncology Drug Products (HFD-150).

Therefore, the program pooled the data of the two batches together to produce one estimate for the expiry dating period as follows. The readers may also consult the appendix for the graphical representation of the estimation procedures.

Specifications	Fitted Line for the Pooled Data	Expiry Dating Period (in month)
%	Total Related Substance = 0.1227 + 0.0515*Month	43
%		51

III. COCLUSION

After the addition of **one data point** at Month **9** for Batch 9711005 and **one data point** at Month **12** for Batch 9709003, the results resulted in maintaining the null hypotheses (1) and (2). Thus, the data of the two batches were combined to produce one expiry dating period for each of specification limits of % and %. The analysis produced an estimate of expiry dating period of **43** and **51** months for the specification limits % and %, respectively.

Although, it seems that the results have provided a support for the claimed expiry dating period of 24 month, however, still, as this reviewer believes, due to lack of sufficient data the support is not concrete and results should be interpreted with a caution.

/S/

Kooros Mahjoob, Ph.D.
Mathematical Statistician

This review consists of 3 pages and one appendix consisting of 1 table and 2 figures.

Concur:

/S/ 12/21/98

Dr. Chen

/S/ acting division direct, 12/21/98

Dr. Chi

(signature for Dr. G. Chi)

CC:
Arch. NDA 20-886/Addendum II Review

HFD-150
HFD-150/Dr. Kim
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HFD-150/Mrs. Chapman, Project Manager
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Dr. Mahjoob
HFD-710/Chron.

K. Mahjoob: 4-5301; first draft 12/16/98/final version 12/21/98.

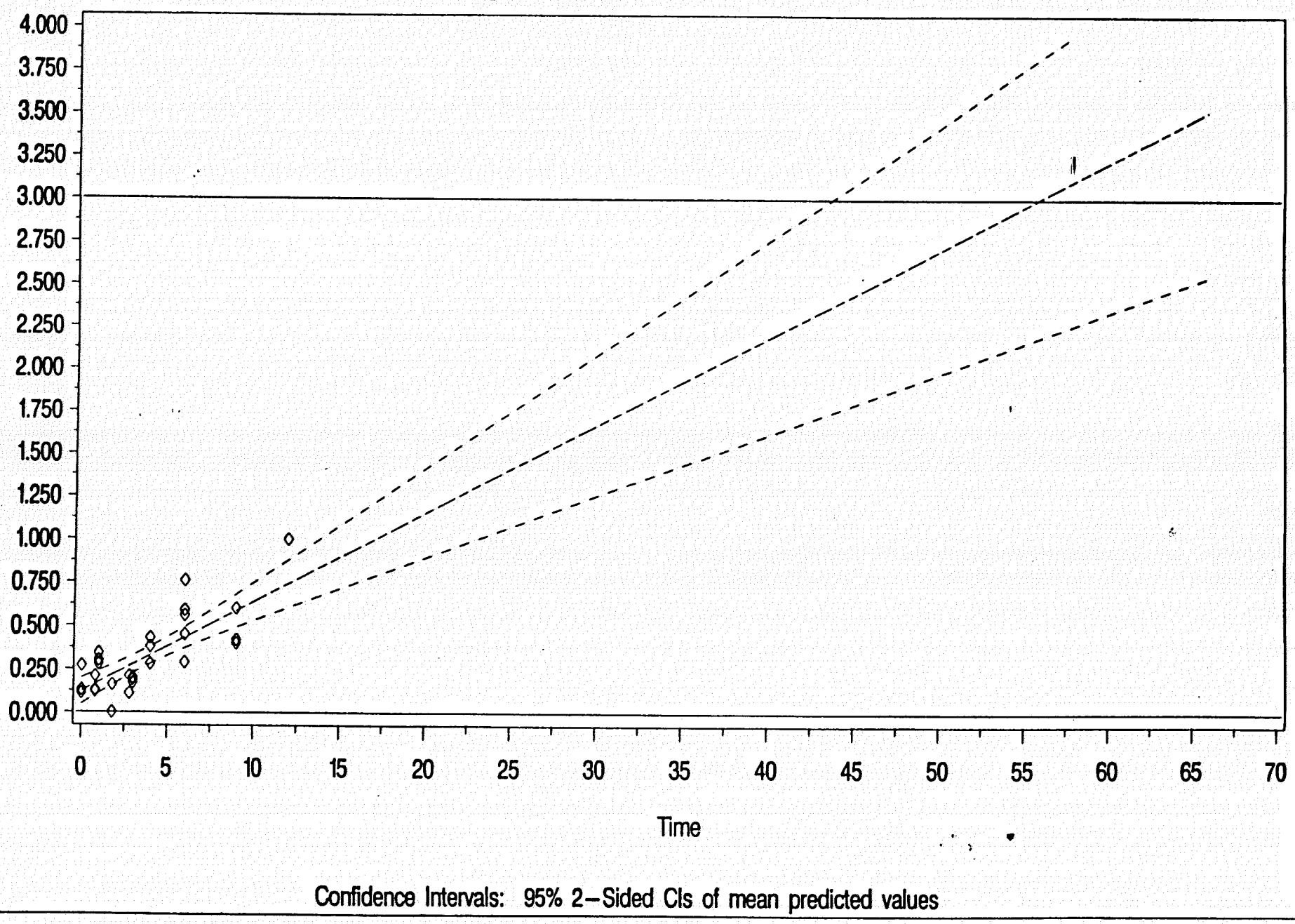
APPENDIX

Variable	Batch	Month	Value
TOTAL RELATED SUBSTANCE	9711005	0	0.27
TOTAL RELATED SUBSTANCE	9711005	1	0.3
TOTAL RELATED SUBSTANCE	9711005	1	0.28
TOTAL RELATED SUBSTANCE	9711005	1	0.34
TOTAL RELATED SUBSTANCE	9711005	3	0.17
TOTAL RELATED SUBSTANCE	9711005	3	0.19
TOTAL RELATED SUBSTANCE	9711005	3	0.2
TOTAL RELATED SUBSTANCE	9711005	6	0.29
TOTAL RELATED SUBSTANCE	9711005	6	0.45
TOTAL RELATED SUBSTANCE	9711005	6	0.56
TOTAL RELATED SUBSTANCE	9711005	9	0.6
TOTAL RELATED SUBSTANCE	9709003	0	0.11
TOTAL RELATED SUBSTANCE	9709003	0	0.13
TOTAL RELATED SUBSTANCE	9709003	0	0.27
TOTAL RELATED SUBSTANCE	9709003	0.8	0.21
TOTAL RELATED SUBSTANCE	9709003	0.8	0.12
TOTAL RELATED SUBSTANCE	9709003	0.8	0.13
TOTAL RELATED SUBSTANCE	9709003	1.8	0.16
TOTAL RELATED SUBSTANCE	9709003	1.8	0
TOTAL RELATED SUBSTANCE	9709003	1.8	0
TOTAL RELATED SUBSTANCE	9709003	2.8	0.21
TOTAL RELATED SUBSTANCE	9709003	2.8	0.21
TOTAL RELATED SUBSTANCE	9709003	2.8	0.11
TOTAL RELATED SUBSTANCE	9709003	4	0.38
TOTAL RELATED SUBSTANCE	9709003	4	0.43
TOTAL RELATED SUBSTANCE	9709003	4	0.28
TOTAL RELATED SUBSTANCE	9709003	6	0.59
TOTAL RELATED SUBSTANCE	9709003	6	0.76
TOTAL RELATED SUBSTANCE	9709003	6	0.45
TOTAL RELATED SUBSTANCE	9709003	9	0.42
TOTAL RELATED SUBSTANCE	9709003	9	0.4
TOTAL RELATED SUBSTANCE	9709003	9	0.42
TOTAL RELATED SUBSTANCE	9709003	12	1

Stability Analysis: Estimation of Expiry Dating Period

Variable Analyzed: Total Related Substance

Pooled Data of Batches 9709003 and 9711005
Specification Limits of %

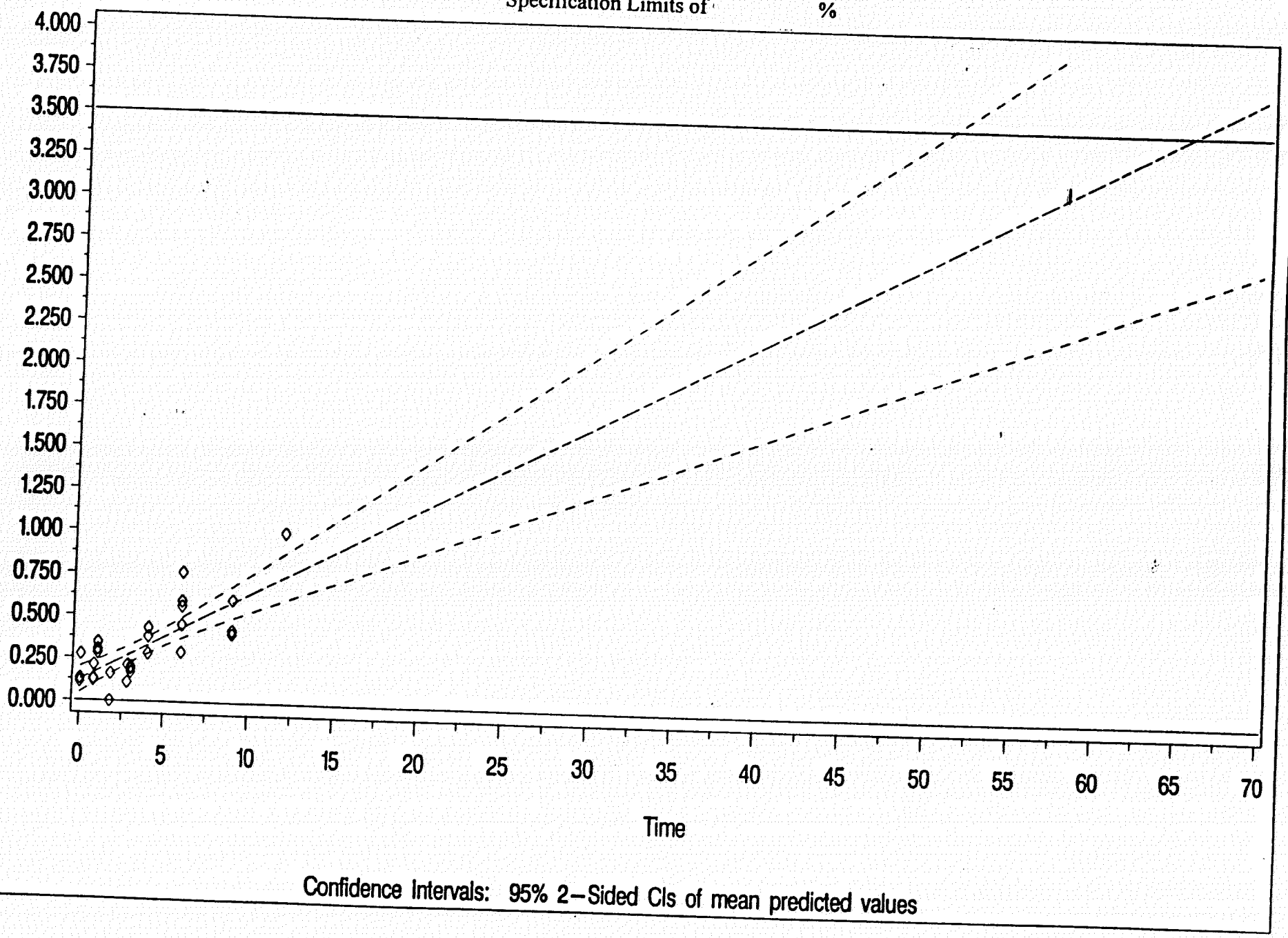


Confidence Intervals: 95% 2–Sided CIs of mean predicted values

Stability Analysis: Estimation of Expiry Dating Period

Variable Analyzed: Total Related Substance

Pooled Data of Batches 9709003 and 9711005
Specification Limits of %



Confidence Intervals: 95% 2–Sided CIs of mean predicted values