Approval Date: December 18, 1987

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-579

B. Sponsor

Hoffmann-LaRoche, Inc.
Nutley, NJ 07110

C. Proprietary Name

Bovatec®, Terramycin

D. Established Name

lasalocid sodium, oxytetracycline (monoalkyl trimethyl ammonium salt)

E. Dosage Form

Medicated Feed

F. Dosage Regimen

Lasalocid sodium: 10 to 30 g/ton of Type C feed for improved feed efficiency; 25 to 30 g/ton of Type C feed for improved feed efficiency and increased rate of weight gain.

Oxytetracycline (monoalkyl trimethyl ammonium salt): 75 mg per head per day.

G. Route of Administration

Oral

H. Indication

For improved feed efficiency, increased rate of weight gain and reduction of the incidence and severity of liver abscesses in beef cattle fed in confinement for slaughter.

I. Effect of Supplement

This supplement provides for <changes being approved> (Delete this section for Original approvals)

II. EFFECTIVENESS

Lasalocid is approved (21 CFR 558.311; 47 FR 34133/4, August 6, 1982) for improved feed efficiency and increased rate of weight gain in beef cattle fed in confinement for slaughter. Oxytetracycline (OTC) is approved (21 CFR 558.450) for reduction of the incidence and severity of liver abscesses in beef cattle weighing over 400 lbs.

A. Pivotal Studies

1. Study C-109

This was a 108 day feedlot study conducted by Mr. Michael Wittler, Colorado Beef Research Feedlot, Lamar, Colorado. One hundred sixty-eight English crossbred steers with average initial weight of 792 lb were blocked by weight and randomly allotted to the following treatment groups: 1) negative control; 2) lasalocid 30 g/t, 3) lasalocid 30 g/t + OTC 75 mg/hd/day, and 4) OTC 75 mg/hd/day. There were six pens of seven animals/pen per treatment. The steers were fed an 82% concentrate ration consisting of steam flaked corn, alfalfa hay, magoferm, mineral supplement and drug supplement. Feed was mixed and fed once daily. Data recorded consisted of individual fasted weights at day one and 108 of test period, pen weights at 28 and 56 days, total feed consumption per pen, and incidence of liver abscesses per pen. The following results were reported:

	Control	**Las**	**Las + OTC**	**OTC**
N	42	42	42	42
ADG (lb)	3.62	3.80	3.67	3.65
ADFI (lb)	27.61	27.94	25.97	27.39
F/G	7.68	7.41	7.09	7.49
Liver Abs.	15/42	9/42	7/42	4/42

2. Study C-205

This was a 182 day feedlot study conducted by Dr. Rodney Preston, Texas Tech University, Lubbock, Texas. One hundred twenty crossbred steers (Hereford, Angus and exotic crosses) with average initial weight of 578 lb were blocked by breed and randomly assigned to the following treatments: 1) negative control, 2) OTC 75 mg/hd/day, and 3) lasalocid 30 g/t + OTC 75 mg/hd/day. There were five pens of eight animals/pen per treatment. The steers were fed an 88% concentrate ration consisting of milo, cottonseed hulls, alfalfa hay, molasses, mineral/vitamin mix and drug supplement. Animals were weighed at 0, 28, 56, 98, 126 154 and 182 (last day on test) days on test. Total feed consumption per pen was determined at time of animal weighing. Liver abscess scores and carcass quality data were recorded. The following results were reported:

	Control	**OTC**	**Las + OTC**
N	39	40	38
ADG (lb)	2.03	2.12	2.18
ADFI (lb)	21.3	21.1	21.3
Feed/Gain	10.49	9.96	9.77
Liver Ab.	5/39	2/40	6/38

3. Study C-207

This was a 132 day feedlot study conducted by Dr. Don Gill, Panhandle University Feedlot, Goodwell, Oklahoma. One hundred twenty steers (734 lb average initial weight) were randomly assigned to the following treatment groups: 1) control, 2) OTC 75 mg/hd/day, and 3) OTC 75 mg/hd/day + lasalocid 30 g/t. There were five pens of eight animals/pen/treatment. The steers were fed a 95% concentrate ration consisting of whole shelled corn,

cottonseed hulls, soybean mean, limestone, and drug supplement. Feed was mixed and fed twice daily. Animals were weighed (shrunk) on days 1 and 132 of study. Interim weights and feed consumption were taken at 28, 62, 111 and 132 days. Carcass and liver abscess data were taken at slaughter. The following results were reported:

	Control	**OTC**	**Las + OTC**
N	39	39	40
ADG (lb)	2.80	2.73	3.02
ADFI (lb)	19.0	18.3	18.9
Feed/Gain	6.80	6.71	6.26
Liver Ab.	4/39	2/39	0.40

4. Study C-225

This was a 145 day feedlot study conducted by Dr. Dallas Horton, Horton Feedlot and Res. Ctr., Wellington, Colorado. One hundred twenty Hereford X Angus crossbred steers with average initial weight of 712 lb. were blocked by weight and randomly assigned to the following treatments: 1) Control, 2) OTC 75 mg/hd/day, and 3) lasalocid 30 g/t + OTC 75 mg/hd/day. There were five pens of eight head/pen/treatment. The steers were fed an 85% concentrate ration consisting of corn, corn silage and drug supplement. Diet was adjusted from 40 % to 85% corn over a three week period. Data reported included individual zero and 145 day weights, 28 day interim pen weights, feed consumption (corrected for weigh backs) and carcass and liver abscess data. The following results are reported:

	Control	**OTC**	**Las + OTC**
N	39	39	40
ADG (lb)	2.65	2.68	2.66
ADFI (lb)	17.63	17.49	17.56
Feed/Gain	6.65	6.53	6.60
Liver Ab.	20/39	18/39	14/40

5. Study C-226

This was a 128 day feedlot study conducted by Dr. Donald Hinman, Univ. of Idaho, Caldwell, Idaho. One hundred twenty steers (Hereford and Hereford X Angus) with average initial weight of 725 lb. were randomly assigned to the following treatments: 1) control, 2) OTC 75 mg/hd/day, 3) lasalocid 30 g/ton + OTC 75 mg/hd/day. There were five pens of eight head/pen/treatment. The steers were fed an 85% ration of barley, alfalfa, corn silage, molasses, and drug supplement. Data recorded consisted of initial and final weights, 28 day interim weights, feed consumption, and carcass liver abscess data. The following results were reported:

	Control	**OTC**	**Las + OTC**
N	40	40	40
ADG (lb)	2.58	2.64	2.26
ADFI (lb)	17.84	18.29	18.04
Feed/Gain	6.92	6.94	6.90
Liver Ab.	16/40	11/40	11/40

6. Study C-83-27

This was a 90 day feedlot study conducted by Dr. Steven Rust, Montana State University, Huntly, Montana. One hundred seventy six steers of British origin (avg. initial weight of 794 lb) were allocated by weight, breed, and previous implant type to the following treatment groups: 1) control, 2) OTC, 3) lasalocid, and 4) OTC + lasalocid. The steers were fed a 90% concentrate diet consisting of barley, alfalfa silage, and supplement. Individual weights were taken initially and at end of trial. Daily feed consumption, carcass quality, and liver abscess data were recorded. The following results were reported:

	Control	**OTC**	**OTC + Las**	**Las**
N	43	44	44	43
ADG (lb)	3.12	3.15	3.15	3.19
ADFI (lb)	23.0	22.7	22.6	22.3
Feed/Gain	6.48	6.36	6.34	6.45
Liver Ab.	12/43	10/44	11/44	11/44

Data from Studies C-109, C-205, C-207, C-225 and C-226 were considered acceptable in support of the effectiveness of lasalocid in combination with OTC for improving feed efficiency and increasing rate of weight gain in cattle fed in confinement for slaughter (Study C-83-27 was not used in the pooled analysis because the cattle had been previously treated with hormonal implants). A total of 648 cattle were involved at five different experimental locations. The locations and management practices employed are representative of major cattle feeding areas and practices in the United States with exception that none of the test cattle received growth promoting implants. The data from the five studies was subjected to a pooled analysis of variance comparing the combination of OTC + Lasalocid to OTC alone and to negative controls for both ADG and Feed/Gain. The means and their standard error are presented as follows:

	Control	**OTC**	**Las + OTC**
ADG (lb)	2.771 ±0.031	2.798 ±0.031	2.861±0.031
Feed/Gain	7.707±0.079	7.529±0.079	7.315±0.079

ADG and Feed/Gain were improved by the addition of both lasalocid and OTC to the diet. ADG for the lasalocid and OTC group was shown to be significantly better than the control group ($P=0.0023$) and tended to be better than the OTC group ($P=0.0777$). Feed/Gain for the combination was shown to be significantly greater than the control group ($P<0.0005$) and OTC group ($P<0.0313$). No differences were seen between groups with respect to carcass quality. Data from Studies C-109, C-225, C-226 and C-83-27 were considered acceptable in support of the effectiveness of lasalocid in combination with OTC for reducing the incidence and severity of liver abscesses in cattle fed in confinement to slaughter. Studies C-205 and C-207 were not used because the incidence of liver abscesses in these trials was too low to draw adequate conclusions.

The data for these studies were subjected to a pooled analysis of variance to determine if lasalocid interfered with the ability of OTC to control liver abscesses. The means of percentages of animals with liver abscesses were 37.51, 24.88, and 24.45 for the control, OTC treated, and Lasalocid + OTC treated groups, respectively. The percentages of incidence of liver abscesses for

the lasalocid + OTC and OTC groups were significantly less than for the control group ($P<0.05$). No significant difference was seen between the lasalocid + OTC and OTC groups with respect to the percentage of incidence of liver abscesses (sensitivity to detect a change of 15% incidence with 80% power for a one sided test at the 0.05 level of significance).

Based on the above studies, it is concluded that OTC fed in combination with lasalocid is more effective than OTC fed alone to feedlot cattle with respect to improving feed efficiency. Furthermore, it is concluded that lasalocid does not interfere with the ability of OTC to reduce the incidence and severity of liver abscesses.

With respect to the Center's Combination Drug Guidelines (November 9, 1983), it must be demonstrated that:

The studies cited above provide a direct comparison between the combination and OTC alone. Lasalocid + OTC was shown to be better than OTC alone for improving feed efficiency. No direct comparison can be made between the combination and lasalocid alone. However, the data demonstrate that both OTC alone and in combination with lasalocid was effective in reducing the incidence of liver abscesses and that lasalocid does not interfere with the ability of OTC in this respect. Furthermore, studies used for the approval of lasalocid in feedlot cattle (see Table below) showed no effect of lasalocid on incidence of liver abscesses. Accordingly, it is concluded that lasalocid + OTC has been demonstrated to be better than lasalocid for reducing liver abscesses.

a. Lasalocid + OTC is better than OTC for performance; and
b. lasalocid + OTC is better than lasalocid for reduced liver abscesses.

Incidence of Liver Abscesses in Feeding Trials Using Lasalocid Alone Submitted Under NADA 96-298 Dated October 17, 1980.

Trial	**Contol (%)**	**Las 30 g/t (%)**
773	5/31 (16.1)	7/31 (22.6)
789	0/24 (0)	3/24 (12.5)
793	5/32 (15.6)	2/32 (6.2)
799	15/120 (12.5)	25/120 (20.8)
C-6	32/40 (80.0)	27/40 (67.5)
C-10	9/32 (28.1)	12/32 (37.5)
C-23	1/15 (6.7)	0/16 (0)
C-24	13/48 (27.1)	12/48 (25.0)
C-29	2/32 (6.2)	0/32 (0)
Total	82/374 (21.9)	88/375 (23.5)

III. ANIMAL SAFETY

Safety studies for lasalocid in feedlot cattle at dosages up to 5X the recommended level arereported in NADA 96-298. OTC is currently approved for cattle at 0.5 to 2.0 grams per head daily for the prevention and treatment of the early stages of shipping fever complex. This dose is 6.7X to 26.7X the dose presently requested.

Two hundred cattle from the studies used in the pooled analysis for efficacy were fed lasalocid and OTC during the entire finishing period at the highest level in the approved ranges and no adverse effects were noted during the entire feeding period.

It is concluded that the combination of lasalocid and OTC is safe in feedlot cattle.

IV. HUMAN FOOD SAFETY

A. Toxicity Tests and Safe Concentration of Residues

Toxicity metabolism and total residue depletion studies, which are used to establish human safety for lasalocid and oxytetracycline, are described in the FOI Summary for NADA 96-298 (approved at 47 FR 34133/4, August 6, 1982) for lasalocid and NADA 8-804 for oxytetracycline as individual entities.

The tolerances of oxytetracycline are established at 0.1 ppm in the uncooked edible tissues of cattle, beef calves, non lactating dairy cattle and dairy calves (21 CFR 556.600) with liver and kidney as the target tissues for feed uses.

The safe concentrations of total lasalocid residues in the livers of cattle have been established at 4.8 ppm. A marker residue concentration of 0.7 ppm of intact lasalocid corresponds to a total residue level of 4.8 ppm (21 CFR 556.347).

B. Residue Depletion/Noninterference Studies

A tissue depletion study in cattle fed lasalocid at 300 mg/head/day using feed with 30 g lasalocid/ton feed and oxytetracycline at 75 mg/hd/day for 34 days was undertaken by Animal Science Research, Hoffmann-LaRoche Inc., Nutley, NJ. The study was conducted at the ASR Experiment Station (ASRES), Wrightstown, NJ using ten cattle of mixed breeds and sexes weighing 628 to 857 lbs. The animals were allocated as shown in the following table with the 34 day medication period from 1/13 - 2/16/87.

	Treatment (mg/hd/day)	**# of Heifers**	**# of Steers**
I Control (a)	0	1	1
II Lasalocid Sodium +	300	4	4
Oxytetracycline	75		

(a) Purpose of control group was to supply control liver for the analytical laboratories.

The animals were slaughtered on the morning of 2/17/87 at ASRES, and a 3 kg liver sample and both kidneys from each animal were collected, identified and frozen as soon as possible. The samples were transported to the HLR Animal Science Research (ASR) Analytical/Metabolic Labs, Nutley, NJ where the liver samples were split in

half. Both kidneys and one half liver sample from each animal were shipped frozen via overnight express on 2/18/87 to Hazleton Labs, America Inc., Madison, WI for oxytetracycline assay. The other one half liver sample was forwarded to the ASRanalytical lab for lasalocid assay. The hplc-fluorescence detection regulatory procedure for the determination of sodium lasalocid in bovine liver with a sensitivity of 0.025 ppm was used by Hoffmann-LaRoche Inc. for all bovine liver assays in this study. The hplc-fluorescence detection tissue residue procedure for lasalocid is described in the Food Additives Manual which is on display in FDA's Freedom of Information Public Room (Room 12A-30, 5600 Fishers Lane, Rockville, MD 20857).

The oxytetracycline tissue residue assays were conducted by Hazleton Labs, America Inc., Madison, WI using a method from "Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports and Protocols," revised October 1968, National Center for Antibiotic and Insulin Analysis, Food & Drug Administration, Dept. of Health, Education and Welfare, Washington, DC modified for a sensitivity of 0.1 ppm oxytetracycline in liver and kidney.

The summary tissue residue results for both lasalocid and oxytetracycline are listed below.

Concentration of Lasalocid and Oxytetracycline in Zero Day Withdrawal Bovine Livers and Oxytetracycline in Zero Day Withdrawal Bovine Kidneys

Animal	Lasalocid - Liver - mean (ppm)	Lasalocid - Liver - standard deviation (ppm)	Oxytetracycline -Liver -mean (ppm)	Oxytetracyline - Kidney - mean (ppm)
S	<0.025	-----	<.010*	<0.010*
F	0.158**	0.243**	<0.10*	<0.10*

* No zones of inhibition were present
** One of the four values included in this determination was an estimate below the limit of sensitivity.

The results of the two residue studies show that the residues do not exceed the established safe concentration for lasalocid and the tolerance for OTC at zero day withdrawal, the assigned withdrawal period of lasalocid and oxytetracycline in cattle.

C. Assay Noninterference Studies

The hplc-fluorescence procedure was evaluated with all the common antibiotics including oxytetracycline prior to initial submission to NADA 96-298 on October 17, 1980, and it was determined that no antibiotic including oxytetracycline was detected in the method or interfered with the lasalocid determination.

The method was validated to a sensitivity of 0.1 ppm and shown to have no interference with lasalocid using a simultaneous 0.7 ppm lasalocid spike in the same tissue sample. This study also included a 14 day stability test of oxytetracycline in frozen tissue which showed no losses over that time period.

D. Analytical Methods for Determination of Residues

The hplc-fluorescence detection tissue residue regulatory procedure for the determination of sodium lasalocid in bovine liver with a sensitivity of 0.025 ppm is described in the Food Additives Manual which is on display in FDA's Freedom of Information Public Room (Room 12A-30, 5600 Fishers Lane, Rockville, MD 20857).

The oxytetracycline tissue residue assays used a method from "Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports and Protocols," revised October 1968, National Center for Antibiotic and Insulin Analysis, Food and Drug Administration, Dept. of Health, Education and Welfare, Washington, DC modified for a sensitivity of 0.1 ppm oxytetracycline in liver and kidney.

E. 21 CFR 558.15

The following studies were conducted to satisfy the animal and human health safety requirements of 21 CFR Section 558.15 for use of OTC at 75 to 80 mg/head/day in cattle (NADA 8-804).

Title: Effect of Oxytetracycline of Tissue Levels, Antimicrobial Resistance and Shedding of Salmonella typhimurium from Cattle.

Report No.: C 110184

Starting Date: April 18, 1985

Termination Date: July 18, 1985

Investigator: Colorado Animal Research Enterprises, Inc.

Location: Ft. Collins, Colorado

Substance Tested: Oxytetracycline administered in feed

Animals: Crossbred heifer and steer calves, seven per treatment group.

This study was conducted to assess the effect of oxytetracycline fed to cattle at 75 mg/hd/day on the quantity, prevalence and duration of shedding of a tetracycline resistant *Salmonella typhimurium* and to evaluate the effect of resistance characteristics and tissue levels of the infecting organism.

Calves, weighing 500 to 600 lb, were orally inoculated with a tetracycline resistant *Salmonella typhimurium* after a four week adjustment period in the test facilities. Medicated diet feeding was initiated to the appropriate treatment group at six days after the challenge and was continued daily for the next eight weeks. Post challenge fecal samples were collected twice prior to treatment initiation and 22 times during the 56 day treatment period. Collected specimens were direct counted for quantities of test salmonellae and enriched for detection of non-countable levels of test salmonellae. From ten of the post challenge sampling periods, five *S. typhimurium* isolates per calf tested by a microdilution, MIC method for susceptibility to amikacin, kanamycin, carbenicillin, cefoxitin, chloramphenicol, gentamicin, and trimethoprim/sulfamethoxazole. At study end, samples of liver, spleen and mesenteric lymph node were surgically removed from all Salmonella-challenged calves and were analyzed for presence of test salmonellae. This study was conducted

in compliance with US FDA Good Laboratory Practice Regulations (21 CFR 58).

Oxytetracycline administered to cattle in their feed at 75 mg/hd/day did not significantly increase the quantity, duration of prevalence of Salmonella shedding, nor increase the incidence of antimicrobial resistance in Salmonella, nor increase the presence of Salmonella in tissue.

Title: Effect of Oxytetracycline on the Incidence of Antimicrobial Resistance in Indigenous Fecal Coliforms from Cattle

Report No.: C 021284

Starting Date: January 28, 1985

Termination Date: April 16, 1985

Investigator: Colorado Animal Research Enterprises, Inc.

Location: Ft. Collins, Colorado

Substance Tested: Oxytetracycline

Animals: Crossbred heifer and steer calves, eight per treatment group.

A study was conducted to evaluate the effect of oxytetracycline fed to cattle at 75 mg/hd/day on the incidence of antimicrobial resistant indigenous fecal coliforms.

Fecal samples from medicated and non-medicated cattle were collected prior to treatment initiation to obtain baseline data, and weekly thereafter over an eight week treatment period. Ten coliform isolates per calf per sampling were tested by a microdilution, MIC method for susceptibility to amikacin, ampicillin, carbenicillin, cefoxitin, chloramphenicol, gentamicin, kanamycin, nalidixic acid, streptomycin, sulfadiazine, tetracycline and trimethoprim/sulfamethoxazole. This study was conducted in compliance with US FDA Good Laboratory Practice Regulations (21 CFR 58).

The administration of oxytetracycline in feed to cattle at 75 mg/hd/day did not significantly increase the frequency of antimicrobial resistance in their indigenous fecal coliforms.

V. AGENCY CONCLUSIONS

For the purpose of the human food safety review, this original NADA has been treated as a Category II supplement under the Agency's Supplemental Policy (42 FR 64367; December 23, 1977). This NADA provides for the combination use of lasalocid and OTC at the levels of 10 to 30 mg/ton of feed and 75 mg/hd/day, respectively, for increased rate of weight gain, improved feed efficiency, and reduction of incidence and severity of liver abscesses in beef cattle fed in confinement for slaughter. Adequate data were submitted which show that the combination resulted in a significant ($P<.05$) improvement in feed efficiency when compared to OTC fed alone and that lasalocid does not interfere with the ability of OTC in reducing the incidence and severity of liver abscesses. Adequate animal safety data was provided to show that the combination is safe for the target animals to consume. Adequate data was presented to show that OTC at a level of 75 to 80 mg/hd/day has met the human and animal safety requirements of

21 CFR 558.15. (Higher levels of OTC for use in cattle feed have not met the requirements for 21 CFR 558.15. Adequate data is also available to show that lasalocid for use in cattle feed to 30 g/ton of total ration has met the requirements for 21 CFR 558.15 (NADA 96-298). No changes were made in the approved levels of either compound or in the target animal and the noninterference of lasalocid and OTC with the analytical methods for OTC and lasalocid, respectively, was demonstrated. According, approval of this change is not expected to increase human exposure to drug residues, and therefore did not require a complete re-evaluation of the human safety data in the original applications. These production drugs are "OTC" because the use of them does not raise any special safety concerns or require any diagnosis.

VI. ATTACHMENTS

1. Blue Bird Cattle Finisher (B) Medicated Feed (Lasalocid 25-30g/ton Oxytetracycline 7.5 g/ton) product label
2. Blue Bird Cattle Finisher (B) Medicated Feed (Lasalocid 25-30g/ton Oxytetracycline 7.5 g/ton) placard
3. Blue Bird Cattle Finisher (B) Medicated Feed (Lasalocid 10-30g/ton Oxytetracycline 7.5 g/ton) product label
4. Blue Bird Cattle Finisher (B) Medicated Feed (Lasalocid 10-30g/ton Oxytetracycline 7.5 g/ton) placard

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

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.