Approval Date: May 12, 2003

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-025

Laidlomycin propionate potassium (Cattlyst®)

1) For improved feed efficiency and increased rate of weight gain in cattle fed in confinement for slaughter.

2) For improved feed efficiency in cattle fed in confinement for slaughter.

Sponsored by:
Alpharma Inc.
One Executive Drive
P.O. Box 1399
Fort Lee, New Jersey 07024

FREEDOM OF INFORMATION SUMMARY

Cattlyst® in Cattle Feeds

1. GENERAL INFORMATION:

a. File Number:	NADA 141-025
b. Sponsor:	Alpharma Inc. One Executive Drive P.O. Box 1399 Fort Lee, New Jersey 07024 Drug Labeler Code: 046573
c. Established Name:	Laidlomycin propionate potassium
d. Proprietary Name:	Cattlyst®
e. Dosage Form:	Type A medicated article
f. How Supplied:	10 lb. plastic bottles
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	50 grams of laidlomycin propionate potassium activity per pound.
i. Route of Administration:	Orally, via the feed
j. Species/Class:	Cattle
k. Recommended Dosage:	1) 5 g/ton for improved feed efficiency and increased rate of weight gain; and 2) 5 to 10 g/ton for improved feed efficiency.
l. Pharmacological Category:	Ionophore

m. Indications:	1) For improved feed efficiency and increased rate of weight gain in cattle fed in confinement for slaughter. 2) For improved feed efficiency in cattle fed in confinement for slaughter.
n. Effect of Supplement:	Codification of Acceptable Daily Intake (ADI) and establishment of a Tolerance for residues.

2. EFFECTIVENESS:

Laidlomycin propionate potassium was previously approved for use in cattle feed (21 CFR 558.305(d)(1 and 2)). Data from five adequate and well-controlled studies demonstrating the effectiveness of laidlomycin propionate potassium for improved feed efficiency and increased rate of weight gain in cattle when administered in accordance with its approved uses and conditions of use are summarized in the Freedom of Information (FOI) summary for NADA 141-025, laidlomycin propionate potassium (Cattlyst®), original approval dated March 4, 1994. This supplemental approval does not affect this section of the summary.

3. TARGET ANIMAL SAFETY:

Data from two adequate and well-controlled studies demonstrating the target animal safety of laidlomycin propionate potassium for improved feed efficiency and increased rate of weight gain in cattle when administered in accordance with its approved uses and conditions of use are summarized in the FOI summary for NADA 141-025, laidlomycin propionate potassium (Cattlyst®), original approval dated March 4, 1994. This supplemental approval does not affect this section of the summary.

4. HUMAN SAFETY:

a. Toxicity:

Data from 10 toxicity studies of laidlomycin propionate potassium are summarized in the FOI summary for NADA 141-025, laidlomycin propionate potassium (Cattlyst®), original approval dated March 4, 1994.

b. Safe Concentration of Total Residues - Determination of No Observed Effect Level (NOEL):

The NOEL is the highest dose that produced no observed effects in the most sensitive species in the toxicity studies. The most sensitive species for laidlomycin propionate potassium

found in the studies in Part 4a was the dog in *Study 36-D-86*, in which a NOEL of 0.75 mg/kg/day was observed during a one-year chronic toxicity study.

c. Safe Concentration of Total Residues – Calculation of the Acceptable Daily Intake (ADI) and the Safe Concentration (SC):

The ADI for total residues of a new animal drug in edible products of food producing animals treated with the new animal drug is given by the equation:

$$\text{ADI, mcg/kg/day} = \frac{\text{NOEL in most sensitive species, mg/kg/day}}{\text{Safety factor}} \text{ X } 1000$$

For data based upon a one-year chronic toxicology study, a safety factor of 100 is assumed. Therefore, the ADI for total residues of laidlomycin propionate is given by the equation:

$$\text{ADI, mcg/kg/day} = \frac{0.75 \text{ mg/kg/day}}{100} \text{ X } 1000 = 7.5 \text{ mcg/kg/day}$$

An Acceptable Daily Intake (ADI) of 7.5 mcg/kg/day is assigned for laidlomycin.

The safe concentration of residues of a new animal drug in an edible product of a food-producing animal treated with the new animal drug is given by the equation:

$$\text{Safe concentration, ppm} = \frac{\text{ADI, mcg/kg/day X 60 kg adult}}{\text{Grams consumed/day}}$$

Using the ADI of 7.5 mcg/kg/day above and the current Food and Drug Administration consumption factors for edible products of food producing animals, the safe concentrations of total residues of laidlomycin propionate for the edible products of cattle are given in the table below.

Edible Product	Grams consumed/day	Safe concentration, ppm
Muscle	300	1.5
Liver	100	4.5
Kidney	50	9.0
Fat	50	9.0

d. Total Residue Depletion and Metabolism Studies:

Data from a total residue depletion and metabolism study of ^{14}C-laidlomycin propionate potassium in cattle, *Study IAS 1109-380,* were summarized in the FOI summary for NADA

141-025, laidlomycin propionate potassium (Cattlyst®), original approval dated March 4,1994. The results of that study are shown in the table below.

Time after last dose, h.	Laidlomycin propionate-derived residue, ppm (mean ± std. dev.)			
	Liver	Kidney	Muscle	Fat
12	0.926 ± 0.004	0.025 ± 0.003	0.010 ± 0.004	0.041 ± 0.009
24	0.487 ± 0.114	0.022 ± 0.006	0.005 ± 0.002	0.032 ± 0.006
72	0.166 ± 0.088	0.017 ± 0.005	0.003 ± 0.002	0.030 ± 0.012
144	0.087 ± 0.018	0.010 ± 0.004	0.004 ± 0.001	0.037 ±0 .013

Study 880l –Characterization of the ^{14}C-Residues Present in the Liver of Cattle Following Oral Administration of ^{14}C-LaidlomycinProprionate Potassium.

The study was conducted at Syntex Research, Palo Alto, California to characterize the residues present in the liver of cattle slaughtered in *Study IAS 1109-380* above.

The ^{14}C-metabolites present in the livers from cattle slaughtered at 12 hours and 24 hours after the last dose were characterized by HPLC of the material extracted with methanol. More than 95% of the radioactivity could be extracted, indicating very little protein-bound residue was present. For continued operation of the HPLC column, however, it was necessary to filter the methanol extracts prior to HPLC analysis, resulting in 37% recovery. Nevertheless, the chromatograms for filtered and unfiltered extract were found to be the same when corrected for recovery. The HPLC analysis of the filtered liver extracts revealed that laidlomycin and despropionyl laidlomycin were present as major metabolites at 12.67% and 13.67% of the extractable residue, respectively. No laidlomycin propionate was found, and no other single metabolite represented more than 10% of the extractable residue.

e. Comparative Metabolism Studies:

Data from a comparative metabolism study of laidlomycin propionate in dogs was summarized in the FOI summary for NADA 141-025, laidlomycin propionate potassium (Cattlyst®), original approval dated March 4, 1994.

f. Residue Depletion Studies:

Study CD-99-20 – Tissue Residues of Laidlomycin and Chlortetracycline in Cattle Fed Cattlyst® (Laidlomycin) in combination with Aureomycin® (chlortetracycline).

The in-life portion of the study was conducted at Alpharma Inc., Wrightstown, NJ, with assays conducted at Analytical Development Corporation, Colorado Springs, Colorado and Colorado Animal Research Enterprises (CARE), Fort Collins, Colorado, to establish that at zero withdrawal time, chlortetracycline in the presence of laidlomycin propionate potassium does not exceed its established tolerance, that laidlomycin propionate potassium in the presence of chlortetracycline does not exceed the residue in cattle fed

only laidlomycin, and that the presence of the drugs in the same cattle tissue do not interfere with the assay for either drug.

Eighteen cattle were assigned to three treatment groups consisting of a nonmedicated control group, a laidlomycin-only medicated treatment group, and a chlortetracycline and laidlomycin medicated treatment group. Crossbred control cattle (1 steer, 1 heifer) were fed unmedicated feed for 14 days. Crossbred laidlomycin-only medicated cattle (4 steers, 4 heifers) received feed containing 150 mg laidlomycin propionate potassium/head/day for 14 days. Crossbred laidlomycin and chlortetracycline medicated cattle (4 steers, 4 heifers) received feed containing 150 mg laidlomycin propionate potassium/head/day and 10 mg chlortetracycline/lb bodyweight/day for 14 days. All cattle were slaughtered within 12 hours after removing the feed. Liver and kidney tissues were collected and analyzed for residue. Laidlomycin liver residues were measured using an HPLC method. Chlortetracycline kidney residues were determined by the approved microbiology method. The results are given in the table below.

Treatment Group	**Laidlomycin (ppm)**	**Chlortetracycline (ppm)**
Laidlomycin	**0.062 ± 0.031**	**---**
Laidlomycin + Chlortetracycline	**0.055 ± 0.017**	**1.266 ± 0.376**

The limit of quantification (LOQ) for laidlomycin in liver was 0.050 ppm. The LOQ for chlortetracycline in kidney was 0.025 ppm.

Residues of chlortetracycline in kidney of cattle medicated with chlortetracycline and laidlomycin were less than the established tolerance limit of 12 ppm at twelve hours withdrawal. Residues of laidlomycin in liver of cattle medicated with laidlomycin plus chlortetracycline did not differ significantly ($p = 0.605$) from that of cattle medicated with laidlomycin alone.

Samples of control kidney were fortified with chlortetracycline and laidlomycin. The data showed that the presence of laidlomycin did not interfere with the assay of chlortetracycline and the presence of chlortetracycline did not interfere with the assay of laidlomycin.

g. Tolerance and Withdrawal Time:

The target tissue is the edible tissue selected to monitor for total residues and is the last tissue in which residues deplete to the safe concentration. The marker residue is a residue whose concentration is in a known relationship to the concentration of total residues in the target tissue. Liver was selected as the target tissue and laidlomycin was selected as the marker residue based on the data in *Study 1109*-380 in Part 4d. The percentage of total residues in liver accounted for by laidlomycin was determined using the data in Part 4d as follows:

Mean total radioactivity in liver at 12 hours post treatment in *Study 1109-380*:	0.926 ppm
Mean recovery of total radioactivity from liver following HPLC in *Study 880l*: ppm	37% of 0.926 = 0.343
Mean recovery of radioactivity corresponding to laidlomycin in *Study 880l*: ppm	12.67% of 0.343 = 0.043
Percentage of total residues accounted for by laidlomycin:	0.043/0.927 = 4.64%

Using the safe concentration for total residues of laidlomycin propionate potassium in liver from Part 4c and the marker to total residue ratio above, the tolerance for laidlomycin in liver would be 4.64% of 4.5 ppm or 0.21 ppm.

Using the data in *Study CD-99-20* in Part 4f and a single time-point calculation with 99% statistical tolerance and 95% confidence with the overall mean of 56.0 and standard deviation of 27.8, the tolerance for laidlomycin in liver would be 0.152 ppm. Using the data for the Laidlomycin treatment only, the tolerance would be 0.197 ppm. Using only the data that are above the LOQ, the tolerance would be 0.166 ppm.

It was concluded that 0.20 ppm is the appropriate value when the variability of the marker data are considered. Therefore, a tolerance of 0.2 ppm is assigned for laidlomycin in cattle liver.

A withdrawal time for use of laidlomycin propionate sodium in cattle was not required under the original approval of laidlomycin propionate potassium (Cattlyst®), dated March 4, 1994, as total drug related residues at zero withdrawal in cattle in *Study 1109*-380 in Part 4d were well below the safe concentrations of residues listed in Part 4c. Results of *Study CD-99-20* in Part 4f confirmed this conclusion.

h. Regulatory Methods for Residues:

A regulatory analytical method for the measurement of residues of laidlomycin propionate in the edible tissues of cattle was not required under the original approval of laidlomycin propionate potassium (Cattlyst®), dated March 4, 1994, as total drug related residues in cattle at zero withdrawal are well below the safe concentrations of residues.

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrates that laidlomycin propionate potassium when administered at 5 g/ton or 5 to 10 g/ton to cattle being fed in confinement for slaughter is safe and effective for the claims indicated in section 1 of this FOI Summary.

Pursuant to 21 CFR 514.106(b)(2), this NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADA.

The drug is to be fed in Type C medicated feeds in accordance with section 1 of the FOI Summary and the Blue Bird labeling that is attached to this document.

This approval does not qualify for marketing exclusivity.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions of use by the layperson have been provided and the product will have over-the-counter (OTC) status. Label directions provide detailed instruction in plain language. The drug product is not a controlled substance. Thus, the OTC status of the NADA is continued. The labeling is adequate for the intended use.

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

Type A Medicated Article

Type C Medicated Feed (Blue Bird)
- BLUEBIRD CATTLYST® (5 -10 g/ton)
- BLUEBIRD CATTLYST® (5 g/ton)

Type B Medicated Feed (Blue Bird)
- BLUEBIRD CATTLYST® (11 – 2000 g/ton) at rate to provide not less than 30 mg nor more than 150 mg/head/day
- BLUEBIRD CATTLYST® (11 – 2000 g/ton) at rate to provide not less than 30 mg nor more than 75 mg/head/day
- BLUEBIRD CATTLYST® LIQUID SUPPLEMENT (100 – 2000 g/ton)