CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-892

STATISTICAL REVIEW(S)

MS. STATEN

Statistical Review and Evaluation

NDA#:	20-892
Applicant:	Anthra
Name of Drug:	AD 32 (Valrubicin)
Indication:	Bladder Cancer
Documents Reviewed:	Vol. .1, .33-.51, Submission Dated 1/2/98
Medical Officer:	Oluwole Odujinrin, M.D.

MAY 17 1998

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Major Statistical Issues of Review

- Insufficient evidence suggesting effectiveness of the drug

I. Background:

AD 32(valrubicin) is a anthracycline cytotoxic agent that has been evaluated for intravesical use in the treatment of patients with biopsy-proven carcinoma in situ of the urinary bladder who are refractory to BCG immunotherapy. Two open-label, phase II/III trials, ***A9301(35 patients) and A9302(55 patients)***, are reported. The population selected in these two trials consisted of patients with pathologically documented CIS who had failed or recurred following two prior intravesical regimens for the treatment of CIS; at least one of the prior treatments must have been BCG. Three supportive studies, A91-0101 (phase I, 32 patients), A9501(22 patients), and A9305(6 patients), are also submitted for review. In this review, the results from the two pivotal trials will be evaluated for efficacy.

II. Description of Trials

Studies A9301 and A9302 were identical in purpose and design and both studies are still ongoing. This submission includes efficacy data from the first 90 patients enrolled in the two studies. All patients received their last scheduled dose of AD 32 before April 30, 1997.

Design Both studies, A9301 and A9302, were open-label, phase II/III trials. Patients who had not responded to more than 2 prior courses of intravesical therapy (including at least one course of BCG, for CIS) were to receive six weekly intravesical administrations of 80 mg of AD 32. A two stage Green and Dahlberg design was adopted for both studies. The two stage design is summarized below.

- Hypothesis: **H0: $p \leq 0.10$** (inadequate efficacy) vs. **Ha $p \geq 0.30$** (efficacy comparable to additional courses of BCG
- Number of patients planned for each stage:
    - Stage I: recruiting 25 patients
    - Stage II: (if not terminated at the first stage) recruiting additional 25 patients.

Primary Objective (Endpoint) The primary objective was to assess the efficacy of intravesical instillation of AD 32. The primary endpoint was to evaluate patients' response to the treatment.

Secondary Objective (Endpoint) The secondary endpoints include

- Disease free duration (time between initiation of therapy and disease recurrence) and time to Cystectomy
- Safety and toxicity

Patient Population & Disposition of Patients Thirty-five patients were enrolled in study A9301 and 55 patients were enrolled in study A9302. Of them, 88 patients completed treatment with AD 32. Two patients dropped out due to either death (patient unrelated to AD 32 administration) or bladder spasms (patient . One patient died (patient , of liver cancer after finishing treatment.

Statistical Analysis Plan

- Descriptive statistics for the primary endpoint (response rate) and safety & toxicity analyses
- Life table analysis for time to events endpoints (time to recurrence & time to Cystectomy)

III. Summary of Efficacy Results and Reviewer's Comments

The primary endpoint for both studies A9301 and A9302 was patient's response to the treatment AD 32. The sponsor also performed statistical tests for homogeneity of results of the two trials for the primary and secondary efficacy endpoints. The results of the two studies were pooled since no statistical evidence that the results were significantly different. The sponsor's results for the primary efficacy endpoint are summarized in the following Reviewer's Table.

Reviewer's Table III.1. Patients with Complete Response, Studies A9301 and A9302

Trial	Response Rate	95% CI (Exact Method)
A9301	7/35 (20.0%)	(8.4%, 36.9%)
A9302	13/55(23.6%)	(13.2%,37.0%)
Pooled Data	20/90(22.2%)	(14.1%,32.2%)

Reviewer's Comments

1. The studies A9301 and A9302 are two independent trials with the identical design. To support the efficacy claim of the drug, both trials need to demonstrate the effectiveness of the drug as specified in the protocols. The pooled data analysis may increase the accuracy of the point estimate if both trials demonstrate similar efficacy.
2. Phase II is in essence an efficacy screen. According to the protocol design, efficacy criterion for the studies was taken to be **30%** of the response rate. Although the sponsor's results of both phase 2 trials demonstrated positive results (favoring the alternative hypothesis, **Ha: $p \geq 0.30$)**, the false positive rate of the trials may be high because of small sample size and prognostic heterogeneity. Reviewer's Table III.1 shows that the upper bound of the 95% confidence interval of the estimated response rate is 32.2% (using pooled data) which merely achieves the efficacy criteria (30%) for the study. Positive phase II trials only demonstrate that the drug has enough efficacy to warrant further large-scale comparative studies. Evidence suggesting effectiveness of the drug obtained solely in Phase 2 trials may be insufficient.
3. According to FDA Medical Reviewer's assessment, however, only 9 (pooled data) patients can be categorized as complete responders. The following Reviewer's Table summarizes the results.

Reviewer's Table III.2. Patients with Complete Response, FDA Assessment, Studies A9301 and A9302

Trial	Response Rate	95% CI (Exact Method)
A9301	3/35 (8.6%)	(%1.8,23.1%)
A9302	6/55(10.9%)	(%4.1,22.2%)
Pooled Data	9/90(10%)	(%5.5,19.5%)

Apparently, based on the FDA's assessment, the test in both studies favors null hypothesis ($p < 10\%$), i.e., there is no evidence that the drug is effective.

4. Since both studies adopted a standard two stage design, the sponsor needs to provide the results of analyses for the first stage of the studies (i.e. number of patients responded to the treatment). According to the study design, for study A9301, 10 more patients need to be enrolled if the trial was not terminated at the end of the first stage of the study.
5. No significant association between prior BCG treatment and patient's response was observed. The following Reviewer's Table summarizes the relationship between the response and number of prior BCG treatment.

Reviewer's Table III.3. Association between Response and Number of Prior BCG Treatment, Pooled Data

Response	Number of Prior BCG Treatment*				
	1	2	3	4	5
Responder	7(25.9%)	6(15.8%)	6(33.3%)	1(20%)	0(0%)
Nonresponder	20(74.1%)	32(84.2%)	12(66.7%)	4(80%)	2(100%)

**: P-value of the association test is 0.88 (CMH test).*

6. No significant relationship was observed between patient's response and age and sex.

All patients who failed to respond to AD 32 or initially responded to treatment but later experienced disease recurrence were contacted approximately every 6 months to ascertain their disease status and whether they had undergone additional treatment for bladder cancer, including Cystectomy. A total 34 patients have undergone Cystectomies after being taking off study. There was no apparent difference in median time to Cystectomy between the two studies. Results of the analyses for time to Cystectomy are summarized in Reviewer's Table III.3.

Reviewer's Table III.4. Analysis of Time to Cystectomy, Studies A9301 & A9302

Trial	Median Time to Cystectomy (years)	95% CI
A9301(n=13)	0.88	(0.54, 1.07)
A9302(n=21)	0.75	(0.46, 0.96)
Pooled Data(n=34)	0.81	(0.58, 0.98)

IV. Summary and Conclusions

Summary: The trials, A9301 and A9302, were designed to show the efficacy of the treatment AD 32 based on patient's response. The two trials were reviewed for statistical design and efficacy analyses. This reviewer's comments are summarized below.

1. Phase II is in essence an efficacy screen. Positive phase II trials only demonstrate that the drug has enough efficacy to warrant further large-scale comparative studies. The false positive rate of phase II trials may be high because of small sample size and prognostic heterogeneity. The discrepancy presented between the Reviewer's Table III.1 (the sponsor's assessment) and III.2 (FDA's assessment) demonstrates that efficacy of the drug is highly questionable. Evidence suggesting effectiveness of the drug obtained solely in Phase 2 trials is insufficient.

2. Since both studies adopted a standard two stage design, the sponsor needs to provide the results of analyses at the end of the first stage (i.e. number of patients responded to the treatment).

3. No significant association between prior BCG treatment and patient's response was observed. Similarly, there was no significant relationship between patient's response and age and sex.

Conclusion: Evidence suggesting effectiveness of the drug obtained in the sponsor's phase 2 trials is very limited. In this reviewer's opinion the evidence submitted provides insufficient support for the sponsor's claim.

/S/

Gang Chen, Ph.D.
Mathematical Statistician

Concur: Dr. G. Chi 5/17/98

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NDA
~~IND~~# 20,892
HFD-150/Division File
HFD-150/Dr. Odujinrin
HFD-150/Dr. Williams
HFD-150/Ms. Staten, CSO
HFD-710/Dr. Chi
HFD-710/Dr. Koutsoukos
HFD-710/Dr. Chen

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STATEN

Statistical Review and Evaluation
Addendum

NDA#:	20-892	MAY 26 1998
Applicant:	Anthra	
Name of Drug:	AD 32 (Valrubicin)	
Indication:	Bladder Cancer	
Medical Officer:	Oluwole Odujinrin, M.D.	

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This review addendum evaluates the response rate of AD 32 based on FDA Medical Reviewer's final assessment of patients with complete response. Fourteen patients (pooled data) are now being categorized as complete responders. The following Reviewer's Table summarizes the results.

Reviewer's Table 1. Patients with Complete Response, FDA Medical Officer's Final Assessment, Studies A9301 and A9302

Trial	Response Rate	95% CI (Exact Method)
A9301	4/35 (11.4%)	(%3.2,26.7%)
A9302	10/55(18.2%)	(%9.1,30.1%)
Pooled Data	14/90(15.6%)	(%8.8,24.7%)

Apparently, based on the FDA's final assessment, the test in study A9301 favors null hypothesis ($p < 10\%$), i.e., there is no evidence that the drug is effective. The result for study A9302 is similar to the sponsor's finding.

/S/

Gang Chen, Ph.D.
Mathematical Statistician

Concur: Dr. G. Chi Ok 5/26/98

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NDA
~~IND~~# 20,892
HFD-150/Division File
HFD-150/Dr. Odujinrin
HFD-150/Dr. Williams
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HFD-710/Dr. Chen

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Statistical Review and Evaluation

AUG 4 1998

NDA#:	20-892 (Amendment #27)
Applicant:	Anthra
Name of Drug:	AD 32 (Valrubicin)
Indication:	Bladder Cancer
Documents Reviewed:	Amendment No. 27, Submission Dated 7/27/98
Medical Officer:	Oluwole Odujinrin, M.D.

****

I. Background:

AD 32(valrubicin) is a anthracycline cytotoxic agent that has been evaluated for intravesical use in the treatment of patients with biopsy-proven carcinoma in situ of the urinary bladder who are refractory to BCG immunotherapy. Two open-label, phase II/III trials, ***A9301(35 patients) and A9302(55 patients)*** were submitted for review in January, 1998 and were discussed at the June ODAC meeting. At the June ODAC meeting, the following issue was raised by the ODAC members.

- Whether administration of AD 32 changed the course of disease in the 19 complete responders in Study A9301/02.

Other issues raised by the committee members including 1) time to cystectomy in responders and nonresponders, 2)homogeneity of the patient population, and 3) clinical benefit are also discussed in the sponsor's submission. Since there are no apparent statistical issues, those concerns will not be addressed in this statistical review.

II. Summary of the Sponsor's Results and Reviewer's Comments

To address the issue, the sponsor compared the patients' responses to prior therapy with their responses to valrubicin. Response to valrubicin was defined as the *time between the first dose of valrubicin and the visit at which the patient was deemed to be off-study*. Response to prior therapy was defined similarly, i.e., the time from the start of a course of induction therapy to whichever of the following occurred first: a biopsy showing transitional cell carcinoma or the start of another course of induction therapy.

The sponsor performed Kaplan-Meier analysis for each response duration. The logrank test was used to compare those response to the therapies. The sponsor's results are summarized in the

following Reviewer's table.

Reviewer's Table II.1. Response to Prior Intravesical Therapy Vs. Response to Valrubicin in CRs (n=19), Studies A9301 and A9302*

	AD32 vs. Last	AD32 vs. 2nd last	AD32 vs. 3rd last
p-value*	.026	.0003	.02

*: Logrank test

Based on this result, the sponsor's stated in the submission that "***the 19 CRs in Study A9301/02 were disease-free longer with valrubicin than with prior intravesical treatments. There was a statistically significance between the response to valrubicin and the response to each of the last three courses of therapy. These results suggest that the use of valrubicin changed the disease course in these 19 patients.***"

Reviewer's Comments

1. The logrank test used to compare the response to the therapies is not appropriate due to dependence of the data (in paired data, each patient serves as his/her own control). P-values are not interpretable.
2. With such small sample size (n=19) the result of any test should be interpreted with caution.

To examine whether 19 CRs were disease-free longer with valrubicin than with the prior intravesical treatments, this reviewer performed an **exploratory analysis** using the Wilcoxon sign rank test. The difference between the two disease free times (Valrubicin - prior chemotherapy) for each patient was calculated. The sign rank test is used to test whether the difference is different from 0. Using the sign rank test may lose information for 7 remaining disease free patients treated with Valrubicin because the ranks of the differences for these 7 patients may become smaller than they ought to be. The following Reviewer's table summarizes the results.

Reviewer's Table II.2. Response to Prior Intravesical Therapy Vs. Response to Valrubicin in CRs (n=19), Studies A9301 and A9302*

	AD32 vs. Last	AD32 vs. 2nd last	AD32 vs. 3rd last
p-value*	.13	.004	.13@

*: Wilcoxon Sign Rank test
@: Only 12 patients had 3rd last therapy.

The above table shows that the 19 CRs were disease-free longer with valrubicin than with the prior intravesical treatments, although the first (column 1) and the 3rd (column 3) test are not statistically significant. This reviewer's analysis supports the claim that ***"the 19 CRs in Study A9301/02 were disease-free longer with valrubicin than with prior intravesical treatments"***.

The other ODAC committee's concerns have been discussed in the FDA medical reviewer's review.

/S/

Gang Chen, Ph.D.
Mathematical Statistician

Concur: Dr. G. Chi 8/14/98

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NDA 20-892
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HFD-150/Division File
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HFD-710/Dr. Chen

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This review consists of 4 pages of text.

Statistical Review and Evaluation

NDA#:	20-892 (Amendment #27)
Applicant:	Anthra
Name of Drug:	AD 32 (Valrubicin)
Indication:	Bladder Cancer
Documents Reviewed:	Amendment No. 27, Submission Dated 7/27/98
Medical Officer:	Oluwole Odujinrin, M.D.

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I. Background:

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Other issues raised by the committee members including 1) time to cystectomy in responders and nonresponders, 2)homogeneity of the patient population, and 3) clinical benefit are also discussed in the sponsor's submission. Since there are no apparent statistical issues, those concerns will not be addressed in this statistical review.

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Reviewer's Comments

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The other ODAC committee's concerns have been discussed in the FDA medical reviewer's review.

/S/

Gang Chen, Ph.D.
Mathematical Statistician

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Statistical Review and Evaluation

NDA#: 20-892 MAY 28 1998
APPLICANT: Anthra Pharmaceuticals, Inc.
NAME OF DRUG: AD32 (Valrubicin) Injection
REVIEWING CHEMIST: Dr. Sung Kim
TOPIC: Stability Testing

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1. **Background**

This review was requested by the reviewing chemist, Dr. Sung Kim. The objective was to review the stability results of three batches (515-44-0003, 515-44-0004 and 515-44-0005) of AD 32 Sterile Liquid at a storage condition of 5°C. Three attributes, assay, related substances and pH after dilution, are evaluated for stability of the drug. Since the stability results of upright storage and inverted storage are similar, only upright storage data are analyzed. The months at which three attributes were examined are listed in the following table.

Table 1. Assay, Related Substances and pH Examination Time Points for All Three Batches

BATCH	MONTH
515-44-0003	0,3,6,9,12,18
515-44-0004	0,3,6,9,12
515-44-0005	0,3,6,9,12

2. **Results and Reviewer's Comments**

2.1. **Assay**

Reviewer's Comments

- Results of the linear regression analyses for assay for the three batches are summarized in the following table.

Table 2. Regression Analyses, All Three Batches

Batch	Intercept (s.e.)	Slope (s.e.)	p-value for slope
515-44-0003	103.8(.84)	.078(.084)	.41
515-44-0004	99.6(.27)	.153(.037)	**.025**
515-44-0005	100.0(.96)	-.067(.130)	.64

- The above table shows that there were no statistically significant changes in assay over the study period for batches 515-44-0003 and 515-44-0005. The 95% confidence limits for the two intercepts are 102.2% - 105.4% (batch 515-44-0003) and 98.1% - 101.9% (515-44-0005) respectively. However, for batch 515-44-0004, there was a statistically significantly (p=.025) increasing time trend present.

2.2. **Related Substances**

The specification limit (upper) is 3.5% for total impurity and 1.5% for individual impurity. Data for total impurity were collected by the sponsor. Linear regression analyses have been used to analyse the data. The 95% confidence bands are established for the estimated regression lines. The sponsor claimed that "The confidence bounds in linear regression plots for lot 515-44-0003 have been narrowed somewhat by addition of the 18-month data point, now supporting 26 to 32 month dating…. The good consistency among results for lots 515-44-0004 and 515-44-0005 allows projections beyond 24 months in both cases on the basis of only 12-month results."(The sponsor's results are attached.) This reviewer's comments are summarised below.

Reviewer's Comments

- Results of the linear regression analyses for related substances for the three batches are summarized in the following table.

Table 3. Regression Analyses, All Three Batches

Batch	Intercept (s.e.)	Slope (s.e.)	p-value for slope
515-44-0003	1.78(.24)	.003(.02)	.91
515-44-0004	1.52(.14)	.01(.02)	.64
515-44-0005	1.62(.04)	.00(.005)	1.0

- The above table shows that there were no statistically significant changes in related substances over the study period for all three batches. The 95% confidence limits for the three intercepts are summarized in the following table.

Table 4. 95% Confidence Intervals for Intercepts, All Three Batches

Batch	Intercept	95% CI
515-44-0003	1.78%	(1.31%, 2.25%)
515-44-0004	1.52%	(1.25%, 1.79%)
515-44-0005	1.62%	(1.54%, 1.70%)

- The above results demonstrate that the upper 95% confidence bounds for all three batches are lower than the specification limit (3.5%).

2.3. **pH**

The specification limits for pH are 4.0 to 7.0. Linear regression analyses have been used to analyse the data. The 95% confidence bands are established for the estimated regression lines. The sponsor claimed that "The plots of pH results show the same very small slops, four of six which are negative in the current analysis, and wide confidence bounds associated with variability among data points as found in previous studies." (The sponsor's results are attached.) This reviewer's comments are summarised below.

Reviewer's Comments

- Results of the linear regression analyses for pH for the three batches are summarized in the following table.

Table 5. Regression Analyses, All Three Batches

Batch	Intercept (s.e.)	Slope (s.e.)	p-value for slope
515-44-0003	5.31(.39)	-.007(.039)	.86
515-44-0004	4.82(.18)	.003(.025)	.90
515-44-0005	4.88(.11)	-.013(.015)	.45

- The above table shows that there were no statistically significant changes in pH over the study period for all three batches. The 95% confidence limits for the three intercepts are summarized in the following table.

Table 6. 95% Confidence Intervals for Intercepts, All Three Batches

Batch	Intercept	95% CI
515-44-0003	5.31	(4.54,6.07)
515-44-0004	4.82	(4.47,5.17)
515-44-0005	4.88	(4.66,5.10)

- The above results demonstrate that the 95% confidence bounds for all three batches are within the specification limits (4.0-7.0).

3. **Summary and Conclusions**

The stability of the product was evaluated at the storage condition 5°C

3.1 **Assay**

3.2 **Related Substance**

In terms of total impurity content, for batch 515-44-0003, an expiration dating period of 24 months can be granted. However,

for the other two batches, 515-44-0004 and 515-44-0005, one needs to be very cautious in extrapolating beyond 18 months since there were only 12 months of data. The sponsor needs to verify this expiration dating period for the two batches by obtaining actual stability data up to the requested expiration time as soon as these data become available.

3.3 **pH**

For batch 515-44-0003, an expiration dating period of 24 months can be granted. Similarly, for the other two batches, 515-44-0004 and 515-44-0005, the sponsor can only extrapolate the expiration dating period to 18 months since there were only 12 months of data.

Overall Conclusions

The following table summarizes the stability results for batches 515-44-0003, 515-44-0004, and 515-44-0005.

Table 7. Suggested Expiration Date, Assay, Related Substances and pH (Based on Upright Storage Data)

	Assay	Related Substances	pH
515-44-0003	?*	24 mon	24 mon
515-44-0004	18 mon	18 mon	18 mon
515-44-0005	18 mon	18 mon	18 mon

*: *The upper 95% confidence limit of the intercept for batch 515-44-0003 was 105.4%, which is slightly over upper specification limit(105%).*

/S/

Gang Chen, Ph.D.
Mathematical Statistician

Concur: Dr. G. Chi Chi 5/28/98

Orig. NDA 20-892
HFD-150/Ms. Staten, CSO
HFD-150/Mr. Kim
HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Chron

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This review consists of 6 pages of text and 7 pages of tables and figures.

TABLE 1

(update of NDA TABLE 3.4.8.2:3)

Summary of Stability Results for AD 32 Sterile Liquid Lot 515-44-0003

(Upright Storage)

Storage Condition		Appearance	Assay (%)	Related Substances (%)	pH	Sterility
Initial		Clear, dark red liq.		1.5	6.0	Sterile
5°C	3 mo.	No change		2.3	4.9	N/A
	6 mo.	No change		1.7	4.8	N/A
	9 mo.	No change		1.5	4.8	N/A
	12 mo.	No change		2.0	5.7	Sterile
	18 mo.	No change		1.8	5.3	N/A

(Inverted Storage)

5°C	3 mo.	No change		2.4	4.5	N/A
	6 mo.	No change		1.7	4.7	N/A
	9 mo.	No change		1.5	4.6	N/A
	12 mo.	No change		2.1	5.6	Sterile
	18 mo.	No change		1.9	5.2	N/A

N/A = test not required at this interval

TABLE 2

(update of NDA TABLE 3.4.8.2:4)

Summary of Stability Results for AD 32 Sterile Liquid Lot 515-44-0004

(Upright Storage)

Storage Condition		Appearance	Assay (%)	Related Substances (%)	pH	Sterility
Initial		Clear, dark red liq.		1.5	5.0	Sterile
5°C	3 mo.	No change		1.4	4.5	N/A
	6 mo.	No change		1.8	4.9	N/A
	9 mo.	No change		1.7	5.0	N/A
	12 mo.	No change		1.5	4.8	*
25°C	1 mo.	No change		1.7	4.9	N/A
	3 mo.	No change		1.4	4.3	N/A
	6 mo.	No change		1.8	4.6	N/A
	9 mo.	No change		1.8	4.9	N/A
	12 mo.	No change		1.7	5.2	*

(Inverted Storage)

5°C	3 mo.	No change		1.4	4.6	N/A
	6 mo.	No change		1.8	5.0	N/A
	9 mo.	No change		1.7	5.2	N/A
	12 mo.	No change		1.5	4.8	*
25°C	1 mo.	No change		1.7	5.2	N/A
	3 mo.	No change		1.5	4.5	N/A
	6 mo.	No change		1.8	5.5	N/A
	9 mo.	No change		1.9	4.8	N/A
	12 mo.	No change		1.8	4.6	*

N/A = test not required at this interval
* Result not available for this report

TABLE 3

(update of NDA TABLE 3.4.8.2:5)

Summary of Stability Results for AD 32 Sterile Liquid Lot 515-44-0005

(Upright Storage)

Storage Condition		Appearance	Assay (%)	Related Substances (%)	pH	Sterility
Initial		Clear, dark red liq.		1.6	5.0	Sterile
5°C	3 mo.	No change		1.6	4.7	N/A
	6 mo.	No change		1.7	4.7	N/A
	9 mo.	No change		1.6	4.9	N/A
	12 mo.	No change		1.6	4.7	*
25°C	1 mo.	No change		1.7	4.9	N/A
	3 mo.	No change		1.5	4.6	N/A
	6 mo.	No change		1.6	4.6	N/A
	9 mo.	No change		1.5	4.7	N/A
	12 mo.	No change		1.8	4.8	*

(Inverted Storage)

5°C	3 mo.	No change		1.5	4.6	N/A
	6 mo.	No change		1.7	4.7	N/A
	9 mo.	No change		1.6	5.1	N/A
	12 mo.	No change		1.6	4.6	*
25°C	1 mo.	No change		1.8	5.0	N/A
	3 mo.	No change		1.5	4.7	N/A
	6 mo.	No change		1.7	4.6	N/A
	9 mo.	No change		1.6	4.8	N/A
	12 mo.	No change		1.8	4.9	*

N/A = test not required at this interval
* Result not available for this report

TABLE 4

(NDA TABLE 3.4.8.2:8)

Summary of Linear Regression Slope Results for Lots 515-44-0001, 515-44-0002, and 515-44-0003

Test parameter	Storage condition	Lot 515-44-0001		Lot 515-44-0002		Lot 515-44-0003*	
		Upright	Inverted	Upright	Inverted	Upright	Inverted
Assay	5°C	+0.044	-0.027	-0.124	-0.137	-0.067	-0.077
	25°C	-0.96	-0.821	-0.997	-0.747		
	30°C	-1.372	-1.293	-1.486	-1.337		
Related substances	5°C	-0.016	-0.014	-0.022	-0.024	+0.007	+0.01
	25°C	+0.73	+0.645	+0.72	+0.535		
	30°C	+1.101	+1.049	+1.092	+0.979		
pH	5°C	+0.002	-0.006	-0.03	-0.021	-0.023	-0.023
	25°C	-0.03	-0.027	-0.023	-0.014		
	30°C	-0.05	-0.042	-0.031	-0.023		

*From 12-month analysis

Updated Data, Including Lots 515-44-0004 and 515-44-0005

Test parameter	Storage condition	Lot 515-44-0003**		Lot 515-44-0004		Lot 515-44-0005	
		Upright	Inverted	Upright	Inverted	Upright	Inverted
Assay	5°C	+0.078	+0.107	+0.153	+0.177	-0.067	+0.087
Related substances	5°C	+0.003	+0.007	+0.01	+0.01	0	+0.003
pH	5°C	-0.007	-0.004	+0.003	+0.007	-0.013	-0.01

**From 18-month analysis

Figure 1 – Linear regression analysis for lot 515-44-0003 (upright storage)

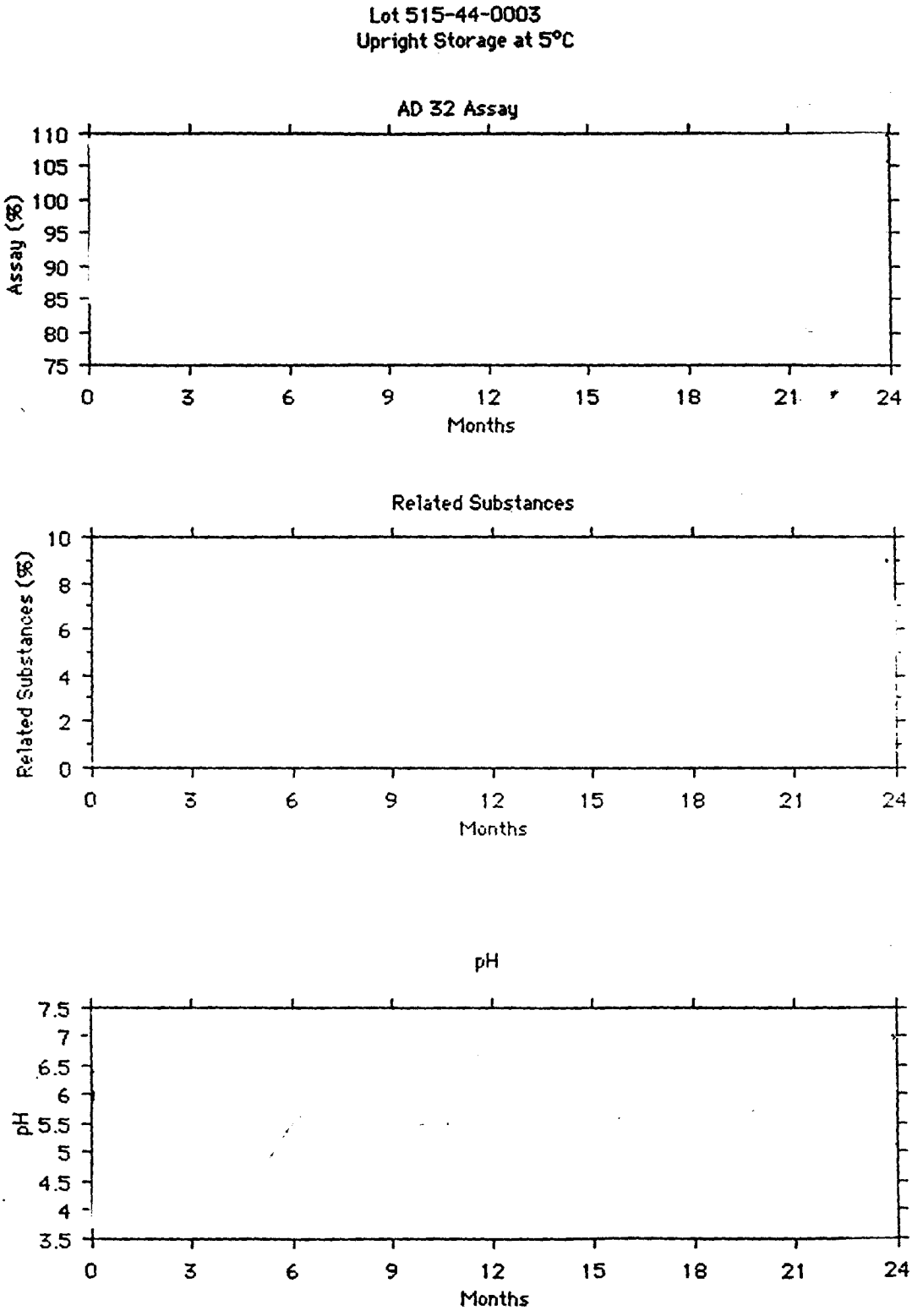


Figure 3 – Linear regression analyses for lot 515-44-0004 (upright storage)

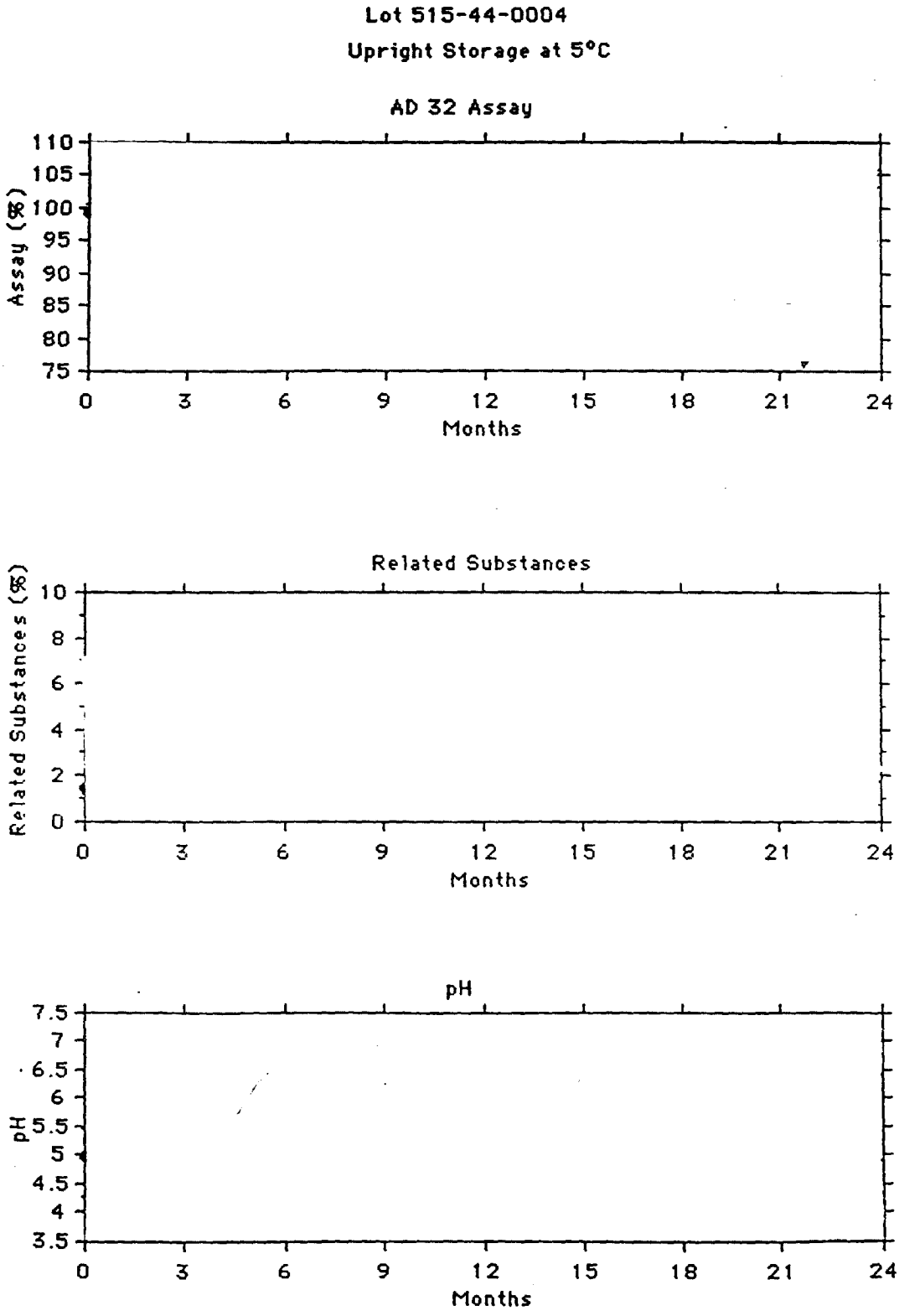
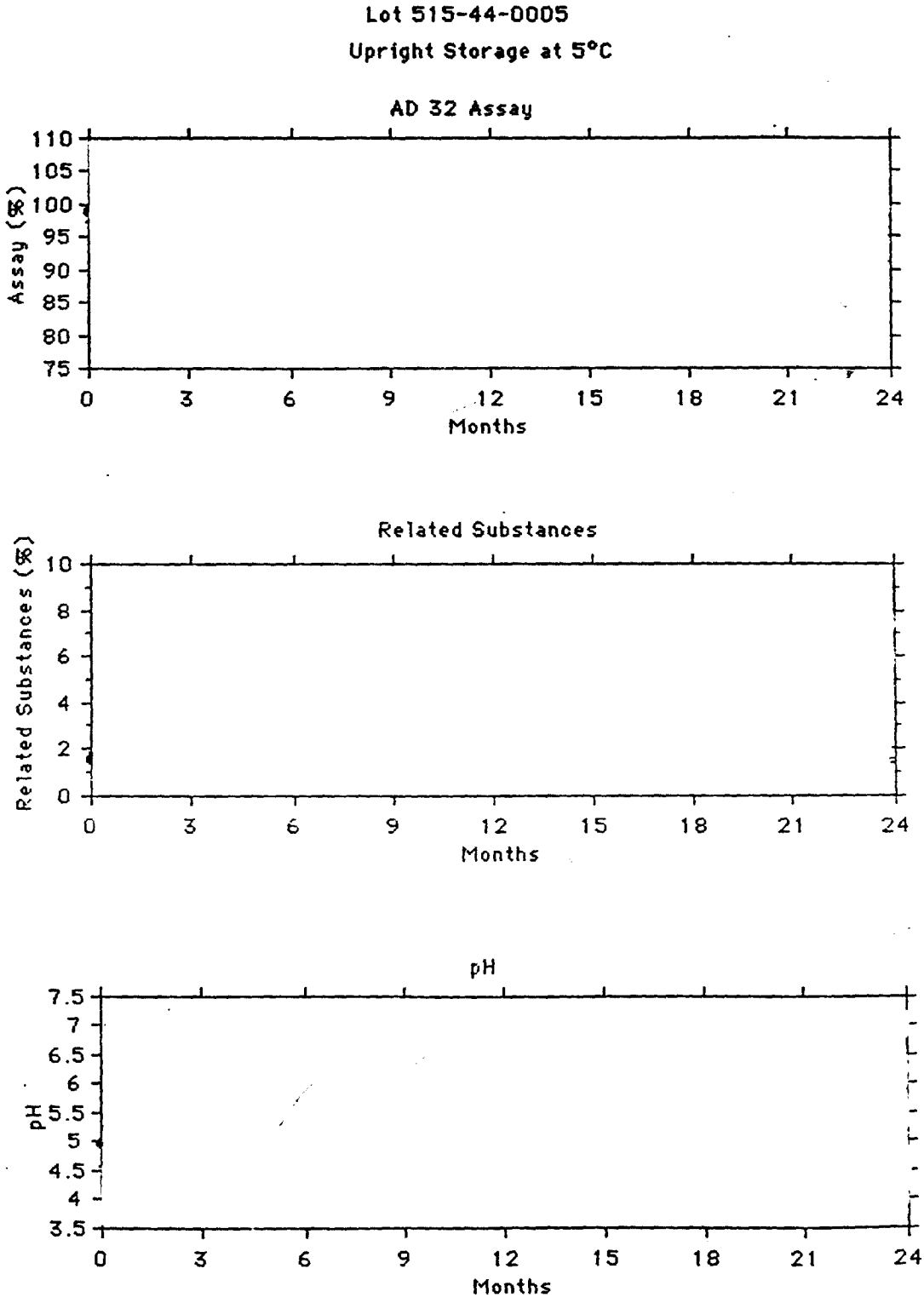


Figure 5 – Linear regression analyses for lot 515-44-0005 (upright storage)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-892

MICROBIOLOGY REVIEW(S)

Staten

REVIEW TO HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF AN NDA

APR 22 1998

April 22, 1998

A. 1. **NDA 20-892**
2. **PRODUCT NAME:** AD 32 (Valrubicin) Injection
3. **APPLICANT:** Anthra Pharmaceuticals, Inc.
103 Carnegie Center, Suite 102
Princeton, NJ 08540

B. 1. **DOSAGE FORM:** Sterile 5 mL Solution in 40 mg/mL Strength for Intravesical Administration
2. **METHOD(S) OF STERILIZATION:**
3. **PHARMACOLOGICAL CATEGORY/PRINCIPAL INDICATION:** Carcinoma in situ of the urinary bladder

C. 1. **INITIAL APPLICATION DATE:** December 18, 1997
2. **ASSIGNED FOR REVIEW:** January 21, 1998

D. REMARKS: The drug product AD 32 was designated an Orphan Drug on May 23, 1994 (#94-821). AD 32 is an anthracycline chemotherapeutic agent intended for the treatment of refractory carcinoma in situ of the urinary bladder.

E. CONCLUSIONS: The NDA 20-892 for AD 32 (Valrubicin) Injection is recommended for approval from the standpoint of product quality microbiology.

/S/ 4/22/98

Patricia F. Hughes, Ph.D.
Review Microbiologist

Fte 4/22/98

cc.: Original NDA 20-892
HFD-160/Division File
HFD-160/PFHughes
HFD-150/AStaten/S.K Kim
HFD-150/Division File
Drafted by PF Hughes, 04/22/98
R/D Initialed by PH Cooney