level. For a standard chronic study in two species, i.e., rats and mice, based on simulations and their experience, Lin & Rahman (1998) proposed a further p-value adjustment for tests of trend. That is, for a roughly 0.10 (10%) overall false positive error rate in tests of trend, rare tumors should be tested at a 0.025 (2.5%) level and common tumors at a 0.005 (0.5%) level. In this analysis in rats the observed incidence in the pooled controls was used to decide if a tumor was rare or common (i.e., incidence ≤ 1 or >1 in the appropriate controls). This approach was intended to balance both Type I error and Type II error (i.e., the error of concluding there was no evidence of a relation to tumorgenicity when there actually was such a relation). These rules were originally designed to apply to Peto tests, but work by Lin and Rahman (personal communication) suggest they are also applicable to the poly-k tests. However, it should be noted these results assume the only relevant tests are single tests of trend in each genders in each of the two species, as well as comparisons between the high dose and controls in both genders in both species. When there are tests of trend among three different subgroups as here, and a large number of pairwise comparisons the overall experiment-wise Type I error can be expected to increase, likely well above the rough nominal 10% level.

1.3.1.5. Validity of the Designs:

When determining the validity of designs there are two key points:
1) adequate drug exposure
2) tumor challenge to the tested animals.

1) is related to whether or not sufficient animals survived long enough to be at risk of forming late-developing tumors and 2) is related to the Maximum Tolerated Dose (MTD), designed to achieve the greatest likelihood of tumorigenicity.

Lin and Ali (1994), quoting work by Haseman, have suggested that a survival rate of about 25 animals, out of 50 or more animals, between weeks 80-90 of a two-year study may be considered a sufficient number of survivors as well as one measure of adequate exposure. Since this study involved more than 50 animals per treatment group, and except for the highest dose group in mice, there were around 25 animals that survived to the end of the study, this criterion seems to have been satisfied. However, in male rats, from the survival plots in Appendix 1 or the incidence tables in Sections 3.2.1.2 and 3.2.2.2, in the benzoyl peroxide only group there is evidence of higher mortality in the highest dose group.

Chu, Ceuto, and Ward (1981), citing earlier work by Sontag et al. (1976) recommend that the MTD "is taken as 'the highest dose that causes no more than a 10% weight decrement as compared to the appropriate control groups, and does not produce mortality, clinical signs of toxicity, or pathologic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animal's natural life span' " The values in the following tables, Tables 5 and 6 are transcribed from the Sponsor's reports. Table 5 gives the mean initial weight and mean final weight. The table for rats also includes the final percent weight change relative to the pooled controls. In the mice the weight and weight changes are very consistent across treatment groups.

Table 5: Weight Summaries

Male Rats - Oral Gavage

Treatment Group	Cntrl1&2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
Week 1	275	272	272	268	278	275	275	270
Week 88	850	866 104%	845 100%	817 95%	868 103%	788 89%	893 107%	803 93%

Female Rats - Oral Gavage

Treatment Group	Cntrl1&2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
Week 1	199	196	272	268	278	275	275	270
Week 95	540	618 124%	556 107%	508 93%	546 104%	527 98%	514 95%	483 85%

Male Mice - Dermal

Treatment Group	Cntrl1&2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
Week 1	28	28	27	28	28	27	27	27
Week 104	40	40	39	40	40	40	39	40

Female Mice - Dermal

Treatment Group	Cntrl1&2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
Week 1	22	21	21	21	21	21	22	21
Week 104	37	35	36	37	36	36	35	36

Table 6 gives the mean food consumption at the end of the study for both species. Note that food consumption seemed to be roughly consistent across treatment groups in rats.

Table 6: Mean Food Consumption g/animal/day at Study End

Rats - Oral Gavage

Treatment Group	Cntrl1&2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
Male Week 87-88	26	25	25	27	26	22	29	26
Female Week 94-95	24	25	25	24	24	23	24	23

Mice - Dermal

Treatment Group	Cntrl1&2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
Male Week 104	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6
Female Week 103	6.7	6.5	6.4	7.1	7.0	6.7	6.4	6.5

Again from 2) above, excess mortality not associated with any tumor or sacrifice in the higher dose groups might suggest that the MTD was exceeded. One way to assess this possibility is to measure mortality not associated with any identified tumor. Note this seems to be a novel way to assess if the high dose is at the MTD. Table 7 below indicates the number of animals in each dose group that died of a natural death or moribund sacrifice, but did not show any tumors:

Table 7: Natural Death or Accident with No Identified Tumor

Male Rats - Oral Gavage

Treatment Group	Cntrl1&2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
Tumor/sacrificed	97	50	52	49	52	43	53	46
Early Deaths	27	12	10	13	10	19	9	16
	21.8%	19.4%	16.1%	21.0%	16.1%	30.7%	14.5%	25.8%

Female Rats - Oral Gavage

Treatment Group	Cntrl1&2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
Tumor/sacrificed	120	58	61	56	58	57	61	54
Early Deaths	4	4	1	6	4	4	1	8
	3.2%	6.5%	1.6%	9.7%	6.5%	6.6%	1.6%	12.9%

Male Mice - Oral Gavage

Treatment Group	Cntrl1&2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
Tumor/sacrificed	103	47	52	49	43	51	51	47
Early Deaths	17	13	8	11	17	9	9	8
	14.2%	21.7%	13.3%	18.3%	28.3%	15%	15%	21.7%

Female Mice - Oral Gavage

Treatment Group	Cntrl1&2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
Tumor/sacrificed	96	48	43	44	53	49	47	44
Early Deaths	24	12	17	16	7	11	13	16
	20%	20%	28.3%	26.7%	11.7%	18.3%	21.7%	26.7%

	Male Rats	Female Rats	Male Mice	Female Mice
Log Rank	<0.0001	0.5701	0.4812	0.8952
Wilcoxon	<0.0001	0.4031	0.7879	0.8430

The test statistics above correspond to tests of differences in dose groups in terms of the time to early non-tumor related death event. In male rats there is a statistically significant difference in these statistics (both Wilcoxon and log rank < 0.0001). This seems to be largely due to high mortality in the high BP7 group and to a lesser degree in the Cl9 group. Tests of differences in mice and female rats were not statistically significant (all six $p \geq 0.4031$), suggesting no treatment related differences. Ignoring other considerations, these results suggest that the MTD may been exceeded in the BP7 and possibly Cl9 group in male rats, while in female rats and both genders in mice this particularly analysis does not provide evidence that the MTD was exceeded.

The pharm/tox reviewers should use their expertise and other information such as clinical signs or severe histopathologic toxic effects that are attributable to the dosed animals in their final evaluation of the appropriateness of the doses used.

1.3.2. Statistical Findings

Please see Section 1.1 above.

2. INTRODUCTION

2.1. Overview

This submission included results from both a dily gavage study in — Sprague Dawley —CD®BR VAF/Plus® and a study in — (UK) —CD-1® (ICR)BR Mice with dermal application of — gel. This is has 5% benzoyl peroxide while — gel has 2.5% benzoul peroxide. b(4)

2.2. Data Sources

Two SAS transport files, one for rats and the other for mice, were provided by the Sponsor and placed in the CDER electronic data room (edr). These files, each labeled tumor.xpt, each contained the single SAS data set tumor.sas7bdat. Several tumors appeared in a number of organs. Both the original incidences and the combined incidences are reported in the incidence tables in Appendix 2.

In the rat data set animals with codes 2448, 2751, and 2963 had correctable errors in several variables in a number of records. Rat 2391 was recorded as a terminal sacrifice even though the animal died on week 50 of the study. This was recoded to a natural death/moribund sacrifice. Also, the time of death of female animal 3230 was missing in all records and this animal was also deleted from the study. Two tumor codes were associated with the same tumor name, so one was recoded to the other. Note that these and several other problems became apparent when reconciling different marginal totals. Where the appropriate value seemed to be apparent, the data were corrected. But the presence of these clear data errors does suggest there may be other data problems in the rat data not so easily detected.

No such data errors were obvious in the mice data. However, the Sponsor's data set distinguished between tumors noted as "[B]" and "[M]", presumably benign and malignant, as well as distinguishing between the presence of the tumor in the organ, multiple tumors in the organ, and metastising tumors in the organ, whether it is unilateral or bilateral, whether it is "associated" or not, etc. But when tumors are broken down into such small subgroups, conventional statistical tests have great difficulty in detecting treatment differences. Thus in the analysis many tumors with similar names were combined. Appendix 3 shows these combinations. Also, many of the tumor names and the organ and tumor codes were too long for some of our software. So these were also recoded, and the new values are also displayed in this appendix. In rats there were also a number of apparent coding problems that were not changed since they did not seem to affect final results.

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

NA

3.2. Evaluation of Safety

More detailed results on the study are presented below.

3.2.1. Study SLS 3242.36: 2 Year Oral (Gavage) Carcinogenicity Study of an Admixture Gel (Benzoyl Peroxide 5% and Clindamycin Phosphate 1%) and Its Components in Rats

RAT STUDY DURATION: Males: High dose Benzoyl Peroxide alone (BP7) to Week 88.
Males: BPCL5 to Week 95.
Males: other treatment groups to Week 97.
Females: to Week 95.
DOSING STARTING DATE: June 29, 1993.
TERMINATION OF IN-LIFE PHASE: May 5, 1995. b(4)
STUDY ENDING DATE (Final Report dated): November 19, 1997.
RAT STRAIN: ——— Sprague Dawley — CD®BR VAF/Plus®
ROUTE: Daily Oral Gavage.

Rats were randomized to the nine treatment groups per gender, numbered by the Sponsor as groups 1-9, with groups 1 and 2 denoting a vehicle control (3 ml/kg/day), group 3 with 5% benzoyl peroxide and 1% clindamycin in a dose of 0.3 ml/kg/day, group 4 with 5% benzoyl peroxide and 1% clindamycin in a dose of 0.9 ml/kg/day, group 5 with 5% benzoyl peroxide and 1% clindamycin in a dose of 3 ml/kg/day, group 6 with 5% benzoyl peroxide in a dose of 0.9 ml/kg/day, group 7 with 5% benzoyl peroxide in a dose of 3 ml/kg/day, group 8 with 1% bclindamycin in a dose of 0.9 ml/kg/day, and group 9 with 1% clindamycin in a dose of 3 ml/kg/day. In this reports these treatment groups were labeled as Cntrl1, Cntrl2, ClBP3, ClBP4, ClBP5, BP6, BP7, Cl8, and Cl9, respectively. Each group was supposed to include 62 animals but one female rat animal in the BP7 group had no time of death or time of detection for tumors and hence was deleted from the study.

According to the Sponsor: "The doses selected for this study are estimated to be 300 to 3000 times the maximum projected exposure of a human to the Admixture Active Gel in a lifetime exposure. In addition, the doses were selected to provide a maximum dose which would not be expected to produce overt nephrotoxicity or more than a 10% body weight loss with continuous daily dosing in the rat through a lifetime. The various treatments were administered via oral intubation (gavage) in this two year study to increase systemic exposure. However, the

combination test article is intended for dermal (topical) application in human therapeutic use." (page 26 of report)

In addition to the primary study animals there were 18 further animals per gender serving as satellite toxicological groups corresponding to the seven treatment groups Cntrl, ClBP3, ClBP5, BP6, BP7, Cl8, and Cl9, respectively. Animals were approximately seven weeks old at first dosing to allow for an extra week to correct for signs of dehydration, apparently due to the automatic watering system. Animals were housed singly during the study. Food and water were available ad libitum, except during procedures. The Sponsor states that detailed physical examinations were made on all animals each week. Body weights were recorded weekly for the first 13 weeks, and every 8 weeks thereafter, while food consumption was measured weekly.

3.2.1.1 Sponsor's Results and Conclusions

This section will present a summary of the Sponsor's analysis on survivability and tumorigencity in rats.

Survival analysis:

The Sponsor notes that: "A number of males and females from each study group were found dead or euthanized prior to study termination (i.e., unscheduled euthanasia). The incidence of death and unscheduled euthanasia is presented in the following table:"

Table 8. Sponsor's Summary of Survival:

Test Article:	Admixture Placebo Gel		Admixture Active Gel			Benzoyl Peroxide 5% Gel		Clindamycin Phosphate 1% Gel	
Group:	1	2	3	4	5	6	7	8	9
Level (cc/kg/day):	3.0	3.0	0.3	0.9	3.0	0.9	3.0	0.9	3.0
Males									
Found Dead	25	20	24	19	23	21	21	22	24
Unscheduled Euthanasia	14	14	17	17	19	20	21	16	14
Total	39	34	41	36	42	41	42	38	38
Females									
Found Dead	8	9	14	8	13	8	7	10	15
Unscheduled Euthanasia	32	33	27	26	25	27	29	28	24
Total	40	42	41	34	38	35	36	38	39

(page 35 of report)

Tumorigenicity analysis:

The Sponsor conclusions about the tumorigenicity are summarized from Appendix P as follows:

"Although there were some statistically significant differences in tumor incidence when control groups 1 and 2 were compared to the various treated groups, there were also statistically significant differences when the control groups were compared to one another. This suggests

that the statistical differences between the control and treated groups may have been entirely, or at least in part, to random variation. The only statistical difference that was significant when compared to each control group separately, as well as the control groups combined, was the incidence of pituitary adenoma in males from the Benzoyl Peroxide groups (i.e., 32.1% in group 7) was below the historical control mean of 38.1% (range of 26.3 to 50.0%) for this tumor in this strain of rats . . . This effect was not considered to be biologically meaningful." (page 42 of report)

Note that if the study is well designed, any differences in the control groups should be due solely to randomization. However, the Sponsor's statement that the statistically significant differences between the control groups "suggests that the statistically significant differences between the control and treated groups may have been due entirely, or at least in part, to random variation" is arguable. While the conclusion may be true, as an implication it does not seem to be statistically defensible.

3.2.1.2 FDA Reviewer's Results

This section will present the current Agency findings on survival and tumorigenicity in male and female rats.

Survival analysis:

The following tables (Table 9 for male rats, Table 10 for female rats) summarize the mortality results for the dose groups among rats. The data were grouped for the specified time period, and present the number of deaths during the time interval over the number at risk at the beginning of the interval. The percentage cited is the percent survived at the end of the interval. Note the BP7 treatment group in males was terminated in week 88.

Table 9. Summary of Male Rat Survival (dose/kg/day)

Period (Weeks)	Cntrl1	Cntrl2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
0-50	7/62[1] 88.7%[2]	6/62 90.3%	9/62 85.5%	3/62 95.2%	5/62 91.9%	1/62 98.4%	7/62 88.7%	7/62 88.7%	8/62 87.1%
51-78	17/55 61.3%	13/56 69.4%	12/53 66.1%	11/59 77.4%	19/57 61.3%	22/61 62.9%	19/55 58.1%	9/55 74.2%	16/54 61.3%
79-87	8/38 48.4%	7/43 58.1%	7/41 54.8%	13/48 56.5%	7/38 50.0%	8/39 50.0%	23/36 21.0%	15/46 50.0%	4/38 54.8%
88-96	7/30 37.1%	6/36 48.4%	13/34 33.9%	8/35 43.5%	11/31 32.3%	10/31 33.9%	13	6/31 40.3%	10/34 38.7%
Terminal 97	23	30	21	27	20	21		25	24

[1] number deaths / number at risk
[2] per cent survival to end of period.

Table 10. Summary of Female Rat Survival (dose/kg/day)

Period (Weeks)	Cntrl1	Cntrl2	ClBP3	ClBP4	ClBP5	BP6	BP7	Cl8	Cl9
0-50	1/62[1] 98.4%[2]	3/62 95.2%	3/62 95.2%	1/62 98.4%	3/62 96.7%	0/62	3/61 95.1%	4/62 93.5%	4/62 93.5%
51-78	19/61 67.7%	21/59 61.3%	18/59 66.1%	18/61 69.4%	15/58 71.0%	12/62 80.6%	14/58 72.1%	12/58 74.2%	17/58 66.1%
79-87	15/42 43.5%	10/38 45.2%	10/41 45.2%	12/43 50.0%	11/43 51.6%	14/50 58.1%	8/44 59.0%	13/46 53.2%	13/41 45.2%
88-94	5/27 35.5%	7/28 33.9%	10/31 33.9%	3/31 45.2%	9/32 38.7%	9/36 43.5%	11/36 41.0%	9/33 38.7%	5/28 37.1%
Terminal 95	22	21	21	28	24	27	25	24	23

[1] number deaths / number at risk

[2] per cent survival to end of period.

Table 11 below presents the result of tests on survival over the dose groups in rats . Overall, in male rats there is some evidence of a lack of homogeneity over all eight treatment groups (with pooled controls), particularly later in the study (logrank p = 0.0064, Wilcoxon p = 0.0723). However, tests of homogeneity in the male treatment group corresponding to proportional increases in both benzoyl peroxide and clindamycin and in the male treatment groups corresponding to the clinamycin only treatment groups were not statistically significant (all four $p \geq 0.3968$). The tests of homogeneity in the three benzoyl peroxide only treatment groups were statistically significant (logrank p = 0.0019, Wilcoxon p = 0.0281). The more powerful test of linear trend in dose among these benzoyl peroxide only groups is highly statistically significant (Wald p = 0.0006), reflecting the increasing mortality in dose apparent in Table 9 above or, somewhat more hidden, in figure A.1.1 in the Appendix 1. However, there is no evidence of heterogeneity among these groups beyond the simple dose related trend (Wald p = 0.8445). Further details are presented in Appendix 1. In female rats there is no statistically significant evidence of heterogeneity overall and among the three treatment subgroups (all six $p \geq 0.1270$).

Table 11. Statistical Significances of Tests of Homogeneity and Trend in Survival in Rats

	Males		Females	
	LR/Wald	Wilcoxon	LR/Wald	Wilcoxon
Homogeneity over all 8 groups	0.0064	0.0723	0.7098	0.5857
Homogeneity over Cntrl1&2, BPCl3-5	0.3968	0.4660	0.5373	0.5847
Trend over 4 groups Cntrl1&2, BPCl3-5	0.2911		0.3827	
Departure from trend	0.4166		0.5197	
Homogeneity over Cntrl 1+2, BP6,BP7	0.0019	0.0281	0.2079	0.1270
Trend over 3 groups Cntrl 1+2, BP6,BP7	0.0006		0.3088	
Departure from trend	0.8445		0.1651	
Homogeneity over Cntrl 1+2, Cl8, Cl9	0.9282	0.8820	0.5897	0.4391
Trend over 3 groups Cntrl 1+2, Cl8, Cl9	0.7018		0.7814	
Departure from trend	0.9917		0.3328	

Tumorigenicity analysis:

A complete incidence table of any tumor that had a trend or comparison that was statistically significant at the usual 0.05 level is presented in Table A.2.1 in Appendix 2. Following the Haseman-Lin-Rahman rules in female rats no trend or pairwise comparisons were statistically significant. However, table 12 below shows those tumors that were statistically significant using the Haseman-Lin-Rahman rules. In the table, for each organ, the following line displays the name of the neoplasm, followed by the incidence of that neoplasm. For each such organ-neoplasm combination, the next line provides the p-values of the various tests of trend and pair-wise comparisons to the pooled controls (groups 1 and 2). The p-values of the test of trend over the pooled controls and dose groups 3, 4, and 5 are labeled "pboth", while the p-values of the pair-wise comparisons of groups 3, 4, 5 appear under the columns "pCvs3", "pCvs4", and "pCvs5", respectively. The p-values of the test of trend over the pooled controls and the benzoyl peroxide treatment groups (with no clindamycin) is labeled "pBP", while the p-values of the corresponding pair-wise comparisons of groups 6 and 7 appear under the columns "pCvs6" and "pCvs7", respectively. The p-values of the test of trend over the pooled controls and the clindamycin treatment groups (with no benzoyl peroxide) is labeled "pBP", while the p-values of the corresponding pair-wise comparisons of groups 6 and 7 appear under the columns "pCvs8" and "pCvs9", respectively.

Note that all tumors in this table would be considered rare (since incidence in controls was less than 1%) The pairwise tests comparing mesenchymal tumors in the kidney and lymphoma in the lymph node in the low dose group with both benzoyl peroxide and clindamycin (i.e. BPCl3) was statistically significantly different from the pooled controls (both $p = 0.049 < 0.05$). The pairwise tests comparing histiocytic sarcoma in each of the lung, mesenteric lymph node, mediastinal lymph node, mammary gland, skeletal muscle, and tail in the low dose of clindamycin alone (i.e., Cl8) to controls were all exactly statistically significant (all $p=0.05$). Similar results were observed in fibroadenoma in the mammary gland, papilloma on the tail, and follicular adenoma of the thyroid compared to the controls (i.e. in Cl8 versus pooled controls $p=0.05$). The pairwise test comparing systemic histiocytic sarcoma in the Cl8 cell to the pooled controls (all $p=0.014 < 0.05$). The pairwise test comparing follicular adenoma of the thyroid in the low benzoyl peroxide group to the pooled controls was also statistically significant (all $p=0.013 < 0.05$). Finally, the pairwise test comparing benign basal cell tumors of the skin in the low benzoyl peroxide group (i.e., BP6) to the pooled controls was also exactly statistically significant (all $p=0.05$). These do suggest that there is some difference associated with the low clindamycin dose (i.e., Cl8). Note however, again, due to the large number of tests these are almost surely anticonservative, that is, the true overall error is likely much higher than the nominal 10%.