Approval Date: November 23, 1983

Freedom of Information Summary
NADA 106-964

I. GENERAL INFORMATION:

NADA: 106-964
Sponsor: Elanco Products Company
A Division of Eli Lilly and Company
740 South Alabama Street
Indianapolis, Indiana 46285

Generic Name: Apramycin Sulfate
Trade Name: APRALAN® Soluble Powder
Effect of Supplement: control of porcine colibacillosis.

II. INDICATIONS FOR USE

For the control of porcine colibacillosis.

III. DOSAGE:

A.	DOSAGE FORM	Mixed in Drinking Water
B.	ROUTE OF ADMINISTRATION	Oral
C.	RECOMMENDED DOSAGES:	Dosage level of 12.5 mg/kg bodyweight (5.7 mg/lb bdwt) daily for 7 days.
	NOTES	

IV. EFFECTIVENESS:

The following studies were conducted to evaluate the best dosage with naturally occurring infections. These studies are both dose-titration and controlled field investigations.

Trial No. TlB 198001

Investigator:

Dr. Vaughn C. Speer
Iowa State Univ.
Ames, Iowa 50011

Primary objective of the study was to evaluate levels of (1, 75, 225, 375, and 750 mg apramycin per gallon of drinking water for 7 days in weanling pigs with naturally occurring colibacillosis. These dosages are equivalent to approximately 0, 2.5, 7.5, 12.5

and 25 mg apramycin/kg/bodyweight/day.

A total of 120 pigs, 12 lbs average bodyweight, were used in the study. Pigs were pooled in a common pen for 2-3 days to allow colibacillosis to develop and were then allotted to treatment groups on the basis of weight and litter of origin. Treatments were randomly assigned to pens.

The trial extended over a 21-day period and parameters observed were growth performance, feed efficiency, and scour scores (scale of l-10 with l normal and 10 the most severe). Diagnosis was confirmed by the isolation of hemolytic E. coli from intestinal contents and rectal swabs.

A representative pig taken from the trial pigs was necropsied immediately prior to initiation of the trial. The intestinal tract contents yielded hemolytic E. coli organisms at liters of 1.7 x 10e6/ml in the duodenum and 6.0 x 10e8/ml in the ileum.

Treatment Groups were:

(Eds. note: The following table consists of 3 columns.)

Number	Days 0-7	Days 8-21
1	Nonmedicated	Nonmedicated
2	75 mg/gal	Nonmedicated
3	225 mg/gal	Nonmedicated
4	375 mg/gal	Nonmedicated
5	750 mg/gal	Nonmedicated

Twenty pens were used (4 pens for each group)

Results:

(Eds. note: The following table consists of 4 columns.)

*Scour Scores
(Average of each group)

Group	Average Score For lst Week	Average Score For 2nd Week	Average Score For 3rd Week
1	3.82	2.32	2.28
2	3.17	2.36	2.00
3	2.14	1.75	2.00
4	2.28	1.28	1.89
5	3.03	1.17	1.71

* 1 = normal - 10 = most severe

(Eds. note: The following table consists of 5 columns.)

----Average gains and feed per unit weight gain----

	--Average gains (kg)--		--Feed/unit gain ratio--	
Group	**1st 7 days**	**l-21 days**	**1st 7 days**	**1-21 days**
1	1.2	7.9	2.72	1.83
2	1.9	8.9	1.77	1.83
3	2.7	10.1	1.46	1.76
4	2.8	10.0	1.54	1.79
5	3.2	11.1	1.31	1.73

Trial No.TIB 058002

Investigator:

Dr. Paul Noland
University of Arkansas
Fayetteville, Arkansas

Primary objective of the trial was the same as trial No TIB198001 and the same protocol was followed.

A total of 120 pigs were used, average bodyweight of 12.5 lbs.

Representative pigs intestinal tracts were cultured and yielded hemolytic E. coli of 9.0 x 10e6, 4.0 x 10e5, 4.0 x 10e4, and 2.3 x 10e3.

Results:

(Eds. note: The following table consists of 4 columns.)

Scour Scores
(Average of each group)

Group	Average Score For 1st Week	Average Score For 2nd Week	Average Score For 3rd Week
1. (Nonmedicated)	5.4	3.1	2.8
2. 75 mg/gal (7 days)	3.7	2.7	3.4
3. 225 mg/gal (7 days)	3.6	2.5	2.6
4. 375 mg/gal (7 days)	4.0	2.7	2.8
5. 750 mg/gal (7 days)	4.6	3.0	2.8

(Eds. note: The following table consists of 5 columns.)

Average gains and feed per unit weight gain

Group	---Average gains (kg)--- 1st 7 days	1-21 days	---Feed/unit gain ratio--- 1st 7 days	1-21 days
1	1.4	8.0	2.96	2.01
2	2.2	9.1	1.89	1.85
3	2.2	8.5	1.99	1.89
4	2.7	10.5	1.55	1.76
5	3.0	10.7	1.53	1.79

Trial No. TIB198003

Investigator:

Dr. Vaughn C. Speer
Iowa State Univ.
Ames, Iowa 50011

The objective and protocol followed in this trial was the same as in the preceding two trials.

A total of 120 pigs averaging 12 pounds bodyweight were used. Representative pig's intestinal tracts were cultured and yielded hemolytic E. coli in the duodenum at titers of l.5 x 10e8 and 6.0 x 10e5 and in the ileum, 1.0 x 10e9 and 2.0 x 10e8.

Results:

(Eds. note: The following table consists of 5 columns.)

Scour Scores
(Average of each group)

Group	Average Score For 1st Week	Average Score For 2nd Week	Average Score For 3rd Week
l. (Nonmedicated)	3.75	2.10	1.61
2. 75 mg/gal (7 days)	3.03	1.70	1.68
3. 225 mg/gal (7 days)	3.14	2.18	2.11
4. 375 mg/gal (7 days)	2.92	2.11	1.68
5. 750 mg/gal (7 .days)	2.71	1.64	1.71

(Eds. note: The following table consists of 5 columns.)

Average gains and feed per unit weight gain

Group	---Average gains (kg)--- 1st 7 days	1-21 days	---Feed/unit gain ratio--- 1st 7 days	1-21 days
1	1.3	7.1	2.23	1.90
2	1.7	8.2	1.75	1.89
3	1.9	8.1	1.58	1.82
4	2.5	9.2	1.39	1.92

5	2.1	8.4	1.47	1.78

The data from the three trials were pooled because a common protocol was used.

Statistical evaluation of the data was conducted as follows:

(Eds. Note: The following table consists of 7 columns.)

TABLE I. DATA MEANS AND STANDARD ERRORS

	---Apramycin Level (mg/gal)--					
Measurement	**0**	**75**	**225**	**375**	**750**	**Standard Error**
Wt. Gain for 1 wk	0.578	0.886	1.019	1.223	1.264	0.070
Wt. Gain for 3 wks	3.475	3.967	4.043	4.547	4.562	0.164
Gain/Feed for 1 wk	0.422	0.575	0.639	0.684	0.706	0.028
Gain/Feed for 3 wks	0.525	0.543	0.552	0.558	0.568	0.009
Scours on 7th day	2.83	2.50	2.08	2.08	2.08	0.314
Scours on 14th day	2.25	2.08	2.00	1.92	2.42	0.297

(Eds. Note: The following table consists of 5 columns.)

TABLE 2. COMPARISON OF 375 AND 750 LEVEL MEANS

Measurement	**Observed Difference**	**t**	**Approx. p**	**Detectable* Difference**
Wt. Gain for 1 wk	0.041	0.413	0.3453	0.273
Wt. Gain for 3 wks	0.015	0.065	0.4742	0.587
Gain/Feed for 1 wk	0.022	0.558	0.2899	0.100
Gain/Feed for 3 wks	0.010	-	-	-
Scours on 7th day	0.	0.	0.5000	1.12
Scours on 14th day	0.50	1.190	0.8658	1.16

* With 80% power when conducting a one-sided test at the 0.05 level of significance.

WEIGHT GAIN:

The means for the data for weight gain (in kilograms) for one week is presented with their standard error in Table l above. These were used to investigate the dose response and to compare the responses at the 375 and 750 mg/gal levels. A best fitting model from the class of polynomial and linear plateau models was found to be the VI-l3 linear plateau model with R-squared equal to 0.9924. The R-squared values is interpreted to mean that 99.24% of the variability among the means is explained by the indicated model. The VI-13 linear plateau model is described as increasing line from 0 to the first non-zero level (75 mg/gal), intersecting an increasing line from the first non-zero level to the third non-zero level (375 mg/gal), intersecting a horizontal line (plateau) over the interval 375 to 750 mg/gal. This model implies that no statistically significant increase in

weight gain occurs beyond the 375 mg/gal level. A t test on the mean for the 0 and 75 mg/gal levels was significant with t (8) = 3.10 and p approximately 0.0073 for a one-sided test. Hence, 75 mg/gal is the statistically effective minimum level. However, the difference in the means for the 375 and 750 levels (0.041 kilograms) was not significant and the pooled studies were only sensitive enough to detect an increase of 0.273 kilograms with an 80% chance when conducting a one-sided test in the 0.05 level of significance. These results are summarized in Table 2 above.

The means for the data for weight gain for three weeks are reproduced in Table 1 along with their standard error. Using the same methodology implied in the previous paragraph, it was found that a best fitting model is the III-3 linear plateau model and that the minimum effective level is 75 mg/gal. The III-3 linear plateau model is described as an increasing line from 0 to the third non-zero level (375 mg/gal), intersecting a horizontal line (plateau) over the interval 375 to 750 mg/gal. No statistically significant increase in weight gain was detected between the 375 and 750 mg/gal levels. However, the combined studies were only sensitive enough to detect an increase of 0.587 kilograms over the mean for the 375 mg/gal level (an approx. increase of 12.9%) with an 80% chance when conducting a one-sided test at the 0.05 level of significance. These results are summarized in Table 2.

FEED EFFICIENCY:

The means for the data for gain/feed for one week are also presented with their standard errors in Table l and were used to investigate the dose response and to compare the responses at the two highest levels appearing in the studies. The statistical results are similar to those for weight gain for one week and are summarized in table 2.

The means for the data for gain/feed for three weeks, were evaluated. A best fitting model of these means was found to be the V-l linear plateau model. This model is described as an increasing line from 0 to the first non-zero level (75 mg/gal), intersecting another increasing line over the interval 75 to 750 mg/gal. Since this model increases over the entire range tested in these studies, the maximum statistically effective level is the maximum level tested, 750 mg/gal. At test on the means for the 0 and 75 mg/gal levels was significant at the 0.10 level of significance with t (44) = l.39 and p approximately 0.0853 for the on-sided test. At test on the means for the 0 and 225 mg/gal levels was significant at a smaller level of significance with t(44) = 2.08 and p approximately 0.0218 for the one-sided test. Since the V-1 model indicates increasing efficacy over the interval 375 to 750 mg/gal, the detectable difference for inclusion in Table 2 does not need to be calculated.

SCOUR SCORES for 7th and l4th Days

An analysis similar to that conducted for the previous measures was conducted for the scour scores on the seventh day. The drug level means and their standard error are displayed in Table 1 and the statistical results are summarized in Table 2.

There was no model that adequately fit the drug level means for the scour scores the fourteenth day, which are given in Table 1 with their standard error. The scour score means numerically, but not statistically, increased for the drug level change of 375 to 750 mg/gal. The statistical analysis results are summarized in Table 2.

To further evaluate effectiveness of the 375 and 750 mg/gallon doses of Apramycin on the scour scores in the trials statistical analysis of the average daily scour scores for the-first seven days of the trial (period of drug administration) was conducted.

(Eds. note: The following table consists of 7 columns.)

AVERAGE DAILY SCOUR SCORES FOR THE FIRST SEVEN DAYS (DURING DRUG ADMINISTRATION)

		-----Apramycin Dose Level----- (mg/gallon drinking water)				
Trial	**Rep**	**0**	**75**	**225**	**375**	**750**
TlBl98001	1	4.86	2.57	1.86	1.57	3.00
	2	2.86	3.86	1.86	2.86	2.43
	3	3.00	3.71	3.43	3.00	3.14
	4	4.57	2.57	1.43	1.71	3.57
TlB058002	1	5.14	2.86	3.71	4.14	3.71
	2	4.28	3.71	2.14	3.57	4.71
	3	8.28	4.86	5.14	4.57	4.43
	4	5.57	3.43	3.57	3.86	5.71
T1B198003	1	3.71	1.57	3.14	2.57	2.86
	2	4.14	4.86	4.57	3.57	3.57
	3	2.86	3.14	1.86	2.86	2.86
	4	4.28	2.57	3.00	2.71	1.57
Mean		4.296	3.309	2.976	3.082	3.463
Std. Error		0.219	0.219	0.219	0.219	0.219

The means were used to investigate the dose response and to compare responses at 375 and 750 mg/gal levels. From the class of polynomial and linear plateau models it was found that the data statistically supported two different linear plateau models: the III-l and V-2 models.

The III-I linear plateau model is a decreasing straight line over the interval 0 to 75 mg/gal intersecting a horizontal line over the interval 225 to 375 to 750 mg/gal. The horizontal line over the interval 75 to 750 mg/gal indicates that there are no statistically significant differences in the means for the 75, 225, 375, and 750 mg/gal levels. A t test on the mean for the control group was statistically significant with p approximately 0.0014 for the one-sided test. This information statistically supports an effective level of 75 mg/gal for increased efficacy over untreated controls measured by the means of the seven-days average scour scores.

The V-2 linear plateau model, is a decreasing straight line over the interval 0 to 75 to 225 mg/gal intersecting an increasing straight line over the interval 225 to 375 to 750 mg/gal. The increasing straight line over the interval 225 to 750 mg/gal indicates that the means for 375 and 750 mg/gal levels are progressively larger than the mean for the 225 mg/gal level. The decreasing straight line over the interval 0 to 225 mg/gal indicates that the means for this measure of efficacy significantly decrease from 0 to 75 to 225 mg/gal. This information together with the t test mentioned in the previous paragraph supports an effective range of 75 to 225 mg/gal for increased efficacy over untreated controls measured by the means of the seven-day average scour scores.

The two models obviously give different results. But they can both be supported statistically and cannot be said to be statistically different. Model III-I fits the beginning of the tested range of levels better than the end, while the V-2 model does the opposite.

Conclusions for the Studies

Scour scores for the evaluation of weanling pig colibacillosis is a subjective parameter that can be expected to show some inconsistencies between evaluators. However, it is an important parameter that gives an indication of disease presence and intensity. Evaluation of the scour scores in the studies indicated that apramycin administered at 75 to 225 mg/gallon water was effective against this parameter as measured by the means of the seven-day average scour scores. The scour scores on day 7 showed no difference between the 225, 375 and 750 mg/gallon levels and on day 14 there was no statistical improvement in the 750 over the 375 mg/gallon level.

Weight gain and feed efficiency are objective parameters that are directly affected by colibacillosis in weanling pigs and hence become at, least of equal importance to scour scores in evaluation of drug effectiveness.

Evaluation of these parameters resulted in the conclusion that there was no advantage in administering apramycin at 750 mg/gallon over 375 mg/gallon for the control of weanling pig colibacillosis and that, 375 mg/gallon is the best dose for the indication for use.

V. ANIMAL SAFETY:

This is a Category II supplement. No reevaluation of data in the parent NADA was required because no adverse effect on animal safety would result from approval of this supplement because less total drug would be used. No new data were required for animal safety.

VI. HUMAN SAFETY:

A. Safe Concentrations of Residues

The tolerances for total residues of apramycin in uncooked edible swine tissues were

established, based upon toxicology studies previously submitted under this NADA, as 0.1 ppm for muscle, 0.3 ppm for liver, and 0.4 ppm for kidney and fat.

B. Metabolism Studies

Under the original NADA, metabolism studies in swine were conducted to select a marker substance and target tissue for apramycin. Swine kidney is the target tissue with parent apramycin being the marker residue. A marker residue concentration of 0.l part per million in kidney corresponds to 0.4 part per million total residue in this target tissue determined by the regulatory method.

C. Regulatory Method

Under the original NADA, a method was developed for the determination of parent apramycin at the tolerance of 0.1 ppm and above in swine kidney.

D. Withdrawal Time

Under the original NADA, it was determined that a withdrawal time of 28 days was necessary for residues of apramycin to deplete to safe concentrations in all tissues after treatment with a dosage of 25 mg/kg BW. Because this supplemental NADA provides for use of apramycin in swine for 7 days at a dosage of 12.5 mg/kg BW with no change in withdrawal time, no additional residue studies were required.

VII. AGENCY CONCLUSIONS:

Under the agency's proposed supplemental approval policy (42 FR 64367) this is a Category II change. This supplement provides for a dosage of apramycin of 12.5 mg/kg BW to swine for the control of porcine colibacillosis The firm also requested withdrawal of the approved 25 mg/kg BW dosage for the treatment of porcine colibacillosis. No change in withdrawal time was requested and the use of the word "control" will not result in more animals receiving the drug. Because such a change will not increase the exposure of humans to residues of apramycin, this Category II supplement did not require a re-review of the human food safety data contained in the original NADA.

The data submitted in support of this application comply with the requirements of section 512 of the Act and demonstrate that Apralan Soluble powder when used under its proposed conditions of use, is safe and effective for the control of porcine colibacillosis caused by strains of E. coli sensitive to apramycin.

In addition, the tissues of animals receiving Apralan Soluble Powder are safe for human consumption, provided the label-recommended 28-day withdrawal period is observed.

VIII. LABELING (Attached)

1. Apralan® product label

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

FOI Summary; NADA 106-964 (supplemental); APRALAN® (Apramycin Sulfate); re: New dosages;
--Editor's abstract

1. General Information:

Identification: NADA

Date: November 23, 1983

Name of Applicant:

Chemical Name: See USAN l980 Page 30
Generic Name:

Proprietary Name:

The sponsor submitted a supplemental new animal drug application on December 22, 1982, amended July 13, 1983.

The supplement provides for the following:

A. A

B. Indications

Animal Safety:

Human Safety:

Agency Conclusions

Labeling

Copies of these labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.