Date of Approval: January 19, 2007

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-269

REVALOR-XS

(Trenbolone Acetate and Estradiol)
Implant (pellets)
for Cattle (Steers Fed in Confinement for Slaughter)

A slow-release delivery system which increases rate of weight gain and improves feed efficiency for up to 200 days in steers fed in confinement for slaughter.

Sponsored by:

Intervet Inc.

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number:	NADA 141-269
B. Sponsor:	Intervet Inc. P.O. Box 318 29160 Intervet Lane Millsboro, DE 19966 Drug Labeler Code: 057926
C. Proprietary Name:	REVALOR-XS
D. Established Name(s):	Trenbolone Acetate and Estradiol
E. Pharmacological Category:	Steroid hormone
F. Dosage Form:	Implant (pellets)
G. Amount of Active Ingredient(s):	Each pellet contains 20 mg trenbolone acetate and 4 mg estradiol One implant (10 pellets) contains 200 mg trenbolone acetate and 40 mg estradiol
H. How Supplied:	Ten implants are provided in a cartridge
I. How Dispensed:	OTC
J. Dosage:	One implant containing 200 mg trenbolone acetate and 40 mg estradiol
K. Route(s) of Administration:	Subcutaneous implantation on the posterior aspect of the middle of the ear by means of an implant gun
L. Species/Class:	Steers fed in confinement for slaughter
M. Indication(s):	A slow-release delivery system which increases rate of weight gain and improves feed efficiency for up to 200 days in steers fed in confinement for slaughter.

II. EFFECTIVENESS:

REVALOR-XS is designed to release trenbolone acetate (TBA) and estradiol in initial and delayed release components to extend the implant treatment period to approximately 200 days. Information in Sections II.A and II.B below provide evidence that REVALOR-XS is effective for increasing rate of weight gain and improving feed efficiency for up to 200 days in steers fed in confinement for slaughter. Information in Section II.C provides evidence that the REVALOR-XS implant delivers trenbolone acetate and estradiol over a period of approximately 200 days, and there are active ingredients left in the implant at the end of this period.

A. Dosage Characterization:

A multi-site clinical effectiveness study supported the approval of REVALOR-IS (80 mg trenbolone acetate, 16 mg estradiol; see approval of June 19, 2000, and associated Freedom of Information Summary filed under NADA 140-897) and REVALOR-S (120 mg trenbolone acetate, 24 mg estradiol; see approval of November 27, 1991, and associated Freedom of Information Summary filed under NADA 140-897) for increased rate of weight gain and improved feed efficiency for steers fed in confinement for slaughter. The doses from the REVALOR-IS and REVALOR-S implants were chosen for the initial and delayed release components of REVALOR-XS.

Using the selected doses for the initial and delayed release components of REVALOR-XS, a dosage characterization study was conducted to examine the effect of two novel REVALOR-XS formulations on average daily gain and feed efficiency in steers fed in confinement for slaughter.

1) Type of Study: Dosage characterization

2) Investigator: David Bechtol, DVM. Agri Research Center Inc., Canyon, TX

3) Study Design:

   a. *Objective*: To compare average daily gain (ADG) and feed efficiency (FE) of a two implant treatment with REVALOR-IS and REVALOR-S (implants given 75 days apart), two experimental REVALOR formulations with delayed release components (REVALOR Formulation 1 and REVALOR Formulation 2), and non-implanted negative controls.

   b. *Experimental Animals*: A total of 480 steers weighing approximately 700 pounds at the start of the study were assigned to one of four treatment groups (n = 120 per group) as shown in Table II.1.

Table II.1: Dosage characterization study treatment groups

Treatment Group	Implant Program	Time of Administration	Release Phase 1 TBA (mg)	Release Phase 1 Estradiol (mg)	Release Phase 2 TBA (mg)	Release Phase 2 Estradiol (mg)
1	None	None	0	0	0	0
2	REVALOR-IS	Day 0	80	16	-	-
	REVALOR S	Day 75	-	-	120	24
3	REVALOR Formulation 1	Day 0	80	16	120	24
4	REVALOR Formulation 2	Day 0	80	16	120	24

* "REVALOR Formulation 1 & 2" = delayed release formulations

c. *Treatment Administration*: Implants were placed subcutaneously in the middle third of the back of the ear.

d. *Measurements and Observations*: Individual weights were collected for all steers on Days 35, 75, and 140. Steers were slaughtered by block when they reached market condition (Days 160, 166, 188, and 195) with steers from each treatment group equally distributed across each block. Final body weights were taken for steers prior to shipment for slaughter. Feed consumption was recorded to allow calculation of feed efficiency.

4) Results: ADG for all three REVALOR treatment groups was significantly better ($P < 0.0001$) than the negative control group at each weigh point (Days 35, 75, and 140, see Figure 1). While overall ADG did not differ between the three REVALOR treatment groups, the interaction between treatment and Study Day was significant ($P = 0.0037$) with ADG for novel REVALOR formulation 1 significantly improved ($P < 0.008$) over the REVALOR IS-S treatment on Study Days 75 and 140.

FE for all three REVALOR treatment groups was significantly improved ($P < 0.003$) compared to the negative control group at all time points (see Figure 2). There were no statistical differences between novel REVALOR formulation 1 and novel REVALOR formulation 2 over the duration of the study; however, on Day 75 both novel REVALOR formulations 1 and 2 had significantly improved FE ($P = 0.005$ and $P = 0.011$, respectively) compared to the REVALOR IS-S treatment group.

Figure 1 - Average Daily Gain Least Square Means by Treatment

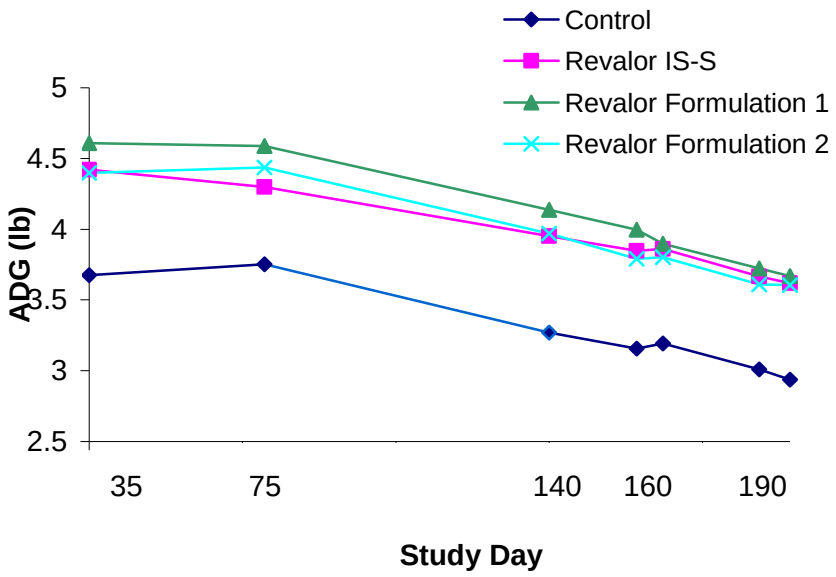
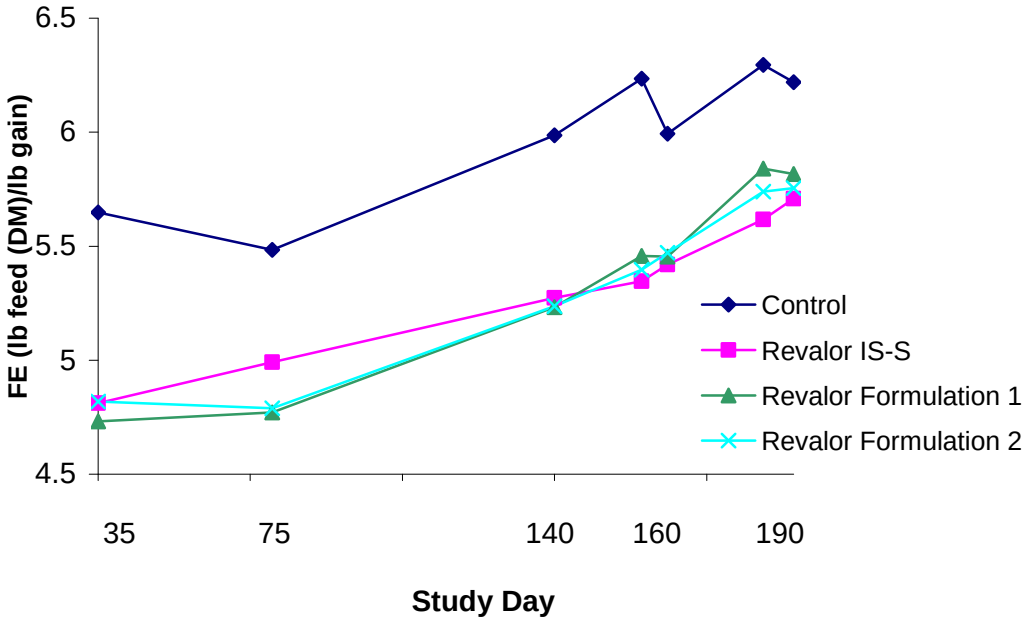


Figure 2 - Feed Efficiency Least Square Means by Treatment



5) Conclusions: The feedlot performance up to 195 days following a single implant of one of the two novel REVALOR formulations was comparable to that of cattle receiving a REVALOR-IS implant followed by a REVALOR-S implant 75 days apart. Based on the results of this study "REVALOR Formulation 1" was selected and refined for use in studies to demonstrate substantial evidence of effectiveness of

REVALOR-XS for increased rate of weight gain and improved feed efficiency for up to 200 days in steers fed in confinement for slaughter (see Section II.B below).

B. Substantial Evidence:

DOSE CONFIRMATION STUDY OF A LONG-ACTING TRENBOLONE ACETATE AND ESTRADIOL IMPLANT FOR INCREASING RATE OF WEIGHT GAIN AND IMPROVING FEED EFFICIENCY IN FEEDLOT STEERS.

1) Type of Study: Multi-center effectiveness study

2) Investigators: David Bechtol, DVM Agri Research Center Inc., Canyon, TX
Edward G. Johnson, DVM Johnson Research LLC, Parma, ID
Mary Wray, PhD Horton Feedlot & Research Center, Wellington, CO

3) Study Design: This was a masked, negative controlled, multi-center study conducted in different geographic regions. The study used a randomized complete block design.

a. *Objective*: To demonstrate that REVALOR-XS increases ADG and improves FE for up to 200 days in steers fed in confinement for slaughter.

b. *Experimental Animals*: A total of 720 steers weighing approximately 600 pounds were enrolled for the study. Each study site enrolled 240 steers randomly assigned to one of two treatment groups (n = 120 per group; 10 per pen; experimental unit was pen).

c. *Treatment Administration*: Implants were placed subcutaneously in the middle third of the back of the ear in treated steers. Control steers were sham implanted (implant needle inserted in ear but no implant was inserted) using identical technique to the implanted steers. Personnel who collected study data (other than data related to test article administration and accountability) were masked to treatments.

d. *Measurements and Observations*: All animals completed the study except six control and seven treated steers for reasons deemed unrelated to treatment. Individual weights were collected on Days 0, 70, and 140 and Final (just prior to shipment for slaughter). All steers were sent to slaughter at the same time within study site, when most of the steers at a site were judged to have reached market condition (Day 173, 205, and 215 for the Colorado, Idaho, and Texas sites, respectively). Feed consumption (feed issued minus feed weighback) was recorded to calculate feed efficiency.

Average daily gain (ADG) was calculated using the formula:

$$ADG = \text{weight gain} \div \text{days on study}$$

Feed Efficiency (FE) was calculated using the formula:

FE = total dry matter intake ÷ total gain

At slaughter, incidence of liver abscesses and carcass data for determining USDA yield and quality grades were collected (United States Standards for Grades of Carcass Beef, USDA, 1997).

For purposes of analysis, quality grades were converted to a 10 point scale in Table II.2:

Table II.2. Scale used for assignment of quality grade scores.

Quality Grade	Score
Standard	1
Select -	2
Select	3
Select +	4
Choice -	5
Choice	6
Choice +	7
Prime -	8
Prime	9
Prime +	10

Similarly, marbling categories were converted to the numeric scale in increments of 10 as per the scale provided in Table II.3.

Table II.3. Scale used for assigment of marbling scores.

Marbling Category	Score
Practically Devoid	10
Traces	20
Slight	30
Small	40
Modest	50
Moderate	60
Slightly Abundant	70
Moderately Abundant	80
Abundant	90

The degree of marbling within a marbling category was further described in increments of 1 (representing 10% increments within the marbling category), such that the two digit marbling score would reflect the degrees of marbling within a given category. For example, a marbling score of Small 60 would have a final numeric score of 46, while a marbling score of Moderate 20 would have a final numeric score of 62.

To evaluate implant safety, the individual ears were evaluated to detect ear abscesses, other ear abnormalities, and the presence of an implant for all steers at Day 35, 70, 140, and Final (just prior to shipment for slaughter; Day 173, 205, and 215 for the Colorado, Idaho, and Texas sites, respectively). In addition, all steers were observed daily during the study for abnormalities. Illnesses, injuries, and treatments were documented and evaluated.

e. *Statistical Methods*: The primary variables, ADG and FE from day 0 to final measurement, and the secondary variables yield grade, quality grade score, and marbling score, were analyzed by mixed model analysis. Treatment was a fixed effect in the model. Study site, study site by treatment interaction, and blocks nested within site were random effects.

4) Results: Both ADG (P = 0.043) and FE (P = 0.006) were significantly improved for the REVALOR-XS group versus the negative control group. The ADG and FE analyses results are summarized in Table II.4.

Table II.4. Analysis of ADG and FE over study period

Efficacy Endpoint	LS Means	Standard	P Value

	Control	Implant	**Error**	
Average Daily Gain (pounds per day)	2.77	3.31	0.23	0.043
Feed Efficiency (pounds feed per pound of gain)	6.82	6.33	0.22	0.006

With respect to carcass characteristics, there were no statistical differences between treatments for quality grade or marbling score (Table II.5). The Least Square Means (LS Means) for quality grade reflect that the majority of cattle in both treatment groups were of the Select^{+} and Choice^{-} quality grades. The average marbling score for both treatment groups translate to marbling of Small^{-}, which corresponds to Choice^{-} quality grade.

Yield grade was statistically higher in treated versus control steers, though the numerical difference was small (Table II.5). Implanted steers had heavier live weights and carcass weights at slaughter (average hot carcass weight of 773 lb in treated steers and 701 lb in control steers). This reflects the greater average daily gains in implanted versus control steers and that all steers were slaughtered on the same calendar date within study site. In the USDA equation for calculating yield grade, increased hot carcass weight and internal and external (at the 12th/13th ribs) fat cause an increase in yield grade, while increased ribeye area (at the 12th/13th ribs) causes a decrease in yield grade. Along with increased hot carcass weight in implanted versus control steers, there was a slight increase in external fat and an increase in ribeye area in implanted versus control steers. These values are a function of implanted steers having heavier live weights at the end of the study. The increase in yield grade in implanted versus control steers does not merit including a statement related to increased yield grade on the approved label for REVALOR-XS.

Table II.5. Analysis of carcass characteristics

Carcass Endpoint	**LS Means** Control	Implant	**Standard Error**	**P-Value**
Quality Grade	4.72	4.53	0.21	0.299
Marbling Score	44.3	42.7	1.55	0.284
Yield Grade	2.88	3.04	0.08	0.038

C. Supportive Data:

As part of the residue depletion study for REVALOR-XS (See Section IV.B below), the sponsor conducted an implant payout study (Study 2034-004-01; Study Director, Mary I. Wray) at the sponsor's research farm in De Soto, Kansas. The study was conducted between October 5, 2004, and June 29, 2005 (in-life portion). Fifty-six crossbred steers (implanted with REVALOR-XS) six to eight months of age, were used to evaluate the

implant payout profiles of trenbolone acetate and estradiol over 210 days. Steers were maintained under conditions typical of the U.S. feedlot industry. Steers were blocked by weight and randomized to one of seven implant collection times (Day 0, 36, 70, 105, 140, 175, and 210) following implantation on Day 0. At each steer's collection time its implant was removed ("explanted") and the amount of estradiol and trenbolone acetate remaining within it was determined.

The following criteria were applied to the results to determine if the payout rate was acceptable.

Evidence of 200+ Day Availability of Actives

Upon explant of the final implants at Day 210 post implantation, the means of both active ingredients (on a per dose basis) will be present in measurable amounts greater than or equal to 2 mg trenbolone acetate and greater than or equal to 1 mg estradiol.

Table II.6. Mean Residual Active Ingredient Concentration at Day 210 from Steers Implanted with REVALOR-XS

Active Ingredient	Mean Amount (mg) on Day 210	Criteria Met?
TBA	79.11	Yes
Estradiol	16.50	Yes

Evidence of Payout over the 200+ Day Period

There will be:

1. A statistically significant ($P<.05$) reduction in the mean concentration of both active ingredients over the 0-210 day period and
2. A measurable drop in the means of both active ingredients over Days 0 to 105 and 105 to 210 of greater than or equal to 3 mg TBA and greater than or equal to 2 mg estradiol.

Table II.7. Difference in Mean Active Ingredient Concentration Recovered from Steers Implanted with REVALOR-XS

Active Ingredient	Day 0 to 210 (mg)	P-value for Day 0 to 210 change	Day 0 to 105 (mg)	Day 105 to 210 (mg)	Criteria Met?
TBA	97.38	0.002	23.90	73.48	Yes
Estradiol	19.43	0.002	3.56	15.86	Yes

Active ingredients remained in the implants at 210 days. Also, there was a significant reduction in the concentration and the percent of the active ingredients over the Day 0 to 210 period and the evidence of change in the amount of each active between Days 0 and 105 and Days 105 and 210. Thus, the established criteria were satisfied and demonstrated implant payout of the active ingredients in a delayed release pattern over the full 210 day period.

III. TARGET ANIMAL SAFETY:

Target animal safety studies used in support of original approvals of the sponsor's REVALOR products also support the current approval of REVALOR-XS (see FOI Summaries for NADA 140-897, approval date – November 27, 1991, and NADA 140-992, approval date - December 13, 1994). There were no animal safety concerns raised by the evaluation of animal health data from the multi-center clinical effectiveness study (see Section II.B above). Taken together, the target animal safety studies cited under NADA 140-897 and NADA 140-992, and the animal health data from the clinical effectiveness study, support the current new animal drug application for steers fed in confinement for slaughter.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

The toxicity studies summarized in the FOI for NADA 138-612 (approved July 2, 1987) have established an acceptable daily intake (ADI) of total residues of trenbolone at 0.4 μg per kg of body weight per day (21 CFR, Part 556.739).

The safe concentration for total residues of trenbolone in the edible tissue is 80 ppb in muscle, 240 ppb in liver, and 480 ppb in kidney and fat, based on the revised food consumption values (59 FR 37499).

Estradiol is regulated on the basis of allowable incremental increases (21 CFR 556.240). No residues of estradiol, resulting from the use of estradiol or any of the related esters, are permitted in excess of the following increments above the concentrations of estradiol naturally present in untreated animals: In uncooked edible tissues of heifers, steers, and calves, (1) 120 parts per trillion for muscle; (2) 480 parts per trillion for fat; (3) 360 parts per trillion for kidney; and (4) 240 parts per trillion for liver.

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

In addition to the residue depletion study summary that follows, the New Animal Drug Application for REVALOR-XS long-acting trenbolone acetate and estradiol implant references residue depletion studies summarized in the FOIs for NADAs 138-612, 140-897 and 140-992 to demonstrate Human Food Safety. Because studies conducted for the previous approvals did not include the long-acting formulation, the following study was conducted to provide data at 70 and 105 days post-implantation of the REVALOR-XS long-acting formulation.

A tissue residue study in steers was conducted to determine residues of estradiol (estradiol-17β) and the two metabolites of trenbolone acetate (trenbolone-17α, trenbolone-17β) in the edible tissues at Day 70 and Day 105 after implantation of REVALOR-XS, and implant payout profiles for the implantation period. The study was entitled "Evaluation of Implant Payout Profiles and Residue Depletion of Trenbolone and Estradiol Following Implantation of Feedlot Steers with a Long-Acting Revalor® Formulation," Intervet Study #2034-004-01.

Study Director: Mary I. Wray, Ph.D., Intervet Inc., De Soto, KS

In-Life Testing Facility: Intervet Inc., De Soto Research Farm, 35040 West 87th Street, De Soto, KS

Analytical Investigators: Donald Henricks, Ph.D., Endocrine Physiology Laboratory, Clemson University, Clemson, SC and Wei Pan, Ph.D., Cardinal Health, Morrisville, NC

Test Articles: Long-Acting REVALOR Formulation for Steers

Animal Species: Cattle/Feedlot Steers

Number of Animals: 56 steers divided into 7 treatment groups of 8 animals each plus 2 control animals

Weight of Animals: Between 223 to 315 kg

Route of Administration: Ear implantation

Duration of Implantation: More than 200 days

Residues of Trenbolone and Estradiol:

After implantation, tissues for residue determination were collected from four implanted animals and one non-treated animal on each of Day 70 and Day 105 after the animals were euthanized. Four replicates were analyzed for the amounts of estradiol-17β (E2), trenbolone-17α (T- α) and trenbolone-17β (T- β) in muscle, fat, liver and kidney, using validated radioimmunoassay methods. The limit of quantitation (LOQ) values of the radioimmunoassay methods are as follows in table IV.1:

Table IV.1. The LOQ (pg/g) Determined for Each Steroid and Tissue

	E2 (pg/g)	T-β (pg/g)	T-α (pg/g)
Muscle	25	125	125
Liver	25	125	175
Kidney	50	250	250
Fat	50	63	125

The concentrations (mean ± standard deviation) of estradiol-17β, trenbolone-17α and trenbolone-17β in each edible tissue at Day 70 and Day 105 after implantation are summarized in Table IV.2. Only the values that were at or above the LOQs were included in the calculation of the means. For all the edible tissues from the Day 105 treatment group, the means were calculated from the results of four animals. For liver, kidney and fat tissues from the Day 70 treatment group, the means were calculated from the results of four animals. However, for muscle, the mean was calculated from only three animals; results from one animal of the treatment group were not included in the calculation of the mean due to the artifact in the sample processing procedures. Concentrations of estradiol-17β,

trenbolone-17α and trenbolone-17β in the edible tissues of the control animals were all below the LOQs of the methods.

Table IV. 2. Mean Concentrations (pg/g ± SD) of Estradiol-17β, Trenbolone-17α, Trenbolone-17β in Tissues of Steers at Day 70 and Day 105 after Implantation

	Animal Number	Muscle[a]	Fat[a]	Liver[a]	Kidney[a]
Estradiol-17 β (Mean ± Std Dev)					
Day 70	4	28.5	53.7	44.4 ± 6.1	-
Day 105	4	36.1	72.6 ± 17.4	58.7 ± 29.3	-
Trenbolone-17 β (Mean ± Std Dev)					
Day 70	4	-	-	-	-
Day 105	4	-	-	167.5	-
Trenbolone -17 α (Mean ± Std Dev)					
Day 70	4	-	-	295.0 ± 3.9	-
Day 105	4	-	-	194.9 ± 21.4	-

[a]: Individual animal residue concentrations below the LOQs were not used in the calculation of means.

"-" represents mean values below the LOQs.

"n" was equal to 4 for liver, kidney and fat tissues; "n" was equal to 3 for muscle tissue.

Conclusions: The method-adjusted total residue equivalents of trenbolone in the liver at Day 70 and Day 105 after the implantation were below half of the safe concentration for the total residues of trenbolone in the liver. The incremental increases of estradiol-17β concentrations in the edible tissues at Day 70 and Day 105 after implantation were below the codified allowable incremental increases for estradiol (21 CFR 556.240).

Implant Payout Profiles:

Implants were collected from eight steers on explantation Days 0, 36, 70, 105, 140, 175, and 210. Concentrations of estradiol and trenbolone acetate in the explants were measured using a validated HPLC method. The data are summarized in Table IV.3.

Table IV.3. Mean and Standard Deviation of Estradiol and Trenbolone Concentration Remaining in the Explants at Explantation Day

Day	Animal Number	Mean ± SD		Mean ± SD	
		Estradiol	% Total*	Trenbolone	% Total*
0	8	35.92 ± 3.93	89.81 ± 9.83	176.5 ± 19.79	88.24 ± 9.90
36	8	36.87 ± 2.60	92.18 ± 6.51	175.5 ± 13.11	87.77 ± 6.56
70	8	35.54 ±1.67	88.84 ± 4.18	164.9 ± 4.40	82.45 ± 2.20
105	8	32.36 ± 2.20	80.90 ± 5.51	152.6 ± 11.33	76.29 ± 5.66
140	8	24.49 ± 7.61	61.23 ± 19.03	111.2 ± 37.33	55.61 ±18.66
175	8	7.61 ± 6.47	19.02 ± 16.17	56.56 ± 32.50	28.28 ± 16.25
210	8	16.50 ± 8.27	41.25 ± 20.67	79.11 ± 34.62	39.56 ±17.31

*: For each group of animals, the percentage of total was calculated by dividing the measured amount by the labeled dose and multiplying by 100. The labeled dose was 40 mg for estradiol and 200 mg for trenbolone.

Conclusions: Data for trenbolone and estradiol concentrations in explants at 0, 36, 70, 105, 140, 175 and 210 days after implantation demonstrated a gradual and steady payout of the steroids from the implants over 210 days.

2. Target Tissue and Marker Residue Assignment

   Neither a target tissue nor a marker residue assignment is needed for trenbolone acetate (see the FOI for NADA 138-612, approved July 2, 1987).

   A specific target tissue is not identified for residues of estradiol. Allowable incremental increases for estradiol residues are assigned for each of the edible tissues.

3. Tolerance Assignments

   A tolerance for trenbolone acetate in uncooked edible tissues of cattle is not needed (21 CFR 556.739; see also the FOI for NADA 138-612, approved July 2, 1987).

   Residues of estradiol are regulated on the basis of the codified allowable incremental increases (21 CFR 556.240).

4. Withdrawal Time

   The data from Intervet Study #2034-004-01 support a zero-day withdrawal for the long-acting REVALOR-XS product.

C. Microbial Food Safety:

REVALOR-XS is not an antimicrobial.

D. Analytical Method for Residues:

A regulatory analytical method is not required for REVALOR-XS.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to REVALOR-XS:

"For Animal Treatment Only. Not for Use in Humans."

The material safety data sheet for REVALOR products indicates there are no special measures for exposure control or personal protection so long as the product is handled according to directions stipulated on product labeling.

VI. 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. The data demonstrate that REVALOR-XS, when used according to the label, is safe and effective as a slow-release delivery system which increases rate of weight gain and improves feed efficiency for up to 200 days in steers fed in confinement for slaughter. Additionally, data demonstrate that residues in food products derived from steers fed in confinement for slaughter treated with REVALOR-XS will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

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.

B. Exclusivity:

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, REVALOR-XS, an implant containing 200 mg trenbolone acetate and 40 mg estradiol as a slow-release delivery system which increases rate of weight gain and improves feed efficiency for up to 200 days in steers fed in confinement for slaughter.

C. Patent Information:

REVALOR-XS is under the following US patent number:

U.S. Patent Number	Date of Expiration
6498153B1	March 22, 2019

VII. ATTACHMENTS:

Facsimile Labeling:
REVALOR-XS Box
REVALOR-XS 5 X 1000 Dose Shipping Container Label
REVALOR-XS 10 X 100 Carton Label
REVALOR-XS Package Insert