

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-886**

**STATISTICAL REVIEW(S)**

**Statistical Review and Evaluation  
Stability Review of Panretin 0.1% Gel**

NOV 4 1998

**DATE:**

**NDA #:** 20-886

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

**APPLICANT:** Ligand Pharmaceuticals.

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

**DOCUMENTS REVIEWED:** Vol. 1 (Vol. 1 of 1).

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

The review of the stability of Panretin 0.1% gel (NDA 20-886) is requested by Dr. Sung Kim, Review Chemist from the Division of Oncology Drug Products (HFD-150).

**I. INTRODUCTION**

The stability data of Panretin (Alitretinoin [LGD1057]) 0.1% gel (Panretin from heron), for which the statistical stability review is requested, is resulted from the conduct of 3 stability protocol (1, 2, and 3) consisting of 10 batches. The stability studies consist of Potency evaluation, using assay method and Total Related Substance evaluation, under various storage and packaging conditions<sup>1</sup>. Table 1 summarizes the layout of the stability studies. The individual observations at each time are displayed in Tables A.1 (Appendix A), B1 (Appendix B), and C1 (Appendix C), for each batch. The readers may also consult the fitted regression line figures, to the data of each batch, presented in appendices A - C.

For all batches, the packaging is aluminum tube, proposed storage temperature is at 20°C - 25°C, and the expiration duration date under the 25°C is claimed to be 24 months. Out of 10 batches, 8 were Panretin with 5% manufacturing overage and 2 without 5% manufacturing overage, as specified in the Table 1.

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1- There were other tests such as package appearance, antioxidant assay, viscosity and microbiology assay, were performed during the stability studies. The statistical review of these tests is not requested.



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### III. SPONSOR'S RESULTS AND CONCLUSION

The sponsor's results (from Pages 127 to 132 of the submission) are summarized in Tables 2 - 4 and consist of:

1. The potency results of 8 Panretin batches with 5% manufacturing overage stored at 25°C/60% RH, with the specification limits of 95% to 110% (see Table 2). We refer to this case "Eight-Batch-Potency Results".

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4- Mathematically it is equivalent to fit the model:

$$(3) \quad Y_j = \mu + T_j + \epsilon_i; \quad i=1, 2, \dots, I$$

<sup>5</sup> - After consultation with Ms. Roswitha Kelly, the Division of Biometrics I Pre Clinical Coordinator, she mentioned that our approach is, if a variable, has two specification limits, the two sided confidence interval is used and either band can set the expiration dating period.

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2. The potency results of 2 Panretin batches without 5% manufacturing overage stored at 25°C/60% RH, with the specification limits of 90% to 110% (see Table 3). We refer to it as "Two-Batch-Potency Results".
3. The total related substance results of 7 Panretin batches without 5% manufacturing overage stored at 25°C/60% RH, with 6°C data a time zero and with the specification limits of % (see Table 4). We call this case as "Seven-Batch-Total-Related-Substance Results".

**III.1 Stability and Expiry Dating Period Results**

**Eight-Batch-Potency Results**

Table 2 presents the stability analysis results of these 8 batches, which shows that, within the 24 months of claimed expiry dating period, for all 8 batches, the potency of Panretin 0.1% gel stays well within the specification limit of 95% to 110%. The minimum of expiry dating period is 46 month determined by Batch 9702002.

**TABLE 2**  
 Point Estimate and Lower 95% Predicted Potency Value and Estimated Expiry dating Period of 8 Panretin Batches With 5% Manufacturing Overage Stored at 25°C/60% RH (Specification Limits of 95% to 110%)

Batch ID	Point Estimate and Lower 95% Predicted Values of Potency				Predicted Expiration Date (Month)
	18 Month		24 Month		
	Point Estimate	L_95% Predicted	Point Estimate	L_95% Predicted	
9510005	104.4	103.9	104.2	103.6	84
9608013	103.9	103.4	103.1	102.4	65
9702002	104.1	102.7	103.4	101.1	46
9510001	103.4	102.8	102.7	102.0	62
9511005	103.1	102.6	102.5	101.9	69
9608005	103.1	102.5	102.2	101.2	53
9609002	104.1	103.3	104.2	102.9	84
9609007	104.0	103.2	103.9	102.5	84

**Two-Batch-Potency Results**

Table 3 presents the results obtained from Batch 9709003. There was no sufficient amount of data for Batch 9711005 to make any valid assessment: out of it. The results show that, within the 24months of the claimed expiry dating period, the potency of Panretin stays within the specification limit of 90% to 110%. The expiry dating period is 25 month.

**TABLE 3**  
**Point Estimate and Lower 95% Predicted Potency Value and Estimated Expiry Period of 2**  
**Panretin Batches Without 5% Manufacturing Overage Stored at 25°C/60% RH**  
**(Specification Limits of 90% to 110%)**

Batch ID	Point Estimate and Lower 95% Predicted Values of Potency				Predicted Expiration Date (Month)
	18 Month		24 Month		
	Point Estimate	L_95% Predicted	Point Estimate	L_95% Predicted	
9709003	95.7	92.9	94.5	90.6	25
9711005	NA	NA	NA	NA	NA

**Comment:**

*Batch 9709003 has not provided a strong support for the potency and the claimed expiry dating period.*

**Seven-Batch-Total-Related-Substance Results**

Table 4 shows the results of 6 stability tests. There was no sufficient amount of data available for Batch 9711005 to be used for a valid stability assessment. The results show that, within the 24 month of claimed expiry dating period, for all 6 batches, the potency of Panretin stays well within the specification limit of 0.0% to 4.0%. The minimum of expiry dating period is 41 month determined by Batch 9702002.

**TABLE 4**  
**Point Estimate and Lower 95% Predicted Values of Total Related Substance and Estimated**  
**Expiry Period of 7 Panretin Gel Batches Stored at 25°C/60% RH With 6°C Data as Time Zero**  
**(Specification Limits of 0.0% to 4.0%)**

Batch ID	Point Estimate and Lower 95% Predicted Values of Potency				Predicted Expiration Date (Month)
	18 Month		24 Month		
	Point Estimate	L_95% Predicted	Point Estimate	L_95% Predicted	
9511005	1.79	1.92	2.24	2.40	43
9510001	1.77	1.98	2.23	2.25	41
9608005	1.3	1.36	1.60	1.68	66
9609002	1.33	1.43	1.69	1.83	55
9609007	1.62	1.76	2.07	2.29	43
9609003	0.95	1.22	1.22	1.60	61
9711005	NA	NA	NA	NA	NA

**III.2 Conclusion**

The sponsor concludes that the results, presented above, justify the proposed viable storage duration of 24 months for Panretin stored at 25°C, both with respect to potency and total related substance.

**IV. REVIEWER'S RESULTS AND CONCLUSION**

This reviewer used the SAS program developed by the FDA's statisticians<sup>6</sup> for the stability evaluation. This statistical program produces the stability evaluation results (similar to those produced by the sponsor which were summarized in Tables 2-4) and in addition, the analysis results for the poolability of data of batches, as discusses in Statistical Analysis Section (Page 2).

**IV.1 Poolability of Batches Results****Eight-Batch-Potency Results**

For the 8 Panretin batches, as Table 5 shows that null hypothesis (I) should be rejected. Therefore, separate regression line for each batch should be fitted and proceed to Stage II for computing the expiry period for each batch.

**Table 5**  
The Results of Poolability Test at  $\alpha=0.25$  for the 8 Batches

Ho vs. Ha	P-Value	Action	Conclusion
(i)	0.1396	Reject Ho	Fit a separate regression line for each batch and proceed to Stage II for computing the expiry period for each batch.

**Two-Batch-Potency Results**

For the case of the 2, although, there was no sufficient amount of data for the Batch 9711005, however, this reviewer included this batch in the analysis. Table 5 shows that the null hypothesis (I) is rejected. Therefore, separate regression line for each batch should be fitted and proceed to Stage II for computing the expiry period for each batch.

6- The early SAS program was developed by Ms. Moh Jee Ng during 1992 and this program has been upgraded to by Dr. Ted Guo in 1998.

**Table 6**  
The Results of Poolability Test at  $\alpha=0.25$  for the 2 Batches

Ho vs. Ha	P-Value	Action	Conclusion
(i)	0.0528	Reject Ho	Fit a separate regression line for each batch and proceed to Stage II for computing the expiry period for each batch.

**Seven-Batch-Total-Related-Substance Results**

For this case, although, there was no sufficient data available for Batch 9711005, however, this reviewer included this batch in the analysis. The results are presented in Table 7 and here as well the null hypothesis (I) is rejected. Therefore, separate regression line for each batch should be fitted and proceed to Stage II for computing the expiry period for each batch.

**Table 7**  
The Results of Poolability Test at  $\alpha=0.25$  for the 7 Batches

Ho vs. Ha	P-Value	Action	Conclusion
(i)	0.036	Reject Ho	Fit a separate regression line for each batch and proceed to Stage II for computing the expiry period for each batch.

**IV.II Stability and Expiry Dating Period Results**

The statistical procedure is similar to those performed by the sponsor and the results are presented in the following paragraphs. The readers may also consult Appendices A – C, for which the assay observations for individual batches are presented (Tables A.1, B.1 and C.1 in Appendices A, B, and C, respectively). These appendices also present the graphs of fitted regression lines along with the 95% confidence bands and the specification limits.

**Eight-Batch-Potency Results**

Table 8 shows the results of the stability test on the 8 batches with 5% manufacturing overage (see also Figures A.1 – A.8 in Appendix A). As can be seen, for the duration of 24 months (even beyond the 24 months) of the claimed expiry dating period, for all 8 batches, the potency of Panretin stays well within the specification limit of 95% to 110%. The minimum of expiry dating period is 42 months determined by Batch 9702002.

Comparison of the results in Table 8 with those in Table 2 (of the sponsor's) shows some minor discrepancies. The reason is unknown to this reviewer, however, both the sponsor's and this

reviewer's results lead to the same conclusion of supporting the claim of 24 months expiry dating period.

**TABLE 8**  
 Point Estimate, Lower and Upper 95% Predicted Potency Value Intercept and the Slope of the Fitted Regression Lines and Estimated Expiry Dating Period of 8 Panretin Batches With 5% Manufacturing Overage Stored at 25°C/60% RH (Specification Limits of 95% to 110%)

Batch ID	Point Estimate and Lower 95% Predicted Values of Potency									Regression Estimates		Expiry Dating Period
	Estimates at 18-Month			Estimates at 24-Month			Estimates at 36-Month			Inter	Slope	
	Point	L-95%	U-95%	Point	L-95%	U-95%	Point	L-95%	U-95%			
9510005	104.4	103.7	105.0	104.2	103.4	104.9	103.7	102.4	105.1	105.0	-0.036	84
9608013	103.1	102.3	103.8	102.2	101.0	103.3	100.4	98.3	102.5	106.0	-0.120	61
9702002	104.0	103.0	105.0	103.9	102.3	105.6	103.8	100.7	106.8	106.3	-0.122	62
9510001	103.4	102.7	104.2	102.7	101.8	103.5	101.2	99.6	102.7	105.7	-0.125	59
9511005	103.1	102.5	103.7	102.5	101.8	103.3	101.3	100.0	102.7	104.9	-0.100	66
9608005	103.1	102.3	103.8	102.2	101.0	103.3	100.4	98.3	102.5	105.7	-0.146	50
9609002	103.9	103.3	104.4	103.1	102.2	104.1	101.7	99.9	103.5	104.0	0.008	62
9609007	104.1	103.1	105.1	104.2	102.6	105.7	104.3	101.4	107.2	104.3	-0.014	65

Two-Batch-Potency Results

Table 9 shows the results of the stability test of the 2 batches without 5% manufacturing overage (see also Figures B.1 & B.2 in Appendix B). As can be seen, between the two batches, the maximum estimated expiry dating period is 23 months, indicated by Batch 9709003. Therefore, the results do not support the claim of 24-month expiry dating period.

Although the comparison of the results in Table 9 with those of sponsor's presented in Table 3 show some differences, however, neither result support the claim of 24-month expiry dating period.

**TABLE 9**  
 Point Estimate, Lower and Upper 95% Predicted Potency Value Intercept and the Slope of the Fitted Regression Lines and Estimated Expiry Period of 2 Panretin Batches Without 5% Manufacturing Overage Stored at 25°C/60% RH (Specification Limits of 90% to 110%)

Batch ID	Point Estimate and Lower 95% Predicted Values of Potency									Regression Estimates		Expiry Dating Period
	Estimates at 18-Month			Estimates at 24-Month			Estimates at 36-Month			Inter	Slope	
	Point	L-95%	U-95%	Point	L-95%	U-95%	Point	L-95%	U-95%			
9709003	95.6	92.3	99.0	94.4	89.8	99.1	92.0	84.6	99.4	99.3	-0.201	23
9711005	90.9	86.5	95.3	87.3	81.2	93.4	80.0	70.4	89.5	101.9	-0.608	14

**Comment:**

To this reviewer's view, the primary reason for which the results failed to provide a support for the claim of 24-month expiry dating period is the lack of sufficient amount of data. This is because: first, only 2 batches were tested under the storage condition of 25°C/60% without 5% manufacturing overage, and second, as can be seen from Table B.1 (Appendix B) there are only 9 months observations for the Batch 9709003 and only 6 months observations for the Batch 9711005.

**Recommendation:**

This reviewer recommends that, the sponsor may provide stability data on sufficient number of batches (6-8 batches) and the time points at which the observations are collected should go beyond 24 months or at least close to 24 months.

**Seven-Batch-Total-Related-Substance Results**

Table 10 presents the results of the 7 total related substance tests.

**TABLE 10**  
 Point Estimate, Lower and Upper 95% Predicted Total Related Substance Value, Intercept and the Slope of the Fitted Regression Lines and Estimated Expiry Period of 7 Panretin Batches Stored at 25°C/60% RH With 6°C Data as Time Zero (Specification Limits of 0.0% to 4.0%)

Batch ID	Point Estimate and Lower 95% Predicted Values of Potency									Regression Estimates		Expiry Dating Period
	Estimates at 18-Month			Estimates at 24-Month			Estimates at 36-Month			Inter	Slope	
	Point	L-95%	U-95%	Point	L-95%	U-95%	Point	L-95%	U-95%			
9511005	1.790	1.627	1.953	2.237	2.044	2.430	3.132	2.814	3.449	0.448	0.075	42
9510001	1.772	1.520	2.041	2.33	1.973	2.493	3.156	2.709	3.603	0.388	0.079	40
9608005	1.302	1.236	1.368	1.598	1.499	1.696	3.132	2.814	3.449	0.415	0.049	65
9609002	1.333	1.216	1.449	1.693	1.521	1.865	2.413	2.122	2.704	0.253	0.060	54
9609007	1.615	1.439	1.792	2.070	1.807	2.333	2.979	2.525	3.434	0.252	0.076	42
9609003	0.851	0.562	1.140	1.221	0.754	1.688	1.776	1.039	2.513	0.115	0.046	58
9711005	0.696	0.133	1.258	0.852	0.069	1.634				0.227	0.026	30

Although there was no sufficient data available for Batch 9711005 to obtain reliable results, however, this reviewer included this batch in the analysis. The results obtained from this batch should be interpreted with extra caution. The results from the 6 batch (excluding Batch 9711005) show that for the duration of the claimed 24 month of claimed expiry dating period, the total related substance of Panretin maintained well within the specification limits of 0.0% to 4.0%. The minimum

of expiry dating period is 40 month determined by Batch 9510001.

There are minor discrepancies between the results presented in Table 10 with those in Table 4 (reason is unknown to this reviewer), however, both the sponsor's and this reviewer's results lead to the same conclusion of supporting the claim of 24 months expiry dating period.

#### IV.4 Summary Conclusion

The stability studies for Panretin, in aluminum tube packages, for which the statistical review is requested, consist of evaluation of potency and total related substance of the drug product under storage condition of 25°C/60%RH. The expiry dating period claimed is 24 months. The following is a brief description of the studies.

1. Eight batches with 5% manufacturing overage, stored at 25°C/60% RH for the potency evaluation. The specification limits were specifies as 95% to 110%.
2. Two batches without 5% manufacturing overage, stored at 25°C/60% RH for the potency evaluation. The specification limits were specifies as 90% to 110%.
3. Seven batches were stored at 25°C/60% RH for the total related substance evaluation. The specification limits were specifies as 0.0% to 4.0%.

The sponsor's results are summarized in Tables 2-4. The sponsor overall, conclusion is that "the results justify the proposed viable storage duration of 24 months of the product, stored at 25°C", both with respect to potency and total related substance.

This reviewer's main results are summarized in Tables 8-10. This reviewer concludes that:

With respect to the potency, the 8 batches with 5% manufacturing overage have provided sufficient evidence to support the proposed viable storage duration of 24 months, when the product stored at 25°C.

With respect to the total related substance, 6 out of 7 batches have provided sufficient evidence to support the proposed viable storage duration of 24 months, of the product stored, at 25°C.

For the case of two batches without 5% manufacturing overage, the results failed to provide any evidence to support the 24-month claim for the product. As far as this reviewer is concerned, the primary reason for the deficiency is the lack of sufficient amount of data. For further explanation the readers may read this reviewers comment on Page 10.

**Recommendation:**

*As Dr. Gang Chen, the Statistical Team Leader from the Division of Biometrics 1 (HFD-710), assigned to the Division of Oncology Drug Products (HFD-150), expressed to me, the main concern of HFD-150 Review Chemist is the Stability of batches without 5% manufacturing overage. In this case, this reviewer recommends that, the sponsor needs to provide, sufficiently, further stability data on batches (6-8 batches) without 5% manufacturing overage. Also, the time points at which the observations are collected should go beyond 24 months (24-30 months).*

/S/

Kooros Mahjoob, Ph.D.  
Mathematical Statistician

This review consists of 12 pages of text and 10 tables, Appendix A consisting of 1 table and 8 figures, Appendix B consisting of 1 table and 2 figures, and Appendix C consisting of 1 table and 7 figures.

Concur:

/S/

Dr. Chen

\_\_\_\_\_ ✓

Dr. Chi

/S/

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CC:

Arch. NDA 20-886

HFD-150

HFD-150/Dr. Kim

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HFD-710/Dr. Chen

HFD-710/Dr. Mahjoob

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K. Mahjoob: 4-5301; first draft 11/02/98/second draft 11/03/98/finalized 11/04/98

Statistical Reviewer: Kooros Mahjoob