

Approval Date: June 13, 2003

FREEDOM OF INFORMATION SUMMARY
ORIGINAL NEW ANIMAL DRUG APPLICATION
NADA 141- 221

Ractopamine Hydrochloride

(OPTAFLEXX™ 45)
Type A Medicated Article
For Beef Cattle

- 1) (8.2 – 24.6 g/ton) - For increased rate of weight gain, and improved feed efficiency in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.
- 2) (9.8 – 24.6 g/ton) - For increased rate of weight gain, improved feed efficiency, and increased carcass leanness in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.

Sponsored by:
Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

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FREEDOM OF INFORMATION SUMMARY

OPTAFLEXX™ 45 (Ractopamine hydrochloride) Type A Medicated Article

1. GENERAL INFORMATION:

- a. File Number: NADA 141-221
- b. Sponsor: Elanco Animal Health
A Division of Eli Lilly & Co.
Lilly Corporate Center
Indianapolis, IN 46285

Drug Labeler Code: 000986
- c. Established Name: Ractopamine hydrochloride
- d. Proprietary Name: OPTAFLEXX™ 45
- e. Dosage Form: Type A Medicated Article
- f. How Supplied: 25 lb bag
- g. How Dispensed: OTC
- h. Amount of Active Ingredients: Ractopamine hydrochloride – 45.4 g per lb
(100 g per kg)
- i. Route of Administration: Oral, in feed
- j. Species/Class: Cattle fed in confinement for slaughter

- k. Recommended Dosage: Feed Ractopamine Hydrochloride (OPTAFLEXX™ 45) at a dietary concentration of 8.2 to 24.6 g per ton (9.1 to 27.3 ppm) of ractopamine hydrochloride/ton of feed (90% dry matter basis) for the last 28 to 42 days on feed. This is equivalent to 9.0 to 27.0 g per ton (10.0 to 30.0 ppm) on a 100% dry matter basis.
- Ractopamine was tested in the clinical trials on a 100% dry matter basis (g/ton); however, the label includes the dosage expressed on a 90% dry matter basis in order to provide labeling comparable with other ruminant feed additives presently approved.
- l. Pharmacological Category: Beta adrenergic agonist
- m. Indications:
- 1) (8.2 – 24.6 g/ton) - For increased rate of weight gain, and improved feed efficiency in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.
 - 2) (9.8 – 24.6 g/ton) - For increased rate of weight gain, improved feed efficiency, and increased carcass leanness in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.

2. EFFECTIVENESS:

A. Summary of pivotal dose titration efficacy trials

Data from five replicated, well-controlled heifer trials and five replicated, well-controlled steer trials involving 860 heifers and 880 steers were pooled and analyzed. Trials were conducted in various geographic areas of the United States. All cattle received a short acting estrogenic implant on arrival at the feedlot. Cattle were fed during the pretreatment phase for at least 90 days prior to being treated with ractopamine HCl. No ionophore or antibiotic was fed during the treatment phase. Ractopamine HCl was fed either 28 or 42 days immediately prior to slaughter. The cattle were fed a variety of diets that ranged in NEg from 61.2 to 69.9 Mcal/CWT of dry matter. Ractopamine HCl was administered in the feed at dietary concentrations that ranged between 0 and 27 g/ton (30 ppm) of feed, on a 100% dry matter basis. An unweighted and in some cases, weighted, mixed model analysis was conducted on data collected from all doses from the ten trials.

The fixed effects for the mixed model analysis were concentration of ractopamine HCl, gender, and ractopamine by gender interaction. Random effects for the mixed model analysis were trial within gender, block within trial within gender, and ractopamine by trial within gender interaction.

Cattle were handled during the trials and at the termination of each trial, under conditions, which represent, as closely as possible, commercial feedlot practices. Cattle were moved from the feedlot pens to the scale, individually weighed, and moved to the cattle loading area, covering distances of at least 50 yards to 1600 yards, depending on the equipment at each feedlot research facility. Cattle were held off feed for between 20-28 hours prior to harvest, depending on trial site and harvest facility location.

Cattle were transported from the feedlot facilities in semi-trucks by commercial livestock haulers. Cattle were exposed to typical weather conditions during the winter, spring, summer and fall months, while being hauled to the harvest plants. Hauling times ranged from 1 to 16 hours depending on trial site and harvest facility locations. Cattle were delivered to the commercial beef packing plants, and held co-mingled overnight prior to harvest. Transportation distances ranged from at least 37 miles to 672 miles in winter, spring, summer and fall conditions, depending on trial sites and season of the trial.

A review of the data from the ten clinical trials showed no treatment-related adverse effects or indications of concerns for animal safety. No animal safety concerns were identified or observed during the conduct of the feedlot phase, livestock hauling or harvest of cattle from these trials. The incidences of digestive death, bovine respiratory disease and other typical feedlot illnesses were not impacted by treatment. During the loading, transport, unloading, and holding of cattle at the beef packing plants prior to harvest, no suspect cattle, “downer cattle” or dead on arrivals (DOA) were observed.

A review of the data collected at the harvest plants showed no adverse treatment related effects or indications of concerns for animal safety. There was no indication of treatment-related elevated stress conditions that may impact the incidence of dark cutting beef, a condition related to and potentially indicative of chronic stress experienced by cattle prior to harvest. The incidences of liver abscesses and liver abnormalities requiring liver condemnation were not different between control and treated animals.

Carcass leanness was evaluated using carcass percent protein as the composition variable. Carcass percent protein is the measure of the protein content in the carcass soft tissue which is ultimately merchandised as edible beef. Carcasses with increased levels of protein have a higher percentage of lean meat, and thus, more merchandisable red meat. The effects of ractopamine HCl on carcass percent protein were evaluated on an “equal weight” basis.

Sides of the “equal weight” carcasses were dissected and weights obtained for soft tissues, bone (plus heavy connective tissue), kidney, pelvic and heart fat (KPH) and any other non-carcass or inedible tissues (glands, aorta, etc.). Bone (plus heavy connective tissue), KPH, and other non-carcass tissues were discarded after being weighed. The soft

tissue from each carcass was ground, blended, and chopped prior to sampling. Samples were analyzed for moisture, crude protein, ether extractable lipids, and ash.

Change in carcass leanness was measured by differences in carcass side soft tissue percent protein which is defined as carcass percent protein (%N * 6.25). The average composition of the dissected carcass sides represented the pen's carcass composition for statistical analysis.

Ractopamine HCl, when fed at 10 to 30 ppm, increases average daily gain and feed efficiency (P < .0001) and, when fed at 12 to 30 ppm, increases carcass leanness (P < .002).

A.1. Pooled Data From Ten Pivotal Efficacy Trials

Table 1: Pooled Trial Analysis - Performance of Cattle Fed Diets Containing Ractopamine HCl^a

Claim Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis				P value ^c
	0/0	10/ 9	20/ 18	30/ 27	
Rate of Weight Gain, lb/d	2.78	3.10	3.24	3.38	<.0001
Carcass Percent Protein, %	14.80	15.00	15.14	15.34	.002
Feed Efficiency, F/G	7.93	7.11	6.75	6.44	<.0001
Gain Efficiency, G/F	0.130	0.144	0.152	0.159	<.0001
Label Panel Variables					
Hot Carcass Weight, lb	724.4	728.6 ^d	734.6 ^d	739.2 ^d	.001
Dressing Percent, %	59.5	59.4	59.6	59.7	-- ^e
Carcass Percent Fat, %	31.69	31.16	30.74 ^d	30.04 ^d	.014
12 th Rib Fat Thickness, in.	0.60	0.60	0.60	0.59	.378
Average Ribeye Area, sq. in.	12.33	12.48 ^d	12.58 ^d	12.77 ^d	<.001
USDA Yield Grade	3.22	3.19	3.17	3.11 ^d	.045
Marbling Score ^b	531.8	529.4	534.4	528.4	.497
Carcass Lean Gain per Day, lb/d	0.104	0.139	0.176 ^d	0.202 ^d	<.001
Efficiency of Carcass Lean Gain per Day	0.005	0.006	0.008 ^d	0.010 ^d	<.001

^a all values are least squares means

^b average of left and right sides, marbling score of 500 equals small 0

^c overall treatment effect

^d significantly different from control (0 ppm) at P<.05

^e significant gender by treatment interaction

Table 2: Pooled Trial Analysis - Performance of Steers Fed Diets Containing Ractopamine HCl^a

Claim Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis				P value
	0/0	10/ 9	20/ 18	30/ 27	
Rate of Weight Gain, lb/d	2.82	3.24	3.26	3.47	-- ^c
Carcass Percent Protein, %	14.82	15.15	15.35	15.35	--
Feed Efficiency, F/G	8.10	7.00	6.81	6.44	--
Gain Efficiency, G/F	0.128	0.146	0.149	0.159	--
Label Panel Variables					
Hot Carcass Weight, lb	753.4	759.9	767.5	771.6	--
Dressing Percent, %	59.4	59.2	59.7 ^d	59.8 ^d	.001
Carcass Percent Fat, %	31.20	30.30	29.53	29.70	--
12 th Rib Fat Thickness, in.	0.57	0.56	0.56	0.56	--
Average Ribeye Area, sq. in.	12.00	12.29	12.39	12.53	--
USDA Yield Grade	3.32	3.23	3.22	3.18	--
Marbling Score ^b	530.5	524.5	534.0	523.5	--
Carcass Lean Gain per Day, lb/d	0.111	0.177	0.223	0.238	--
Efficiency of Carcass Lean Gain per Day	0.006	0.008	0.011	0.011	--

^a all values are least squares means

^b average of left and right sides, marbling score of 500 equals small 0

^c refer to table for pooled analysis

^d significantly different from control (0 ppm) at P<.05

Table 3: Pooled Trial Analysis - Performance of Heifers Fed Diets Containing Ractopamine HCl^a

Claim Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis				P Value
	0/0	10/ 9	20/ 18	30/ 27	
Rate of Weight Gain, lb/d	2.74	2.96	3.22	3.30	-- ^c
Carcass Percent Protein, %	14.78	14.85	14.94	15.33	--
Feed Efficiency, F/G	7.77	7.23	6.68	6.44	--
Gain Efficiency, G/F	0.132	0.143	0.154	0.159	--

Label Panel Variables

Hot Carcass Weight, lb	695.5	697.3	701.8	706.8	--
Dressing Percent, %	59.7	59.5	59.5	59.6	.426
Carcass Percent Fat, %	32.19	32.03	31.95	30.38	--
12 th Rib Fat Thickness, in.	0.63	0.63	0.63	0.62	--
Average Ribeye Area, sq. in.	12.66	12.68	12.76	13.01	--
USDA Yield Grade	3.11	3.15	3.11	3.03	--
Marbling Score ^b	533.0	534.3	535.3	533.2	--
Carcass Lean Gain per Day, lb/d	0.098	0.101	0.128	0.167	--
Efficiency of Carcass Lean Gain per Day	0.005	0.004	0.006	0.009	--

^a all values are least squares means

^b average of left and right sides, marbling score of 500 equals small 0

^c refer to table for pooled analysis

A.2 Individual Pivotal Efficacy Trials

Study T4V189551. One hundred sixty Angus x Hereford x Simmental crossbred steers were used in a 28-day feeding trial to study the effect of ractopamine HCl on feedlot performance and carcass effects. The trial was conducted by Dr. Ron Lemenager, Purdue University, West Lafayette, IN. Cattle were fed a high concentrate diet based on corn and corn silage. Three steers were removed from the trial due to physical injuries related to being raised on slatted floors. No adverse reactions due to ractopamine HCl were observed.

Cattle from this trial site were exposed to winter and early spring conditions. Cattle were removed from feed, individually weighed, and moved between 50 and 100 yards from the feedlot research pens to the cattle loading area. Cattle were loaded on semi-trucks and hauled at least 240 miles from the feedlot to the harvest plant by a commercial livestock

hauler. Cattle were held co-mingled overnight prior to harvest. There were no animal safety concerns or treatment-related adverse conditions observed at the end of the trial and during the harvest of the cattle.

Table 4: Performance of Steers Fed Diets Containing Ractopamine HCl, T4V189551^a

Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis			
	0/0	10/ 9	20/ 18	30/ 27
No. of Replicates	5	5	5	5
Total no. of Steers starting on trial	40	40	40	40
Total no. of Steers completing trial	37	40	40	40
Initial Weight, lb	1288.1	1285.4	1285.9	1285.0
Final Weight, lb	1378.9	1394.9	1401.1	1400.3
Rate of Weight Gain, lb/d	3.21	3.91	4.11	4.12
Carcass Percent Protein ^b , %	14.95	15.21	15.87	15.28
Pounds of Feed / lb of Gain	7.16	6.06	5.93	5.97

^a all values are arithmetic means

^b a maximum of 2 carcasses per replicate per treatment were evaluated for carcass percent protein

Study T4V089553. Two hundred Hereford steers were used in a 28-day feeding trial to study the effect of ractopamine HCl on feedlot performance and carcass effects. The trial was conducted by Dr. Mary I. Wray, Horton Feedlot and Research Center, Wellington, CO. Cattle were fed a high concentrate diet based on corn and corn silage. Four steers were removed from the trial due to health-related reasons. No adverse reactions due to ractopamine HCl were observed.

Cattle from this trial site were exposed to winter conditions. Cattle were removed from feed, individually weighed, and moved between 400-800 yards from the feedlot research pens to the cattle loading area. Cattle were loaded on semi-trucks and hauled at least 611 miles from the feedlot to the harvest plant by a commercial livestock hauler. Cattle were held co-mingled overnight prior to harvest. There were no animal safety concerns or treatment related adverse conditions observed at the end of the trial and during the harvest of the cattle.

Table 5: Performance of Steers Fed Diets Containing Ractopamine HCl, T4V089553^a

Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis			
	0/0	10/ 9	20/ 18	30/ 27
No. of Replicates	5	5	5	5
Total no. of Steers starting on trial	50	50	50	50
Total no. of Steers completing trial	49	49	49	49
Initial Weight, lb	1240.7	1239.3	1253.1	1240.9
Final Weight, lb	1334.6	1352.9	1378.6	1366.1
Rate of Weight Gain, lb/d	3.19	3.92	4.48	4.36
Carcass Percent Protein ^b , %	15.25	15.00	15.04	15.27
Pounds of Feed / lb of Gain	7.51	6.08	5.55	5.53

^a all values are arithmetic means

^b a maximum of 2 carcasses per replicate per treatment were evaluated for carcass percent protein

Study T4V319557. Two hundred Angus x Hereford steers were used in a 42-day feeding trial to study the effect of ractopamine HCl on feedlot performance and carcass effects. The trial was conducted by Dr. Kelly Lechtenberg, Midwest Veterinary Services, Oakland, NE. Cattle were fed a high concentrate diet based on corn, corn liquor and chopped alfalfa hay. No adverse reactions due to ractopamine HCl were observed.

Cattle from this trial site were exposed to harsh winter conditions. Cattle were removed from feed, individually weighed, and moved between 350-700 yards from the feedlot research pens to the cattle loading area. Cattle were loaded on semi-trucks and hauled at least 672 miles from the feedlot to the harvest plant by a commercial livestock hauler. Cattle were held co-mingled overnight prior to at the harvest. There were no animal safety concerns or treatment-related adverse conditions observed at the end of the trial and during the harvest of the cattle.

Table 6: Performance of Steers Fed Diets Containing Ractopamine HCl, T4V319557^a

Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis			
	0/0	10/ 9	20/ 18	30/ 27
No. of Replicates	5	5	5	5
Total no. of Steers starting on trial	50	50	50	50
Total no. of Steers completing trial	50	50	50	50
Initial Weight, lb	1076.6	1076.6	1076.5	1073.3
Final Weight, lb	1164.5	1183.0	1180.4	1178.6
Rate of Weight Gain, lb/d	2.10	2.55	2.49	2.52
Carcass Percent Protein ^b , %	14.82	15.63	15.60	15.80
Pounds of Feed / lb of Gain	9.38	8.00	7.98	7.55

^a all values are arithmetic means

^b a maximum of 2 carcasses per replicate per treatment were evaluated for carcass percent protein

Study T4V069559. One hundred sixty Angus steers were used in a 42-day feeding trial to study the effect of ractopamine HCl on feedlot performance and carcass effects. The trial was conducted by Dr. Terry Terhune, Health Management Services, Tulare, CA. Cattle were fed a high concentrate diet based on corn, barley and corn silage. No adverse reactions due to ractopamine HCl were observed.

Cattle from this trial site were exposed to very warm late spring and hot summer conditions in California. Cattle were removed from feed, individually weighed, and moved between 100-800 yards from the feedlot research pens to the cattle loading area. Cattle were loaded on semi-trucks and hauled at least 37 miles from the feedlot to the harvest plant by a commercial livestock hauler. Cattle were held co-mingled overnight prior to harvest. There were no animal safety concerns or treatment-related adverse conditions observed at the end of the trial and during the harvest of the cattle.

Table 7: Performance of Steers Fed Diets Containing Ractopamine HCl, T4V069559^a

Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis			
	0/0	10/ 9	20/ 18	30/ 27
No. of Replicates	5	5	5	5
Total no. of Steers starting on trial	40	40	40	40
Total no. of Steers completing trial	40	40	40	40
Initial Weight, lb	1185.3	1184.7	1182.9	1181.7
Final Weight, lb	1307.0	1316.7	1309.4	1325.2
Rate of Weight Gain, lb/d	2.90	3.14	3.01	3.42
Carcass Percent Protein ^b , %	14.45	15.09	14.92	15.06
Pounds of Feed / lb of Gain	8.36	7.67	7.63	6.98

^a all values are arithmetic means

^b a maximum of 2 carcasses per replicate per treatment were evaluated for carcass percent protein

Study T4V089603. One hundred sixty Brangus x Angus steers were used in a 42-day feeding trial to study the effect of ractopamine HCl on feedlot performance and carcass effects. Dr. John J. Wagner, Continental Beef Research, Lamar, CO, conducted the trial. Cattle were fed a high concentrate diet based on corn, corn silage and alfalfa haylage. One steer was removed from the trial due to physical injury. No adverse reactions due to ractopamine HCl were observed.

Cattle from this trial site were exposed to hot late summer and early fall conditions in Colorado. Cattle were removed from feed, individually weighed, and moved between 1300-1600 yards from the feedlot research pens to the cattle loading area. Cattle were loaded on semi-trucks and hauled at least 336 miles from the feedlot to the harvest plant by a commercial livestock hauler. Cattle were held co-mingled overnight prior to harvest. There were no animal safety concerns or treatment-related adverse conditions observed at the end of the trial and during the harvest of the cattle.

Table 8: Performance of Steers Fed Diets Containing Ractopamine HCl, T4V089603^a

Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis			
	0/0	10/ 9	20/ 18	30/ 27
No. of Replicates	5	5	5	5
Total no. of Steers starting on trial	40	40	40	40
Total no. of Steers completing trial	39	40	40	40
Initial Weight, lb	1056.2	1057.1	1055.9	1055.3
Final Weight, lb	1158.9	1171.1	1169.5	1183.1
Rate of Weight Gain, lb/d	2.39	2.71	2.71	3.04
Carcass Percent Protein ^b , %	14.63	14.80	15.31	15.32
Pounds of Feed / lb of Gain	8.09	7.17	6.89	6.19

^a all values are arithmetic means

^b a maximum of 2 carcasses per replicate per treatment were evaluated for carcass percent protein

Study T4V189550. One hundred forty crossbred heifers of mixed genetics (predominant influence of Salers, Angus, Hereford, with some Charolais, Chi-Angus, Simmental and Gelbvieh genetics) were used in a 28-day feeding trial to study the effect of ractopamine HCl on feedlot performance and carcass effects. The trial was conducted by Dr. Ron Lemenager, Purdue University, West Lafayette, IN. Cattle were fed a high concentrate diet based on corn and corn silage. One heifer was removed from the trial due to severe foot rot. No adverse reactions due to ractopamine HCl were observed.

Cattle from this trial site were exposed to winter and early spring conditions. Cattle were removed from feed, individually weighed, and moved between 50 and 100 yards from the feedlot research pens to the cattle loading area. Cattle were loaded on semi-trucks and hauled at least 240 miles from the feedlot to the harvest plant by a commercial livestock hauler. Cattle were held co-mingled overnight prior to harvest. There were no animal safety concerns or treatment-related adverse conditions observed at the end of the trial and during the harvest of the cattle.

Table 9: Performance of Heifers Fed Diets Containing Ractopamine HCl, T4V189550^a

Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis			
	0/0	10/ 9	20/ 18	30/ 27
No. of Replicates	5	5	5	5
Total no. of Heifers starting on trial	35	35	35	35
Total no. of Heifers completing trial	35	35	34	35
Initial Weight, lb	1113.5	1114.0	1111.9	1114.6
Final Weight, lb	1195.4	1196.8	1203.7	1213.0
Rate of Weight Gain, lb/d	2.93	2.96	3.33	3.51
Carcass Percent Protein ^b , %	14.94	15.33	15.20	15.84
Pounds of Feed / lb of Gain	6.90	6.92	6.27	5.70

^a all values are arithmetic means

^b a maximum of 2 carcasses per replicate per treatment were evaluated for carcass percent protein

Study T4V089552. Two hundred Hereford heifers were used in a 28-day feeding trial to study the effect of ractopamine HCl on feedlot performance and carcass effects. The trial was conducted by Dr. Mary I. Wray, Horton Feedlot and Research Center, Wellington, CO. Cattle were fed a high concentrate diet based on corn and corn silage. One heifer was removed from the trial due to health-related reasons. No adverse reactions due to ractopamine HCl were observed.

Cattle from this trial site were exposed to winter conditions. Cattle were removed from feed, individually weighed, and moved between 400-800 yards from the feedlot research pens to the cattle loading area. Cattle were loaded on semi-trucks and hauled at least 611 miles from the feedlot to the harvest plant by a commercial livestock hauler. Cattle were held co-mingled overnight prior to harvest. There were no animal safety concerns or treatment related adverse conditions observed at the end of the trial and during the harvest of the cattle.

Table 10: Performance of Heifers Fed Diets Containing Ractopamine HCl, T4V089552^a

Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis			
	0/0	10/ 9	20/ 18	30/ 27
No. of Replicates	5	5	5	5
Total no. of Heifers starting on trial	50	50	50	50
Total no. of Heifers completing trial	50	49	50	50
Initial Weight, lb	1119.5	1121.1	1120.4	1119.3
Final Weight, lb	1210.6	1223.7	1231.8	1229.6
Rate of Weight Gain, lb/d	3.25	3.58	3.98	3.94
Carcass Percent Protein ^b , %	14.97	14.95	14.87	15.31
Pounds of Feed / lb of Gain	6.83	6.19	5.59	5.48

^a all values are arithmetic means

^b a maximum of 2 carcasses per replicate per treatment were evaluated for carcass percent protein

Study T4V319556. Two hundred Angus x Hereford heifers were used in a 42-day feeding trial to study the effect of ractopamine HCl on feedlot performance and carcass effects. The trial was conducted by Dr. Kelly Lechtenberg, Midwest Veterinary Services, Oakland, NE. Cattle were fed a high concentrate diet based on corn, corn liquor and chopped alfalfa hay. No adverse reactions due to ractopamine HCl were observed.

Cattle from this trial site were exposed to harsh winter conditions. Cattle were removed from feed, individually weighed, and moved between 350-700 yards from the feedlot research pens to the cattle loading area. Cattle were loaded on semi-trucks and hauled at least 672 miles from the feedlot to the harvest plant by a commercial livestock hauler. Cattle were held co-mingled overnight prior to harvest. There were no animal safety concerns or treatment-related adverse conditions observed at the end of the trial and during the harvest of the cattle.

Table 11: Performance of Heifers Fed Diets Containing Ractopamine HCl, T4V319556^a

Variables	Ractopamine HCl (ppm/g/ton); 100% DM basis			
	0/0	10/ 9	20/ 18	30/ 27
No. of Replicates	5	5	5	5
Total no. of Heifers starting on trial	50	50	50	50
Total no. of Heifers completing trial	50	50	50	50
Initial Weight, lb	1017.4	1015.4	1015.0	1020.0
Final Weight, lb	1106.5	1121.0	1133.1	1135.0
Rate of Weight Gain, lb/d	2.15	2.55	2.85	2.78
Carcass Percent Protein ^b , %	15.38	15.13	15.60	15.84
Pounds of Feed / lb of Gain	9.70	8.12	7.41	7.54

^a all values are arithmetic means

^b a maximum of 2 carcasses per replicate per treatment were evaluated for carcass percent protein

Study T4V069558. One hundred sixty Angus heifers were used in a 42-day feeding trial to study the effect of ractopamine HCl on feedlot performance and carcass effects. The trial was conducted by Dr. Terry Terhune, Health Management Services, Tulare, CA. Cattle were fed a high concentrate diet based on corn, barley and corn silage. One heifer was removed from the trial for health reasons. No adverse reactions due to ractopamine HCl were observed.

Cattle from this trial site were exposed to very warm late spring and hot summer conditions in California. Cattle were removed from feed, individually weighed, and moved between 100-800 yards from the feedlot research pens to the cattle loading area. Cattle were loaded on semi-trucks and hauled at least 37 miles from the feedlot to the harvest plant by a commercial livestock hauler. Cattle were held co-mingled overnight prior to harvest. There were no animal safety concerns or treatment-related adverse conditions observed at the end of the trial and during the harvest of the cattle.

Table 12: Performance of Heifers Fed Diets Containing Ractopamine HCl, T4V069558^a

Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis			
	0/0	10/ 9	20/ 18	30/ 27
No. of Replicates	5	5	5	5
Total no. of Heifers starting on trial	40	40	40	40
Total no. of Heifers completing trial	40	40	40	39
Initial Weight, lb	1056.7	1051.2	1055.1	1057.9
Final Weight, lb	1169.5	1162.8	1176.3	1186.6
Rate of Weight Gain, lb/d	2.69	2.66	2.89	3.01
Carcass Percent Protein ^b , %	14.30	14.84	14.35	14.78
Pounds of Feed / lb of Gain	8.09	8.18	7.62	7.37

^a all values are arithmetic means

^b a maximum of 2 carcasses per replicate per treatment were evaluated for carcass percent protein

Study T4V089602. One hundred sixty Brangus x Angus heifers were used in a 42-day feeding trial to study the effect of ractopamine HCl on feedlot performance and carcass effects. Dr. John J. Wagner, Continental Beef Research, Lamar, CO, conducted the trial. Cattle were fed a high concentrate diet based on corn, corn silage and alfalfa haylage. No adverse reactions due to ractopamine HCl were observed.

Cattle from this trial site were exposed to hot late summer and early fall conditions in Colorado. Cattle were removed from feed, individually weighed, and moved between 1300-1600 yards from the feedlot research pens to the cattle loading area. Cattle were loaded on semi-trucks and hauled at least 336 miles from the feedlot to the harvest plant by a commercial livestock hauler. Cattle were held co-mingled overnight prior to harvest. There were no animal safety concerns or treatment-related adverse conditions observed at the end of the trial and during the harvest of the cattle.

Table 13: Performance of Heifers Fed Diets Containing Ractopamine HCl, T4V089602^a

Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis			
	0/0	10/ 9	20/ 18	30/ 27
No. of Replicates	5	5	5	5
Total no. of Heifers starting on trial	40	40	40	40
Total no. of Heifers completing trial	40	40	40	40
Initial Weight, lb	1026.3	1025.8	1024.4	1026.1
Final Weight, lb	1141.3	1152.9	1151.9	1161.5
Rate of Weight Gain, lb/d	2.74	3.03	3.04	3.22
Carcass Percent Protein ^b , %	14.29	14.01	14.70	14.89
Pounds of Feed / lb of Gain	7.31	6.73	6.50	6.10

^a all values are arithmetic means

^b a maximum of 2 carcasses per replicate per treatment were evaluated for carcass percent protein

A.3 Summary Comments for Ancillary Sensory Data Collected from Nine Efficacy Trials

The objective of this study was to determine the effect of feeding various levels of ractopamine HCl on trained sensory panel evaluation properties, and Warner-Bratzler shear force properties of boneless cooked beef strip loin steaks. Dr. Ken Prusa, Ph.D., was the investigator for this study, which was conducted at Iowa State University, Food Science and Human Nutrition, Ames, IA 50011.

Because no single method has been perfected to predict the ultimate consumer satisfaction (either taste panels or Warner-Bratzler shear force), a balanced combination of objective and subjective measurements was employed to evaluate the effects and differences which may be meaningful to consumers.

Sensory and instrumental evaluations were conducted on cooked beef strip loin steaks samples (longissimus dorsi muscle) obtained from a representative group of carcasses from five steer and four heifer clinical dose titration field trials conducted in different geographic locations. Boneless strip loin samples were collected from two carcasses (cattle) per pen in each treatment, which were slaughtered at the end of the live phase of the ractopamine feeding.

The boneless strip loin steaks evaluated in this study were collected from trials for which the experimental design was a randomized complete block. A block consisted of four pens, thus four treatments (one control and three levels of ractopamine). The treatments evaluated were: 0, 10, 20, and 30 ppm.

Samples were identified by animal number and trial number. The objective descriptive variables of raw weight, cooked weight, cooking loss, pH and Warner-Bratzler shear force were evaluated for each sample. The trained sensory panelists evaluated the sensory variables of juiciness, initial tenderness, sustained tenderness, beef flavor, and off flavor. Conduct of the sensory panels and preparation of samples was consistent with

the procedures described in the *Research Guidelines for Cookery, Sensory Evaluation and Instrumental Tenderness Measurements of Fresh Meat*, American Meat Science Association. Sensory evaluation was conducted by panelists trained to clearly distinguish differing amounts of juiciness, tenderness, flavor, and off-flavors. This training enables differentiation of the variables in increments more discrete and refined than the typical consumer could detect. Panelists were trained to use a 15 cm semi-structured line scale to critically evaluate and detect small differences in sensory traits. In the opinion of the sensory investigator, the subjective sensory panel variables must shift by 15 mm to 22.5 mm in order for the average consumer to detect a difference.

Results from this study demonstrated that any effects on subjective or objective sensory variables were within the normal variation observed today in the meat industry. No practical or meaningful changes in the objective descriptive variables of raw weight, cooked weight, cooking loss, and pH were caused by ractopamine HCl treatments.

As shown in the table below, no sensory variables were shifted by more than 15 mm compared to controls. Only for initial tenderness and sustained tenderness was a statistical difference observed at the 30 ppm level ($P < 0.05$) compared to controls. However, a change of 5.7 to 6.6 mm units in the initial and sustained tenderness, respectively, should not be detected by the consumer. These differences are considered well within the normal variation observed in the meat industry. Therefore it was concluded that no differences in palatability would be detected by the consumer. The cause of the slight increase in initial tenderness and sustained tenderness scores may be partially due to an increase in the muscle fiber area.

For the objective variable of Warner-Bratzler shear force, most literature published and cited by meat scientists consider meat to be acceptably tender if the shear force value is below 4.5-4.6 kg of shear force. According to most published literature references, a shear force of over 4.5-4.6 kg is necessary before a consumer panel considers meat to be tough. The Warner-Bratzler shear force analysis showed the mean values for all concentrations of ractopamine were within the normal ranges observed in the meat industry. The data from this study (see table below) shows that all values for Warner-Bratzler shear force were under the 4.5-4.6 kg threshold of shear force. Only in the 30 ppm dose group was Warner-Bratzler shear force increased ($P = .0007$) compared to controls, however, this increase was still well below the threshold shear force of 4.5 kg shear force. The magnitude of this difference was similar to or less than observed changes resulting from the widely variable genetic effects on meat palatability or changes observed during the use of various implant programs currently in use by the beef industry (Morgan, 1997). Therefore, it was concluded that no differences in palatability would be detected by the consumer. The cause of the slight increase in Warner-Bratzler shear force may be partially due to an increase in the muscle fiber area.

Table 14: Pooled Summary of Sensory Panel Evaluation and Warner-Bratzler (WB) Shear of Strip Loin Steaks from Ractopamine Beef Trials^a

Variables	Ractopamine HCl (ppm/g per ton); 100% DM basis				P Value
	0/0	10/ 9	20/ 18	30/ 27	
Juiciness ^b	104.6	104.5	106.0	103.3	.423
Initial Tenderness ^c	111.7	110.7	111.5	106.0 ^d	.004
Sustained Tenderness ^c	101.8	100.5	100.3	95.2 ^d	.004
Flavor ^b	90.3	89.0	90.5	88.7	.077
Off Flavor ^b	0.252	0.222	0.156	0.157	.733
WB Shear, kg ^b	3.54	3.49	3.62	3.95 ^d	.001

^a Least squares means

^b Unweighted Mixed Model Analysis

^c Weighted Mixed Model Analysis

^d Significantly different from control (0 ppm) at P<.05

3. TARGET ANIMAL SAFETY

A. Pivotal Studies

A.1 Target Animal Safety in Beef Cattle with Ractopamine HCL at 0, 30, 90, and 300 ppm in Feed for 42 Days. Study (T4V VX9402)

A specifically designed Target Animal Safety and Drug Tolerance Study in beef cattle was conducted to address the tolerance to and safety of feeding up to 300 ppm of ractopamine in the diet during a 42-day feeding period. Based on the results of this study, ractopamine is safe when administered in the diet up to 30 ppm for 42 consecutive days.

- a. Type of Study: This was a 42-day study in cattle which were fed a complete diet containing 0, 30, 90, or 300 ppm of ractopamine hydrochloride and observed for adverse effects.
- b. Study Director: T. N. TerHune, D.V.M., Ph.D., Health Management Services (HMS), Tulare, CA 93274
- c. General Design:
 - 1) Purpose: This study was designed to determine the toxicological effects (if any) of ractopamine hydrochloride administered in the diet to cattle. Potential target organs and tissues were identified through clinical observations, gross necropsy, and histological examination. Hematological variables, body weight, and feed consumption were other variables of interest.

- 2) Animals: Cattle (4/sex/dose) were used in this study.
- 3) Control: Cattle (4/sex) which received the same basal diet as the treated cattle, but without ractopamine.
- 4) Dosage form: A Type A Medicated Article containing 9.1 grams of ractopamine hydrochloride per pound was used to make a Type C Medicated Feed containing 30, 90, or 300 ppm of ractopamine hydrochloride. The Type A Medicated Article is the marketed form of OPTAFLEXXTM 45.
- 5) Dose: The diets, which were fed for *ad libitum* intake, contained 0, 30, 90, or 300 ppm of ractopamine hydrochloride.
- 6) Route of Administration: Oral, in the diet, provided for *ad libitum* intake.
- 7) Study Duration: The live phase spanned 42 days of feeding the medicated feed.
- 8) Pertinent measurements/observations: Daily clinical observations, mortality, hematological measurements, body weight, feed consumption, gross necropsy, and histopathology were evaluated to assess potential toxicity in cattle.
- 9) Experimental Design: Randomized Complete Block.
- 10) Experimental Unit: Individual steer or heifer.

d. Data Analysis:

Data from steers and heifers were pooled and analyzed. The pre-treatment values were used as covariates. For all variables except organ weights, the mixed models included the fixed effects of covariate, treatment, gender, treatment by gender, time, treatment by time, gender by time, and treatment by gender by time and the random effects of blocks nested within gender, and treatment by blocks within gender. For organ weights, the mixed models included the fixed effects of treatment, gender and treatment by gender and the random effects of block within gender. Treatment contrasts of 0 versus 30 ppm, 0 versus 90 ppm, and 0 versus 300 ppm were used. P-value plots with 99% confidence bands were constructed to evaluate the interactions and contrasts.

e. Results:

Test article-related effects at the 30 ppm (1X dose) and 90 ppm (3X dose) doses were not observed. Test article-related effects at the elevated dose were noted in Average Daily Gain, Gain to Feed ratio, and creatinine (steers only). Other significant variables at the 300 ppm (10X dose) were decreased platelet count, gamma GGT,

aspartate transaminase; increased creatinine phosphokinase, leukocyte count, and absolute eosinophils. These variables were considered equivocal and not test article-related. There was a mild decrease in kidney weight in animals treated at 90 and 300 ppm. The mild decrease in kidney size and elevation of blood creatinine at doses higher than the intended use range do not diminish the effectiveness or safety of the drug at the intended dose, however the producer and herd health team who use this drug should be aware of these effects in the instance of an accidental overexposure.

In conclusion, this study has shown that ractopamine can be safely administered to cattle at the recommended dose of 30 ppm in the feed for 42 consecutive days.

B. Corroborative Studies

Additional information related to the evaluation of the safety and effectiveness of ractopamine HCl when fed to cattle under feedlot conditions and shipped, and harvested under commercial conditions is included in the effectiveness section. No treatment related adverse reactions or indications of safety concerns were observed in any of the larger scale feedlot trials conducted under conditions which represented commercial conditions as closely as possible.

4. HUMAN SAFETY

A. Toxicity

Studies in laboratory animals conducted to establish a NOEL and an acceptable daily intake (ADI) for humans are summarized in the Freedom of Information Summary for Paylean™ Type A Medicated Article for swine, NADA 140-863, approved December 22, 1999. The ADI for total residues of ractopamine is 1.25 micrograms ractopamine hydrochloride per kilogram of body weight per day.

B. Safe Concentrations of Total Residues

The safe concentrations for total residues of ractopamine hydrochloride are: 0.25 ppm in muscle, 0.75 ppm in liver, and 1.5 ppm in kidney and fat (see the FOI Summary for the original NADA 140-863, approved December 22, 1999).

C. Total Residue Depletion and Metabolism Studies

C.1 ¹⁴C-Ractopamine HCl Tissue Residue Steady-State Study in Cattle. Study ABC-0398.

INVESTIGATORS: J. E. Dalidowicz, Ph.D., and
T. D. Thomson, Ph.D.
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, IN 46140

The length of time required for radioactive residues to reach steady state in cattle tissues was determined. Three sets of three cattle were dosed equivalent to 45 ppm (1.5 times the highest anticipated dose) of ¹⁴C- ractopamine hydrochloride for four, seven, or ten days. The dose was administered into the rumen via a rumen fistula twice daily with half the daily dose. Approximately 12 hours (practical zero withdrawal) after the last feeding, animals in each group were euthanized and total radioactive residues were measured in muscle, fat, liver, and kidney.

No detectable residues (NDR) were measured in the fat or muscle of the three groups of animals. The mean levels of total radioactivity, expressed as ppm of ractopamine hydrochloride equivalents, in each group ranged from 0.49-0.75 ppm for livers, and 0.40 - 0.50 ppm for kidneys. Statistical analysis of the residues from the three groups of animals showed that total residues reached steady state levels in kidney four days after initiating ractopamine hydrochloride feeding and in the liver seven days after initiating ractopamine hydrochloride feeding .

The mean levels of non-extractable residues were also measured. Non-extractable residues reached steady state in the liver after four days and in kidney after seven days following initiation of feeding ractopamine hydrochloride. The amount of ractopamine hydrochloride as a percentage of total ¹⁴C residues was statistically the same for all dosing periods and amounted to a mean of 12.7% and 14.2% in liver and kidney, respectively.

Table 15

Tissue	Total Radioactive Residues (ppm)		
	Days Fed		
	4	7	10
Muscle	NDR ¹	NDR	NDR
Kidney	0.40	0.50	0.50
Liver	0.49	0.75	0.50
Fat	NDR	NDR	NDR

¹NDR = No detectable residues

C.2 ¹⁴C- Ractopamine HCl Tissue Depletion Study in Cattle. Study ABC- 0375.

INVESTIGATORS: J. E. Dalidowicz, Ph.D., J.J. Lewis, Ph.D.,
 T.D. Thomson, V.M.D., Ph.D. and R.J. Herberg, M.S.
 Lilly Research Laboratories
 Division of Eli Lilly and Company
 Greenfield, IN 46140

The purpose of this study was to characterize ¹⁴C- residues in edible tissues of cattle fed ¹⁴C -ractopamine hydrochloride for seven days followed by withdrawal times of zero, two, four, and seven days. The dose was one and one half times the highest anticipated use level (equivalent to 45 ppm in the feed).

Six steers and six heifers received ¹⁴C-ractopamine hydrochloride in a capsule for seven days. Groups of three cattle of mixed sex were then slaughtered after zero-, two-, four- and seven-day withdrawal periods and the ¹⁴C-residue concentration was determined in the kidneys, liver, muscle, and fat.

The average radioactivity found in each of the four tissues at the different withdrawal times, calculated as net ppm of ractopamine hydrochloride, is summarized in the following table (NDR = no detectable residues):

Table 16

Tissue	Total Radioactive Residues (ppm)			
	Withdrawal Time			
	Zero	One-Day	Four-Day	Seven-Day
Muscle	0.02	NDR	NDR	NDR
Kidney	0.46	0.10	0.07	0.04
Liver	0.62	0.09	0.06	0.03
Fat	0.01	NDR	NDR	NDR

The amount of ractopamine HCl present in liver and kidneys at zero-time withdrawal, measured by high performance liquid chromatography and calculated as a percentage of total radioactivity, was 22.1 and 13.4%, respectively. After a two-day withdrawal period, the percentage of ractopamine declined to 18.9% in liver and 8.8% in kidneys.

Cattle eliminate ractopamine HCl and its metabolites quickly with no detectable residues in muscle and fat two days after withdrawal of ractopamine HCl. Total residues in all edible tissues were below the safe tissue concentration at the zero-day withdrawal period.

C.3 Tissue Residue Study in Cattle Dosed with 30 ppm of ¹⁴C-Ractopamine Hydrochloride. Study ABC-0408.

INVESTIGATORS: J. E. Dalidowicz, Ph.D., and T. D. Thomson, Ph.D
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, IN 46140

The relationship between parent ractopamine hydrochloride (marker residue) and the total radioactive residue was established in target tissues so that the total residue in a tissue could be calculated by measuring only the marker residue in cattle fed non-radioactive ractopamine hydrochloride under field conditions. Two heifers and a steer (166 – 230 kgs) were dosed with a capsule containing ¹⁴C-ractopamine into the rumen via a rumen fistula each day for seven consecutive days. The dosage was 0.67 mg/kg/day. Twelve hours after the last feeding (a practical zero-time withdrawal period) each animal was euthanized and both the total radioactive residue in liver and kidney and the amount of residue present as parent compound were determined. The relationship between parent ractopamine hydrochloride and total residue is shown below.

Table 17

Tissue	Concentration (ppm)		%
	¹⁴ C Residues	Ractopamine HCl	Ractopamine HCl
Kidney	0.189	0.043	22.5
Liver	0.250	0.036	13.2

D. Comparative Metabolism

D.1. Comparative Metabolism of ^{14}C -Ractopamine in Cattle, Dogs, and Rats. Studies ABC-0375, ABC-0398, ABC-0369, and ABC-0387.

INVESTIGATORS: J. E. Dalidowicz, Ph.D.,
Lilly Research Laboratories
Division of Eli Lilly and Company
Greenfield, IN 46140

The purpose of this study was to compare the metabolism of ractopamine hydrochloride in cattle, dogs, and rats. Radiochemically equivalent amounts of two lots of 98% pure ^{14}C -ractopamine hydrochloride, one uniformly labeled in Ring A, the other uniformly labeled in Ring B, were mixed with unlabeled ractopamine hydrochloride to make the test article for these studies.

Three crossbred ruminating cattle (two steers and one heifer) weighing approximately 172-239 kg each were dosed with ^{14}C -ractopamine hydrochloride in a capsule (at 1.01 mg/kg/d) and administered into the rumen via a rumen fistula twice daily with half daily dose for four days. The dose was equivalent to 45 ppm of ractopamine hydrochloride in the feed on a dry weight basis. The cattle were euthanized 12 hours after the last dose.

Two adult beagle dogs (one male and one female) weighing 7-8 kg were dosed by gavage with the test article at 0.5 mg/kg (0.25 mg/mL H_2O) three times daily for four days and once on the fifth day. The dogs were euthanized three hours after the last dose.

Twelve male and twelve female Fisher 344/NHSD rats approximately 8-9 weeks of age and weighing approximately 120-200 g, were dosed with the test article by gavage at 2 mg/kg/day (10 mL/kg) for five days. The rats were euthanized three hours after the last dose.

Liver and kidney tissues from the cattle, dogs, and rats were analyzed by HPLC and scintillation counting.

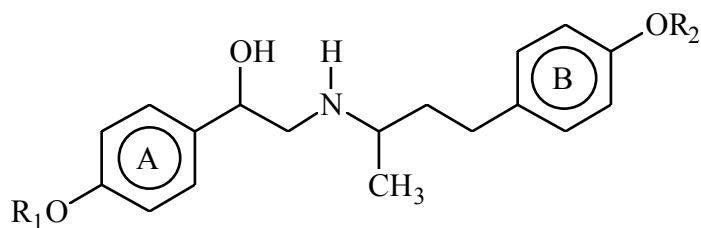


Table 18

	R ₁	R ₂	Isomers
Ractopamine	H	H	Mixture
Metabolite A	H	Glucuronide	RS, SR
Metabolite B	H	Glucuronide	RR,SS
Metabolite C	Glucuronide	H	Mixture

The mean amounts in ppm of ractopamine hydrochloride and its metabolites (calculated as ractopamine hydrochloride) in kidney and liver tissues were:

Table 19

	Liver			Kidney		
	Cattle	Dog	Rat	Cattle	Dog	Rat
Ractopamine HCl	0.08	0.59	0.40	0.05	0.50	0.33
Metabolite A	0.02	0.46	0.17	0.02	0.18	0.52
Metabolite B	0.02	0.77	0.15	0.02	0.27	0.57
Metabolite C	0.24	1.76	0.10	0.25	0.63	0.08
Metabolite D	0.13	0.71	0.17	0.03	0.15	0.10

It was concluded that the dogs and rats used in the toxicological studies were exposed to the same metabolites as those found in the edible tissues of cattle.

Cattle metabolize ractopamine to four major metabolites: Metabolites A and B (ring A monoglucuronides), Metabolite C (ring B monoglucuronide), and Metabolite D (diglucuronide). The same metabolites are also present in dog and rat liver and kidney tissue and are excreted in the urine of the two species. Moreover, the concentrations of the metabolites, for the most part, are higher in dog and rat tissues than that of cattle tissues. The nonextractable and uncharacterized residues in dog and rat tissues also were higher than in cattle tissues.

The animals chosen for the chronic, subchronic and acute toxicity studies, therefore, have been exposed to the same metabolites as those found in the edible tissues of cattle, but at higher concentrations.

E. Tolerance and Withdrawal Time

Data from two residue studies utilizing ¹⁴C- ractopamine hydrochloride were analyzed to determine the total residues in edible tissues of cattle at zero days of withdrawal of the drug from the diet. These studies demonstrate that the total residues in edible tissues of cattle fed a diet containing 45 ppm of ractopamine hydrochloride do not exceed the safe tissue concentrations. Therefore, these studies support the approval of the use of ractopamine hydrochloride in cattle rations at up to 30 ppm with a zero-day withdrawal.

Although the application included sufficient data to support a zero-day withdrawal period, the Agency has determined it is appropriate to set a tissue residue tolerance for monitoring purposes. After examining the data from studies submitted for characterizing

the metabolites and residues of ractopamine hydrochloride in the target tissue (liver) at zero-day withdrawal, it was decided that a conservative value of 12% for the amount of marker residue (ractopamine parent) in the total would be used for setting the tolerance in liver and muscle. The safe tissue concentration for total residues in liver is 0.75 ppm; therefore, the tolerance (Rm) for ractopamine parent in liver is set at 0.09 ppm (12% of 0.75). The safe tissue concentration for total residues in muscle is 0.25 ppm; therefore, the tolerance (Rm) for ractopamine parent in muscle is set at 0.03 ppm (12% of 0.25).

F. Regulatory Method for Residues

Although the application included sufficient data to support a zero-day withdrawal period, normally making an official regulatory method unnecessary, the Agency has determined it is appropriate to evaluate a regulatory method for tissue residues. Therefore, analytical methods suitable for use by regulatory authorities for the detection and confirmation of ractopamine hydrochloride residues in cattle tissues have been developed and validated. The determinative assay for measuring ractopamine residues in treated cattle consists of extraction of the parent drug from liver or muscle, and measurement of the parent drug in the extract by high performance liquid chromatography (HPLC).

Ground cattle liver or muscle is homogenized with methanol and centrifuged to separate the solids. A portion of the methanol extract is evaporated to dryness, reconstituted in borate buffer, and partitioned with ethyl acetate. Ractopamine is further isolated from the matrix by passing the ethyl acetate extract through an Alumina A solid-phase extraction cartridge. Ractopamine is eluted from the cartridge with methanol. The methanol extract is evaporated to dryness and reconstituted in two percent aqueous acetic acid for HPLC analysis. HPLC analysis is carried out using a reversed-phase octadecylsilyl stationary phase with fluorescence detection at 305 nm (excitation at 226 nm).

The limit of quantification of the method is 2 ppb.

To confirm the identity of ractopamine in tissues, ground cattle liver or muscle is homogenized with methanol and centrifuged to separate the solids. A portion of the methanol extract is evaporated to dryness, reconstituted in borate buffer, and partitioned with ethyl acetate. Ractopamine is further isolated from the matrix by passing the ethyl acetate extract through an Alumina A solid-phase extraction cartridge. Ractopamine is eluted from the cartridge with methanol. The methanol extract is evaporated to dryness and reconstituted in ammonium acetate buffer for analysis. Samples are subjected to analysis by reversed-phase high performance liquid chromatography/ion spray mass spectrometry (HPLC/ISP-MS). The mass spectrometer operating parameters are set up to monitor three structurally-indicating fragment ions unique to ractopamine.

Method trials of the determinative and confirmatory assays for liver were satisfactorily completed by a combination of FDA, USDA, and private laboratories.

The validated regulatory methods for detection and confirmation of residues of ractopamine in liver and muscle are on file with the Center for Veterinary Medicine.

G. User Safety Concerns

The User Safety Concerns section of the FOI Summary for the original NADA 140-863, approved December 22, 1999, states:

Ractopamine (RACT) is pharmacologically active as a partial beta adrenergic agonist. Acute and chronic exposures of mammals to RACT at sufficiently high levels by the oral, inhalation, or intravenous injection routes results in the signs expected from this class of compounds: increased heart rate, increased blood and pulse pressure, peripheral dilation of blood vessels, and increased cardiac output. Monkeys exposed for four hours per day for 8 days to airborne levels of RACT of 0.38 mg/m³ or greater experienced increased heart rates while 15 minute inhalation exposures resulted in increased heart rate at concentrations of 13.9 mg/m³ and greater (2.4 mg/m³ was a no-effect-level). The Paylean® Type A Medicated Article was formulated with an oil coating to minimize the inhalation exposure during use of the product. To estimate the potential for feed mill operators to experience significant inhalation exposures to ractopamine during handling and mixing operations, an exposure monitoring study was conducted. Under the conservative conditions of the on-site study, measurements from the mill operators' personal air samplers demonstrated mean exposure values of < 0.001 mg/m³ during short term weighing and bagging operations and long term operations in the mill resulted in exposure values of <0.0002 mg/m³.

RACT is an eye irritant in rabbits and at very high exposure levels (5,000 mg/kg) is a slight skin irritant. In Guinea pigs, RACT was a contact sensitizer. In rodents there were no effects on mating performance or fertility, but increased mortality, growth retardation, and structural abnormalities were seen in offspring where doses were high enough to be maternally toxic.

User safety concerns associated with effects of accidental inhalation or direct contact have been satisfactorily addressed by formulating the product to minimize dust generation and by establishing label warnings. In addition, a toll-free telephone number will be available on the label to inform users of where they can obtain additional information concerning user safety, request an MSDS, and to report adverse effects.

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 demonstrate that ractopamine hydrochloride (8.2 to 24.6 g per ton or 9.8 to 24.6 g per ton for the last 28 to 42 days on feed) is safe and effective for the claims indicated in section 1 of this FOI Summary.

Based on a battery of toxicology tests, the safe concentrations for total residues of ractopamine hydrochloride are 0.25 ppm in muscle, 0.75 ppm in liver, and 1.5 ppm in kidney and fat. The total residue data showed that the mean concentrations of total ractopamine hydrochloride residues at 12 hours after feed withdrawal were well below the permitted safe concentration in the edible tissues of finishing cattle. Husbandry practices for cattle are such that they will not enter the human food chain until 12 or more hours after they are removed from feed. Therefore, a withdrawal period will not be required for this use of ractopamine hydrochloride in finishing cattle.

Analytical methods suitable for use by regulatory authorities for the detection and confirmation of ractopamine hydrochloride residues in cattle tissues have been developed and validated.

Under section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the use of the product (OPTAFLEXX™ 45) containing 1) 8.2 to 24.6 g per ton for increased rate of weight gain, and improved feed efficiency in cattle fed in confinement for slaughter during the last 28 to 42 days on feed or 2) 9.8 to 24.6 g per ton for increased rate of weight gain, improved feed efficiency, and increased carcass leanness in cattle fed in confinement for slaughter during the last 28 to 42 days on feed for which this original New Animal Drug Application is approved.

The drugs are 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.

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for 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 drug product is assigned OTC status, and the labeling is adequate for the intended use.

Ractopamine hydrochloride is under the following US patent numbers:

<u>U.S. Patent Number</u>	<u>Date of Expiration</u>
4,690,951	September 1, 2004
4,734,437	September 1, 2004
5,643,967	July 1, 2014

6. ATTACHMENTS:

Facsimile Labeling is attached as indicated below:

- A. OPTAFLEXXTM 45 Type A Medicated Article Bag Label
- B. OPTAFLEXXTM Type B Medicated Feed Bluebird Bag/Tag Labels
- C. OPTAFLEXXTM Type C Medicated Feed Bluebird Bag/Tag labels