Date of Approval: July 18, 2022

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-348

SYNOVEX® ONE FEEDLOT

(trenbolone acetate and estradiol benzoate extended-release implants)

Growing beef steers and heifers fed in confinement for slaughter

This supplement provides for the approval of the indication for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later.

Sponsored by:

Zoetis Inc.

Executive Summary

SYNOVEX® ONE FEEDLOT (trenbolone acetate and estradiol benzoate extended-release implants) is approved for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter ("feedlot" beef cattle) in a reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later. (SYNOVEX Choice® is another implant in the SYNOVEX® family of products approved under a different application.)

Each implant is placed subcutaneously in the middle one-third of the back of the ear, between the skin and the cartilage, using a SYNOVEX® applicator. The implants dissolve slowly under the skin and do not need to be removed later. The ears of treated cattle are not used for human food.

FDA previously approved SYNOVEX® ONE FEEDLOT for increased rate of weight gain and improved feed efficiency for up to 200 days in feedlot cattle. The previous approval is for the one-time administration of a single implant during the time the cattle are in the feedlot, which may range from 90 to more than 300 days.

Proprietary Name	Established Name	Application Type and Number	Sponsor
SYNOVEX® ONE FEEDLOT	trenbolone acetate and estradiol benzoate extended-release implants	New Animal Drug Application (NADA) 141-348	Zoetis Inc.

Each SYNOVEX® ONE FEEDLOT implant contains eight pellets, with each pellet containing 25 mg trenbolone acetate and 3.5 mg estradiol benzoate in an extended-release coating (for a total of 200 mg trenbolone acetate and 28 mg estradiol benzoate per implant). The implant slowly releases the two hormones over an extended period of time. Trenbolone is a synthetic steroid. Estradiol is a naturally-occurring estrogen. Both hormones act by redirecting how nutrients are used by the animal, resulting in increased muscle growth and weight gain in castrated male beef cattle (steers) and non-pregnant beef heifers.

FDA approved SYNOVEX® ONE FEEDLOT as an over-the-counter drug because the agency determined that adequate "directions for use" can be written on the labeling in such a way that non-veterinarians can use the drug safely and effectively.

Safety and Effectiveness

The sponsor conducted four-site field effectiveness studies to show that a SYNOVEX® ONE FEEDLOT implant increases average daily weight gain (ADG) in feedlot beef cattle when administered 60 to 120 days after a SYNOVEX Choice® implant. The sites were located throughout the U.S. with a range of management and environmental conditions that are representative of the U.S. feedlot industry. Healthy purebred or crossbred English or Continental beef steers and heifers were sourced from livestock auctions or ranches from major beef cattle-producing regions of the U.S.

Cattle were assigned to one of four groups:

Group	First Implant on Day 0	Second Implant on Day 60 ± 2 or 120 ± 2 after First Implant
1 (Control)	SYNOVEX Choice®	Sham-Implanted (the implant needle was inserted with no delivery)
2	SYNOVEX Choice®	SYNOVEX Choice®*
3	SYNOVEX Choice®	SYNOVEX PLUS®*
4	SYNOVEX Choice®	SYNOVEX® ONE FEEDLOT

* The results of these treatment groups are addressed in the July 2022 FOI Summary under NADA 141-043.

All cattle were individually weighed on Day 0 before the first implant was administered and again on the final day of the study (200 or 201 days after the first implant). Two sites reimplanted cattle on Day 60 ± 2 and two sites reimplanted cattle on Day 120 ± 2.

Over the study period, and regardless of sex or study site, cattle in the three treatment groups had a greater ADG (from 3.432 to 3.511 pounds of weight gain per day for steers and from 3.077 to 3.119 pounds of weight gain per day for heifers) compared to cattle in the control group (3.261 and 2.976 pounds of weight gain per day for steers and heifers, respectively).

Adverse reactions at the implant site were uncommon. The most common abnormal health events seen during the study were pneumonia or pleuritis, ruminal bloat, foot rot, and coccidiosis, which are all common conditions that occur in feedlot beef cattle. The abnormal health events generally resolved; however, some animals were removed from the study early due to severe illness, injury, death, or for showing bulling behavior (when a steer or heifer allows excessive mounting by other cattle). Reimplantation did not increase the risk of death or of being removed from the study.

The sponsor developed a literature-based database of growth performance and carcass characteristics of implanted steers and heifers. The sponsor used the database to then develop models to estimate the potential effects on carcass quality of feedlot beef cattle when they are given a second implant with SYNOVEX® ONE FEEDLOT 60 to 120 days after the first implant with SYNOVEX Choice®. The models predicted that the effects on carcass quality would be similar to those previously reported for one-time administration of a single implant. Therefore, the labeling for SYNOVEX® ONE FEEDLOT states that the implant, when used either once or as part of a reimplantation program, "may result in decreased marbling scores when compared to non-implanted steers and heifers."

FDA did not require the sponsor to conduct new target animal safety studies for this supplemental approval. The safety of SYNOVEX® ONE FEEDLOT in beef cattle was supported by the following:

- Target animal safety information for previous approvals of SYNOVEX PLUS® for growing beef steers and heifers fed in confinement for slaughter

(SYNOVEX PLUS® contains the same total amounts of both active ingredients as SYNOVEX® ONE FEEDLOT);
- Pharmacovigilance information for the currently approved uses of SYNOVEX® ONE FEEDLOT, SYNOVEX Choice®, and SYNOVEX PLUS®;
- Target animal safety information evaluated in the field effectiveness study described above. The study did not raise any animal safety concerns.

Taken together, this information supports the target animal safety of SYNOVEX® ONE FEEDLOT when it is used according to the labeled reimplantation program.

The labeling for SYNOVEX® ONE FEEDLOT includes animal safety warnings that bulling behavior has occasionally been reported in implanted steers and heifers; and that vaginal and rectal prolapse, udder development, ventral edema, and elevated tailheads have occasionally been reported in implanted heifers.

The safety and effectiveness of SYNOVEX® ONE FEEDLOT have not been evaluated in beef calves less than 2 months of age, dairy calves, and veal calves; in cattle intended for breeding; or in dairy cows. Therefore, the product should not be used in these groups of animals. Additionally, SYNOVEX® ONE FEEDLOT should not be used for repeated implantation with any other cattle ear implant other than what's described on the labeling.

Human Food Safety
FDA conducted an assessment to ensure that residues of trenbolone acetate (TBA) and estradiol benzoate (EB) in the edible tissues of treated cattle during and after reimplantation do not cause safety concerns for food for human consumption. This human food safety assessment was conducted from the perspectives of microbial food safety, toxicology, and residue chemistry.

For microbial food safety, FDA reviewed information submitted by the sponsor and also information that was publicly available regarding the impact of TBA and EB on antimicrobial resistance among bacteria of public health concern. The agency determined that TBA and EB 1) do not exert selection pressure for the development of resistant bacteria in food-producing animals; 2) are not used to treat gastroenteritis or other bacterial diseases in people; 3) are not being developed to treat a bacterial disease in people; and 4) are not used to treat a bacterial disease in food-producing animals. Therefore, FDA determined the sponsor did not need to provide additional information regarding microbial food safety when TBA and EB are used according to the labeled reimplantation program.

FDA did not require the sponsor to conduct new toxicology studies for this supplemental approval. The agency determined that it was not necessary to reassess the acceptable daily intake (ADI) for total residue of trenbolone. (The ADI is the largest amount of drug residues that will not cause harm to people even if they consume that amount every day.) FDA previously established the ADI for total residue of trenbolone as 0.4 µg/kg of body weight per day and the safe concentrations in individual edible tissues of treated cattle as 80 parts per billion (ppb) for muscle, 240 ppb for liver, 480 ppb for kidney, and 480 ppb for fat.

FDA regulates EB on the basis of allowable incremental increases, meaning EB residues are not allowed to be higher than a certain increment above the naturally-

occurring estradiol concentrations in untreated cattle. The agency determined that it was not necessary to reassess the allowable incremental increases of EB which are as follows: 0.2 ppb for muscle, 0.6 ppb for liver, 1.2 ppb for kidney, and 1.2 ppb for fat.

FDA did not require the sponsor to conduct new residue chemistry studies for this supplemental approval. The agency reviewed information submitted by the sponsor and data from a previous ^{14}C total residue depletion study. The previous study was used to support the original approval of SYNOVEX PLUS® and the approvals of other implants in the SYNOVEX® family of products. Carbon-14 (^{14}C) is a radioactive isotope of carbon that is used to radiolabel a drug. The radiolabeled drug is then administered to an animal to allow the concentration of drug residues in certain tissues to be measured as well as to determine how quickly the residues deplete from those tissues. FDA used the data from the previous ^{14}C to conclude that TBA and EB residues resulting from the labeled reimplantation program do not cause human food safety concerns and to support a 0-day withdrawal period assignment for cattle treated with SYNOVEX® ONE FEEDLOT when it is used according to the labeled reimplantation program.

Tolerances for residues of trenbolone and estradiol are not required. FDA concluded that it is not necessary to assign tolerances for residues of trenbolone because the previous ^{14}C study showed that total trenbolone residues in individual edible tissues of treated cattle depleted rapidly to their safe concentrations and that no withdrawal period (*i.e.*, zero withdrawal) is needed for the labeled reimplantation program. FDA established allowable incremental increases, not tolerances, for estradiol residues because estradiol is a naturally-occurring endogenous substance. (The tolerance is the highest concentration of drug residues legally allowed to be in or on food products made from treated animals. The withdrawal period allows for drug residues in the animal's body to get to levels that are at or below the tolerance. For naturally-occurring endogenous substances, such as estradiol, allowable incremental increases function as tolerances.)

Because tolerances for trenbolone and estradiol are not required, an official analytical method for monitoring their residues in cattle is not required.

Conclusions

Based on the data submitted by the sponsor for the approval of SYNOVEX® ONE FEEDLOT, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-348

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

SYNOVEX® ONE FEEDLOT

D. Drug Product Established Name

trenbolone acetate and estradiol benzoate extended-release implants

E. Pharmacological Category

Steroid hormone

F. Dosage Form

Extended-release implants

G. Amount of Active Ingredient

One implant contains 200 mg of trenbolone acetate and 28 mg of estradiol benzoate with a porous polymer film coating that extends the pay-out period of the final formulation up to 200 days. Each implant consists of 8 pellets.

H. How Supplied

One pouch contains 10 cartridges. Each cartridge contains 10 implants (100 implants total).

I. Dispensing Status

Over the counter (OTC)

J. Dosage Regimen

Administer one SYNOVEX® ONE FEEDLOT implant (eight pellets), containing 200 mg trenbolone acetate and 28 mg estradiol benzoate, to each steer or heifer by subcutaneous implantation in the middle-third of the ear. If using in a reimplantation program, reimplant steers or heifers with a SYNOVEX® ONE FEEDLOT implant 60 to 120 days after administering a SYNOVEX Choice® implant.

K. Route of Administration

Subcutaneous

L. Species/Class

Growing beef steers and heifers fed in confinement for slaughter

M. Indication

For increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later.

N. Effect of Supplement

This supplement provides for the approval of the indication for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summaries for the supplemental approvals of NADA 141-043 (SYNOVEX Choice®) dated October 3, 2002, and August 3, 2014, and for the original approval of NADA 141-348 (SYNOVEX® ONE FEEDLOT) dated July 31, 2014, contain dosage characterization information for increased rate of weight gain in growing beef steers fed in confinement for slaughter and growing beef heifers fed in confinement for slaughter.

B. Substantial Evidence

1. Dose Confirmation Studies

   Titles: Efficacy of Synovex Choice® Initial Implant Followed by Terminal Reimplant for Increased Rate of Weight Gain in Feedlot Steers. (Study No. A131C-US-15-350) and Efficacy of Synovex Choice® Initial Implant Followed by Terminal Reimplant for Increased Rate of Weight Gain in Feedlot Heifers. (Study No. A131C-US-15-385)

   Study Dates: October 24, 2019 to August 3, 2020

   Study Locations: The studies were conducted in four locations in the United States: Canyon, TX (Site A), Parma, ID (Site B), Reedley, CA (Site C), and Oakland, NE (Site D). Sites were selected to represent a broad range of management and environmental conditions to provide inferential value to the U.S. beef cattle feedlot industry.

Study Design:

Objective: The primary objective of the studies was to evaluate the effectiveness of a SYNOVEX Choice®, SYNOVEX PLUS®, or SYNOVEX® ONE FEEDLOT implant administered 60 to 120 days after initial implantation (day 0) with a SYNOVEX Choice® implant for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter.

Study Animals: Seventy-five steers and seventy-five heifers per treatment group were utilized at each site for a total of 300 animals of each sex per treatment group. Each pen contained cattle from all four treatments (equal number from each treatment, ranging from 18 to 25 animals per treatment per pen). Overall, a total of 1201 steers and 1202 heifers were enrolled in the study due to replacement of three animals early in the study due to health problems. Animal body weights ranged from 488 to 845 lb on the day of enrollment (day 0), with average body weights for steers and heifers of 661 and 652 lb, respectively. Steers and heifers were acquired from livestock auctions or ranches from major cattle-producing regions of the United States. The study included healthy purebred or crossbred English or Continental breed cattle, approximately 5 to 10 months of age, and not given any other implants in the 21 days prior to treatments. Pregnant females and intact males were excluded. Study animals were housed in outdoor pens typical of U.S. commercial feedlot design, relative to pen size, pen density, and bunk space. The cattle were fed rations typical of feedlots in their region that complied with or exceeded National Research Council Nutrient Requirements of Beef Cattle (2016). Animals had *ad libitum* access to water.

Experimental Design: Each study was a multi-site, randomized complete block, positive control study replicated across multiple sites. Within sex, animals were blocked by pen location and body weight at pre-enrollment (days -3
to -2). Animals of similar pre-enrollment body weights were randomly assigned to a pen. Within a pen, animals were blocked by body weight, with equal numbers of blocks of four animals per treatment per pen, with up to 25 blocks per pen of 100 animals. Within a block of four, animals were randomly assigned to treatment. Personnel who collected study data (other than data related to test article administration and accountability) were masked to treatment assignments. The treatment administrators did not conduct or record post-treatment data observations. Personnel performing necropsies were masked to treatment assignments. The studies were conducted according to Good Clinical Practices guidelines.

Drug Administration: On the day of enrollment (day 0), all animals were implanted with a SYNOVEX Choice® implant containing 100 mg trenbolone acetate and 14 mg estradiol benzoate, placed subcutaneously in the middle-third of the back of the ear using a Synovex® applicator, per labeling instructions. On the designated day of reimplantation (day 60 ± 2 or day 120 ± 2), animals were reimplanted with the assigned treatment implant: T01, control; T02, SYNOVEX Choice®; T03, SYNOVEX PLUS® containing 200 mg trenbolone acetate and 28 mg estradiol benzoate; or, T04, SYNOVEX® ONE FEEDLOT containing 200 mg trenbolone acetate and 28 mg estradiol benzoate

in an extended-release implant (see Table II.1), each placed subcutaneously in the middle-third of the back of the opposite ear from the initial implant using a Synovex® applicator, per labeling instructions. Control animals were sham-implanted, in which the implant needle was inserted with no delivery.

Table II.1. Treatment Groups

Treatment Group	Initial Implant	Terminal Implant
T01 (Control)	SYNOVEX Choice®	Sham
T02	SYNOVEX Choice®	SYNOVEX Choice®
T03	SYNOVEX Choice®	SYNOVEX PLUS®
T04	SYNOVEX Choice®	SYNOVEX® ONE FEEDLOT

Prior to study start, sites were randomly assigned to either a 60 or 120 reimplantation day. Two of the sites reimplanted cattle on day 60 ± 2 days and two sites reimplanted cattle on day 120 ± 2 days, as shown in Tables II.2 and II.3.

Table II.2. Reimplantation interval by site - Steers

Site	Interval	Number of Pens
A (TX)	119	3
B (ID)	119	4
C (CA)	61	3
D (NE)	60	4

Table II.3. Reimplantation interval by site - Heifers

Site	Interval	Number of Pens
A (TX)	61	3
B (ID)	120	4
C (CA)	120	3
D (NE)	60	4

Measurements and Observations: Individual body weights were collected for all animals at pre-enrollment, day 0, and at the end of the study (200 to 201 days after implantation). For animals removed from the study prior to the scheduled end, body weights were obtained at the time of removal and used in the analyses.

To evaluate implant site safety, individual ear evaluations were conducted for the initial implant on the day of reimplantation and on the final study day for both the initial and terminal implants. Ear evaluations were also conducted for any animals removed early from the study. Ears were visually inspected and palpated to detect ear abscesses or other abnormalities, and the presence of an implant.

All animals were observed twice daily for any general health abnormalities, with any illnesses or injuries requiring further evaluation and documentation of treatment. Animals were removed from the study in cases of severe illness, injury, or inappropriate enrollment. In case of death, animals were necropsied to determine cause.

Animals were shipped to the slaughter facility after final body weight measurement (same day or up to 35 days after, depending on site and slaughter facility availability). Animals were observed for overall health and mobility and ambulatory status when loading by trained professionals. Due to the restrictions imposed by the COVID-19 pandemic, carcass variables were not collected. To estimate the potential impacts of reimplantation on carcass characteristics, the sponsor developed a literature-based database of growth performance and carcass characteristics of implanted steers and heifers. Refer to Section II.B.2, below.

Statistical Methods:

The primary effectiveness variable, ADG, was calculated using the following equation:

$$\text{ADG} = \frac{(\text{Final animal weight} - \text{Initial animal weight})}{\text{Total number of animal days}}$$

Twelve steers were removed early from the study for eligibility or health reasons (summarized below) and excluded from the analysis: one steer in T03 died within the first week of the study, one steer in T04 was removed immediately following implantation on day 0, and ten steers were removed before reimplantation (one in T01, one in T02, four in T03, and four in T04). Seventeen heifers were removed early from the study for eligibility or health reasons and excluded from the analysis: four heifers were incorrectly identified as eligible during their pre-study pregnancy evaluation (two in T01, one in T02 and one in T04), two heifers in T03 and T04 were removed immediately following implantation on Day 0, and eleven heifers were removed before reimplantation (five in T01, one in T02, three in T03, and two in T04).

For each study, ADG was analyzed using a mixed linear model with fixed effects of treatment and random effects of site, pen within site, block within pen and site, and site by treatment interaction. Success criteria was based on significant improvement in ADG over the duration of the study; each of the reimplant treatment groups was compared to the single implant positive control for the purpose of demonstrating treatment success.

The occurrence of deaths and removals was analyzed using a generalized linear mixed model with logit link with fixed effects the same as those described above.

Results:

Initial and final body weights for steers and heifers in the control and reimplantation groups are shown in Table II.4. The final analysis included 1157 steers and 1160 heifers.

Table II.4. Initial and Final Mean Body Weights (lb) Across Sex and Site

Measurement	Initial Body Weight	Final Body Weight	Initial Body Weight	Final Body Weight
Sex	Steers	Steers	Heifers	Heifers
No. of Animals	1189	1157	1185	1160
T01 (CON)	660.5	1314.5	651.1	1246.7
T02	660.2	1355.3	653.6	1274.8
T03	661.7	1370.3	651.9	1283.1
T04	662.2	1356.0	652.5	1274.0

Initial and final body weights were used to calculate ADG, as described above. The steer and heifer studies were analyzed separately. As shown in Table II.5 and Table II.6, ADG (lb/d) was significantly different and greater for animals in the reimplantation treatment groups compared to the positive control for steers (*P-values* < 0.0079) and heifers (*P-values* < 0.0167).

Table II.5. Statistical Analysis of Average Daily Gain of Steers

Treatment	Number of Steers	LS Means (lb/d)	Standard Error	*P-value**
T01	299	3.261	0.080	n/a
T02	299	3.444	0.082	0.0055
T03	295	3.511	0.082	0.0008
T04	296	3.432	0.081	0.0079

**P-values are reported as the contrasts for the treatment group to the control group.*

Table II.6. Statistical Analysis of Average Daily Gain of Heifers

Treatment	Number of Heifers	LS Means (lb/d)	Standard Error	*P-value**
T01	293	2.976	0.119	n/a
T02	298	3.096	0.119	0.0074
T03	297	3.119	0.121	0.0030
T04	297	3.077	0.120	0.0167

**P-values are reported as the contrasts for the treatment group to the control group.*

The initial mean body weights of steers and heifers within each site are shown in Table II.7. The initial body weights of animals varied by sex and by site, but within sex and site the initial body weights were similar between animals assigned to the control and reimplantation treatment groups.

Table II.7. Summary of Initial Mean Body Weight (lb) by Sex and Site

Sex	Treatment	Site A	Site B	Site C	Site D
Steers	T01	665.5	675.6	600.7	700.4
Steers	T02	668.2	674.8	598.3	699.7
Steers	T03	666.5	674.2	603.3	704.3
Steers	T04	668.3	676.7	603.5	701.1
Heifers	T01	610.9	643.1	669.6	688.7
Heifers	T02	610.7	632.3	679.9	691.1

Sex	Treatment	Site A	Site B	Site C	Site D
Heifers	T03	610.4	636.8	672.5	686.7
Heifers	T04	611.1	634.4	676.5	687.3

The final mean body weights of steers and heifers within each site are shown in Table II.8.

Table II.8. Summary of Final Mean Body Weight (lb) by Sex and Site

Sex	Treatment	Site A	Site B	Site C	Site D
Steers	T01	1301.7	1345.7	1276.5	1334.6
Steers	T02	1334.0	1373.5	1330.7	1381.1
Steers	T03	1341.6	1414.4	1349.4	1375.8
Steers	T04	1356.7	1385.9	1329.4	1352.0
Heifers	T01	1188.2	1294.5	1265.3	1238.6
Heifers	T02	1222.5	1331.2	1269.4	1280.0
Heifers	T03	1231.2	1333.9	1292.4	1272.8
Heifers	T04	1224.5	1265.3	1272.2	1274.8

Reimplantation with a SYNOVEX Choice®, SYNOVEX PLUS®, or SYNOVEX® ONE FEEDLOT implant 60 to 120 days after initial implantation with a SYNOVEX Choice® implant on day 0 increased ADG over 200 days across both sexes and all four study sites.

Adverse Reactions:

Adverse reactions at the implant sites were uncommon. Reactions to the initial SYNOVEX Choice® implant occurred in only 0.5% of steers (6/1190 steers). Reactions to the terminal implant occurred in only 0.17% of steers (2/1158 steers): both in the SYNOVEX Choice®-SYNOVEX® ONE FEEDLOT treatment group. Reactions to the initial SYNOVEX Choice® implant occurred in only 0.6% of heifers (7/1189 heifers). Reactions to the terminal implant occurred in only 0.17% of heifers (2/1160 heifers): one heifer each in the SYNOVEX Choice®-SYNOVEX PLUS® and SYNOVEX Choice®-SYNOVEX® ONE FEEDLOT treatment groups. The implantation site reactions in both steers and heifer were mild, such as small or hard swelling, scar tissue, or small abscess.

Abnormal health events occurred for common conditions in beef cattle fed in confinement for slaughter. Of the 2,374 steers and heifers appropriately enrolled in the study and included in the final analysis, 249 abnormal health events were reported (control, n = 56; T02, n = 58; T03, n = 85; T04, n = 50), see Table II.9 and Table II.10. The most common abnormal health events were pneumonia or pleuritis, ruminal bloat, foot rot, and clinical signs of coccidiosis (the latter two occurred only at a single site).

Table II.9. Summary of abnormal health events in steers by treatment

Diagnosis	T01	T02	T03	T04	Total
Anxiety	0	0	1	0	1
Arthritis	1	1	0	0	2
Dermatitis and eczema	3	7	6	4	20

Diagnosis	T01	T02	T03	T04	Total
Diarrhea	0	1	0	0	1
Eye disorder	0	1	1	1	3
Hemorrhagic diarrhea	2	1	1	1	5
Hepatic abscesses	0	0	1	0	1
Hyperthermia	0	1	1	0	2
Lameness	1	0	2	2	5
Laminitis	0	0	1	0	1
Loss of condition	0	0	0	1	1
Mechanical injury	1	1	1	2	5
Paralysis	0	1	0	0	1
Pericarditis	0	1	0	0	1
Pleuritis	0	1	0	0	1
Pneumonia	7	7	5	5	24
Pulmonary disorder	0	0	0	1	1
Ruminal bloat	10	8	17	7	42
Sexual disorder	0	2	1	2	5
Skin lesion	0	0	1	0	1
Urinary bladder disorder	1	0	2	0	3
Urolithiasis	0	2	0	1	3
Total	26	35	41	27	129

Table II.10. Summary of abnormal health events in heifers by treatment

Diagnosis	T01	T02	T03	T04	Total
Arthritis	0	0	0	1	1
Calved*	1	1	0	1	3
Cardiac insufficiency	0	0	1	1	2
Death	1	0	0	0	1
Dermatitis and eczema	1	2	1	1	5
Dyspnea	0	0	0	1	1
Dystocia*	1	0	0	0	1
Emphysema	1	0	0	0	1
Enteritis	0	1	0	0	1
Hemorrhagic diarrhea	2	4	7	5	18
Hepato-biliary disorder	0	0	1	0	1
Hyperthermia	0	1	0	0	1
Lameness	3	0	3	1	7
Laminitis	1	0	0	0	1
Mechanical injury	0	3	2	2	7
Otitis	1	0	1	0	2
Pleuritis	0	1	0	0	1

Diagnosis	T01	T02	T03	T04	Total
Pneumonia	15	8	17	5	45
Ruminal bloat	3	2	11	5	21
Total	30	23	44	23	120

* Occurred in inappropriately enrolled reproducing (pregnant) females.

Abnormal health events generally resolved; however, some enrolled animals were removed from the study early due to severe illness, injury, death, or for exhibiting "buller steer" behaviors (a steer experiencing excessive mounting by other steers). Three steers were removed for exhibiting "buller steer" behaviors (T02, n = 1; T03, n = 1; T04, n = 1). There were no significant effects of reimplantation treatment on the early removal rate compared to the control group, as shown in Table II.11.

Table II.11. Animals Removed Early from Study

Sex	Treatment	Number Enrolled	Number Removed	Removal Rate (%)
Steers	T01	300	11	3.5
Steers	T02	300	14	4.5
Steers	T03	300	17	5.5
Steers	T04	300	13	3.8
Heifers	T01	300	10	3.3
Heifers	T02	300	12	4.0
Heifers	T03	300	19	6.0
Heifers	T04	300	16	5.0

Removals and abnormal health events were primarily for common conditions that occur in cattle fed in confinement for slaughter. The studies support the safe use of these products under the labeled conditions of use. There were no statistically significant treatment effects on the frequency of deaths and removals during the studies. Further, the adverse events reported are those for which cattle feeders in the U.S. are experienced with treating and managing.

Conclusions: The studies demonstrated substantial evidence of effectiveness of SYNOVEX® ONE FEEDLOT for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later.

2. Carcass Characteristics Literature Database and Modeling

A literature-based database of growth performance and carcass characteristics of implanted steers (30 sources; 11,091 animals) and heifers (17 sources; 6,152 heifers) was developed. Models were developed to use the live growth performance of growing beef steers and heifers fed in confinement for slaughter to estimate the potential effects of reimplantation with a SYNOVEX Choice®, SYNOVEX PLUS®, or SYNOVEX® ONE FEEDLOT implant 60 to 120 days following initial implantation with a SYNOVEX Choice® implant on carcass characteristics. Based upon the observed effects of reimplantation on

ADG as shown in Table II.5 and Table II.6 above, the models to estimate the effects of reimplantation on carcass characteristics of growing beef steers and heifers predicted that treatment effects would be similar to those previously reported for the implants, as summarized in the supplemental approvals of NADA 141-043, dated September 30, 1998, March 16, 1999, October 3, 2002, and August 3, 2014, and the original approval of NADA 141-348 dated July 31, 2014. Thus, the SYNOVEX® ONE FEEDLOT labeling contains the following statement:

> "NOTE: Administration of a single SYNOVEX® ONE implant or its use in a reimplantation program with a SYNOVEX Choice® implant may result in decreased marbling scores when compared to non-implanted steers and heifers."

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-043 dated February 22, 1996, and a supplemental approval dated September 30, 1998, contain a summary of target animal safety studies for growing beef steers and heifers fed in confinement for slaughter, respectively, for SYNOVEX PLUS®, containing 200 mg trenbolone acetate and 28 mg estradiol benzoate per implant.

The FOI Summaries for the supplemental approvals for NADA 141-043, dated October 3, 2002, and August 3, 2014, for SYNOVEX Choice®, containing 100 mg trenbolone acetate and 14 mg estradiol benzoate per implant, in growing beef steers and heifers fed in confinement for slaughter, respectively, indicated that these approvals utilized data from the studies conducted to support the target animal safety of SYNOVEX PLUS®. Similarly, the original approval for NADA 141-348 for SYNOVEX ONE® FEEDLOT, containing 200 mg trenbolone acetate and 28 mg estradiol benzoate per extended-release implant, utilized data from the studies conducted to support the target animal safety of SYNOVEX PLUS® (see FOI Summary for NADA 141-348 dated July 31, 2014).

As summarized in the original and supplemental approvals of NADA 141-043 for SYNOVEX PLUS®, steers and heifers were implanted once with 1, 3, or 5 implants on day 0. The 5x group received 1000 mg trenbolone acetate and 140 mg estradiol benzoate and there were no adverse effects on any production factor, clinical pathology parameters, or in gross pathologic findings. The target animal safety of SYNOVEX Choice® when used in a reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later was evaluated under intended use conditions in the dose confirmation effectiveness studies. There were no animal safety concerns raised by the evaluation of animal health data in these studies. In addition, pharmacovigilance information for NADA 141-043 and NADA 141-348 was evaluated for the currently approved uses. Taken together, the target animal safety studies cited under NADA 141-043 and the animal health data from the effectiveness study support the current approval for the use of SYNOVEX® ONE FEEDLOT for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later.

To provide for safe and effective use of the products, the labeling for SYNOVEX Choice® and SYNOVEX® ONE FEEDLOT includes animal safety warnings that bulling has occasionally been reported in implanted steers and heifers, and vaginal and rectal prolapse, udder development, ventral edema and elevated tailheads have occasionally been reported in heifers administered SYNOVEX Choice® and SYNOVEX® ONE FEEDLOT implants. In addition, because safety and effectiveness have not been evaluated, labeling prohibits the use of these products:

- In beef calves less than 2 months of age, dairy calves, and veal calves.
- In animals intended for subsequent breeding, or in dairy cows.
- For repeated implantation (reimplantation) with any other cattle ear implant other than described on the labeling for growing beef steers and heifers fed in confinement for slaughter.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

The Agency evaluated the need to address the impact of the use of SYNOVEX Choice® (100 mg trenbolone acetate and 14 mg estradiol benzoate) for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant (200 mg trenbolone acetate and 28 mg estradiol benzoate) is administered 60 to 120 days later, on public health with respect to antimicrobial resistance among bacteria of public health concern in or on treated cattle. After reviewing information (literature, data, *etc*.) both submitted by the sponsor and available in the public domain, the Agency determined:

–TBA and EB are not regularly considered to have properties that would exert pressure towards the emergence or selection of resistant bacteria of public health concern in food-producing animals,

– TBA and EB are not used to treat gastroenteritis or other bacterial diseases in humans,

– TBA and EB (or similar class representatives) are not under development to treat a bacterial disease in humans, and

– TBA and EB are not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined there was no need to provide additional microbial food safety (antimicrobial resistance) information or data regarding this approved use of TBA and EB in cattle.

B. Toxicology

Trenbolone

The codified Acceptable Daily Intake (ADI) for total residue of trenbolone is 0.4 µg/kg of body weight *per* day, as listed under 21 CFR §556.739. Reassessment of the codified ADI was not needed for this supplemental approval.

Based on the codified ADI of 0.4 µg/kg of body weight *per* day and revised food consumption values of 300 g (muscle), 100 g (liver), 50 g (kidney) and 50 g (fat), the safe concentrations for total residues of trenbolone in edible tissues are: 80 parts per billion (ppb) for muscle, 240 ppb for liver, 480 ppb for kidney, and 480 ppb for fat. The FOI Summaries for the original approval of NADA 141-043, dated February 22, 1996, and the supplemental approval, dated September 30, 1998, contain summaries of all toxicology studies and information.

Estradiol

Estradiol is regulated on the basis of allowable incremental increases for residues. As listed under 21 CFR §556.240, residues of estradiol are not permitted in excess of the following increments above the concentrations of estradiol naturally present in untreated animals (cattle): 0.2 ppb for muscle, 0.6 ppb for liver, 1.2 ppb for kidney, and 1.2 ppb for fat.

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

Rationale

To demonstrate the human food safety of trenbolone and estradiol tissue residues resulting from the treatment under the reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later and to support a zero-day withdrawal period assignment for the reimplantation program, the sponsor needs to demonstrate that trenbolone and estradiol tissue residues during and after the reimplantation treatment do not cause human food safety concerns.

CVM did not require residue chemistry studies for this approval. The sponsor submitted a written discussion with data/information to support the human food safety of the tissue residues resulting from the treatment under the reimplantation program. CVM evaluated the sponsor's written discussion and related data/information and determined that:

- While the total dose in the administered implants is important information, the actual amount of TBA and EB released daily (*i.e.*, daily release) from the implants provides an indicator for the amount of TBA and EB that is absorbed by the cattle and the resulting tissue residue concentrations.

- It is unlikely that the daily overlapping release of TBA and EB in treated cattle from the SYNOVEX Choice® and SYNOVEX® ONE FEEDLOT implants administered according to the reimplantation program will exceed the highest daily release of TBA and EB in treated cattle from the single implant containing 300 mg ^{14}C-TBA and 42 mg EB tested in the total residue depletion study conducted by Syntex (referred to hereafter as Syntex's ^{14}C total residue depletion study).

- Therefore, it is unlikely that the predicted tissue concentrations of trenbolone and estradiol residues in cattle resulting from the reimplantation treatment will exceed the highest tissue concentrations of trenbolone and estradiol residues determined in Syntex's ^{14}C total residue depletion study.

- As such, the highest tissue concentrations of trenbolone and estradiol residues in cattle determined in Syntex's ^{14}C total residue depletion study represent a worst-case for the predicted trenbolone and estradiol tissue residues resulting from the reimplantation treatment. If the highest tissue concentrations of trenbolone and estradiol residues determined in Syntex's ^{14}C total residue depletion study do not cause human food safety concerns, then the trenbolone and estradiol tissue residues resulting from the reimplantation treatment do not cause human food safety concerns, and the reimplantation program qualifies for a zero-day withdrawal period assignment.

Assessment of Human Exposure to Trenbolone and Estradiol Residues

CVM's human food safety assessment for trenbolone and estradiol tissue residues in cattle resulting from the reimplantation treatment is summarized below:

Regulatory History

a. SYNOVEX Choice® and SYNOVEX PLUS® have been approved individually under NADA 141-043, and SYNOVEX® ONE FEEDLOT has been approved under NADA 141-348, for subcutaneous administration as a single implant in the ears of cattle. A zero-day withdrawal period is assigned for these approvals. Each implant of SYNOVEX® Choice® consists of 4 uncoated pellets and contains a total dose of 100 mg TBA and 14 mg EB. Each implant of SYNOVEX PLUS® consists of 8 uncoated pellets and contains a total dose of 200 mg TBA and 28 mg EB. Each implant of SYNOVEX® ONE FEEDLOT consists of 8 coated pellets and contains a total dose of 200 mg TBA and 28 mg EB.

   Syntex's ^{14}C total residue depletion study provided data on the tissue concentrations of total residues of trenbolone and concentrations of estradiol in cattle treated with an implant consisting of all uncoated pellets and containing 300 mg ^{14}C-TBA and 42 mg EB (equivalent to 1.5 x SYNOVEX PLUS® labeled dose). This study was the pivotal study in support of the individual approvals of SYNOVEX Choice®, SYNOVEX PLUS® and of other implants in the SYNOVEX® family of products. A summary of

the study is included in the FOI Summaries for the approvals of SYNOVEX® PLUS® in beef steers and beef heifers, dated February 22, 1996, and September 30, 1998, respectively.

b. Fort Dodge Safety Study 0738-B-US-1-98, owned by Zoetis Inc., compared the release of TBA and EB in cattle from SYNOVEX® ONE FEEDLOT with that from SYNOVEX PLUS® over a 200-day period post implantation. A summary of the study is included in the FOI Summary (Section II.A.2) for SYNOVEX® ONE FEEDLOT (NADA 141-348, original approval dated July 31, 2014). The study showed that, in the early phase after implantation, the release rate of TBA and EB in cattle from SYNOVEX® ONE FEEDLOT implants, consisting of all coated pellets, was lower than the release rate of TBA and EB in cattle from SYNOVEX PLUS® implants, consisting of all uncoated pellets. While both SYNOVEX PLUS® and SYNOVEX® ONE FEEDLOT implants contain the same dose of 200 mg TBA and 28 mg EB, the release of TBA and EB in cattle from SYNOVEX PLUS® continued for more than 120 days and less than 160 days post implantation. However, the release of TBA and EB in cattle from SYNOVEX® ONE FEEDLOT continued beyond 200 days post implantation.

   For SYNOVEX PLUS®, the release rate of TBA is higher in the early phase than in the late phase after implantation. The release rate of EB also is higher in the early phase than in the late phase after SYNOVEX PLUS® implantation. As the pellets in SYNOVEX Choice® and SYNOVEX PLUS® are all uncoated, the release characteristics of TBA and EB from SYNOVEX Choice® would be similar to those from SYNOVEX PLUS®. However, the daily release rate of TBA and EB from SYNOVEX Choice® would be proportionally lower than that from SYNOVEX PLUS®.

c. Fort Dodge Pharmacokinetic Study 0738-B-US-2-98, also owned by Zoetis, compared serum concentrations of 17β-trenbolone and 17β-estradiol in beef cattle treated with a SYNOVEX® ONE FEEDLOT implant with those in beef cattle treated with a SYNOVEX PLUS® implant during a 200-day period after implantation. A summary of the study is included in the FOI Summary (Section II.A.3) for SYNOVEX® ONE FEEDLOT (NADA 141-348, original approval dated July 31, 2014). The study showed that, while SYNOVEX PLUS® and SYNOVEX® ONE FEEDLOT both provided sustained release of TBA and EB from the implants, the maximum serum concentrations of 17β-trenbolone and 17β-estradiol in SYNOVEX® ONE FEEDLOT-treated cattle were delayed compared with those in SYNOVEX PLUS-treated cattle. However, the maximum serum concentrations of 17β-trenbolone and 17β-estradiol in SYNOVEX® ONE FEEDLOT-treated cattle were similar and not greater than the maximum serum concentrations in SYNOVEX PLUS®-treated cattle.

   In addition, the study showed that in SYNOVEX PLUS®-treated cattle, the maximum serum concentrations of 17β-trenbolone and 17β-estradiol were found in the early phase post SYNOVEX PLUS® implantation, which is consistent with the Agency's use of trenbolone and estradiol tissue residue data collected at Days 15 and 30 post implantation in Syntex's ^{14}C total

residue depletion study as the highest incurred tissue residue concentrations resulting from the treatment in support of the individual approvals of SYNOVEX PLUS® as a standalone treatment.

Justification that the tissue trenbolone and estradiol residue data from Syntex's ^{14}C total residue depletion study represent a worst-case scenario for the residues resulting from the reimplantation treatment.

a. Under the reimplantation program, SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later. Because SYNOVEX Choice® has been approved as a standalone treatment, the human food safety of trenbolone and estradiol residues resulting from its use in the first 60 to 120 days of the reimplantation program has been demonstrated by data in support of the standalone approval of SYNOVEX Choice®.

b. The reimplantation program in which a SYNOVEX Choice® implant is followed by a SYNOVEX® ONE FEEDLOT implant 60 to 120 days later provides a combined labeled dose of 300 mg TBA and 42 mg EB, which is the same as the dose in the implant containing 300 mg TBA and 42 mg EB that was tested in Syntex's ^{14}C total residue depletion study. All the pellets in SYNOVEX Choice® are uncoated while all the pellets in SYNOVEX® ONE FEEDLOT are coated. All the pellets in the implant tested in the Syntex study were uncoated. Based on the TBA and EB release characteristics from implants consisting of uncoated pellets and coated pellets (Study 0738-B-US-1-98), when a SYNOVEX® ONE FEEDLOT implant consisting of all coated pellets and containing 200 mg TBA and 28 mg EB is administered 60 to 120 days after a SYNOVEX Choice® implant consisting of all uncoated pellets and containing 100 mg TBA and 14 mg EB, the release of TBA and EB from the SYNOVEX Choice® implant would no longer be as robust as in the earlier phase after its administration. On the other hand, the time of peak release of TBA and EB in cattle from a SYNOVEX® ONE FEEDLOT implant is later than that from a SYNOVEX PLUS® implant. As such, the daily overlapping release of TBA and EB from a SYNOVEX Choice® implant and a SYNOVEX® ONE FEEDLOT implant is unlikely to exceed the highest daily release of TBA and EB from the single implant consisting of all uncoated pellets and containing 300 mg TBA and 42 mg EB that was tested in Syntex's ^{14}C total residue depletion study. Therefore, it is unlikely that the predicted tissue concentrations of trenbolone and estradiol residues in cattle during and after the reimplantation treatment in the reimplantation program will exceed the highest tissue concentrations of trenbolone and estradiol residues determined in Syntex's ^{14}C total residue depletion study.

Use of Syntex's ^{14}C total residue depletion study to show that trenbolone and estradiol tissue residues resulting from the reimplantation treatment do not cause human food safety concerns.

In the Syntex's ^{14}C total residue depletion study, each animal in the two treatment groups with 4 steers and 4 heifers *per* group was treated with an implant consisting of all uncoated pellets and containing 300 mg ^{14}C-TBA and

42 mg EB. The animals were slaughtered by group at 15 or 30 days after the implantation. Samples of liver, kidney, muscle, fat, and bile were collected from each animal. Concentrations of the total residues of trenbolone and concentrations of 17β-estradiol in these samples were determined. A summary of the study, including the mean concentrations of total residues of trenbolone and the mean concentrations of 17-β estradiol in the four edible tissues of beef steers, may be found in the FOI Summary for the approval of SYNOVEX PLUS® in beef steers (NADA 141-043, dated February 22, 1996). These total residue concentration data also are shown in Table IV.1 below.

Table IV.1. Concentrations of Total Residues of Trenbolone and Concentrations of 17β-Estradiol in Steers

Tissue	Radio-Equivalent Concentration of TBA (ppb) Mean ± S.D. (15 days)	Radio-Equivalent Concentration of TBA (ppb) Mean ± S.D. (30 days)	Estradiol-17β (ppt) Mean ± S.D. (15 days)	Estradiol-17β (ppt) Mean ± S.D. (30 days)
Liver	51.83 ± 12.47	85.23 ± 45.15	No value	No value
Kidney	14.25 ± 2.54	21.40 ± 9.25	No value	No value
Muscle	1.12 ± 0.42	1.99 ± 0.91	16.63 ± 2.85	24.43 ± 10.32
Fat	1.20 ± 1.29	1.41 ± 1.25	74.93 ± 20.71	95.23 ± 38.71

A summary of the study, including the mean concentrations of total residues of trenbolone and the mean concentrations of 17β-estradiol in the four edible tissues of beef heifers, may be found in the FOI Summary for the approval of SYNOVEX PLUS® in beef heifers (NADA 141-043, dated September 30, 1998). These total residue concentration data also are shown in Table IV.2 below.

Table IV.2. Concentrations of Total Residues of Trenbolone and Concentrations of 17β-Estradiol in Heifers

Tissue	Radio-Equivalent Concentration of TBA (ppb) Mean ± S.D. (15 days)	Radio-Equivalent Concentration of TBA (ppb) Mean ± S.D. (30 days)	Estradiol-17β (ppt) Mean ± S.D. (15 days)	Estradiol-17β (ppt) Mean ± S.D. (30 days)
Liver	64.98 ± 13.56	62.05 ± 17.30	No value	No value
Kidney	16.75 ± 4.15	16.15 ± 1.78	No value	No value
Muscle	1.11 ± 0.35	1.46 ± 0.20	19.10 ± 5.25	13.61 ± 2.98
Fat	1.68 ± 0.90	1.63 ± 1.48	92.25 ± 23.99	68.33 ± 21.81

Because the dose of TBA and EB contained in the implant tested in Syntex's ^{14}C total residue depletion study is the same as the combined labeled dose for the reimplantation program in which the administration of a SYNOVEX Choice® implant is followed by the administration of a SYNOVEX®

ONE FEEDLOT implant 60 to 120 days later, we compared the mean concentrations of total residues of trenbolone in the edible tissues of beef steers and heifers, shown in Table IV.1 and Table IV.2, respectively, to one-half of the corresponding safe concentrations for total residues of trenbolone in the edible tissues (*i.e.*, 80 ppb for muscle, 240 ppb for liver, 480 ppb for kidney, and 480 ppb for fat, calculated based on the ADI for total residues of trenbolone codified under 21 CFR §556.739, and the revised food consumption values of 300 g for muscle, 100 g for liver, 50 g for kidney and 50 g for fat). The mean concentrations of total residues of trenbolone in all of the sampled tissues from both steers and heifers at all of the sampled time points were below one-half of the corresponding safe concentrations for total residues of trenbolone in these tissues.

We also compared the mean concentrations of 17β-estradiol in the edible tissues of beef steers and heifers to one-half of the corresponding allowable incremental increases of 0.2 ppb for muscle, 0.6 ppb for liver, 1.2 ppb for kidney, and 1.2 ppb for fat based on the revised food consumption values. The mean concentrations of 17β-estradiol in all of the sampled tissues from both steers and heifers at all of the sampled time points were well below one-half of the corresponding allowable incremental increases for estradiol residues in these tissues.

Conclusion of the assessment

The trenbolone and estradiol tissue residue data from Syntex's ^{14}C total residue depletion study represented a worst-case scenario for evaluating the human food safety of the predicted trenbolone and estradiol tissue residues resulting from the reimplantation treatment. Based on the results of Syntex's ^{14}C total residue depletion study, we concluded that the trenbolone and estradiol tissue residues resulting from the reimplantation treatment do not cause human food safety concerns and support a zero-day withdrawal period assignment for the reimplantation program.

2. Target Tissue and Marker Residue

Neither a target tissue nor a marker residue is needed for trenbolone in cattle. See the FOI Summaries for NADA 141-043, dated February 22, 1996, and September 30, 1998.

Neither a target tissue nor a marker residue is needed for estradiol in cattle. Residues of estradiol are regulated on the basis of the codified allowable incremental increases. See Section IV.B of this summary.

3. Tolerances

A tolerance for trenbolone in cattle is not required (21 CFR §556.739). See the FOI Summaries for NADA 141-043, dated February 22, 1996, and September 30, 1998.

A tolerance for estradiol in cattle is not required. Residues of estradiol are regulated on the basis of the codified allowable incremental increases. See Section IV.B of this summary.

4. Withdrawal Period

No withdrawal period is required (*i.e.*, zero-day withdrawal) for growing beef steers and heifers fed in confinement for slaughter where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later. Based on the results of Syntex's ^{14}C total residue depletion study, we concluded that the trenbolone and estradiol tissue residues resulting from the reimplantation treatment do not cause human food safety concerns and support a zero-day withdrawal period assignment for the reimplantation program.

D. Analytical Method for Residues

Because neither a tolerance nor a withdrawal period is required for the reimplantation program, an official analytical method is not required for either trenbolone or estradiol residues in cattle.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to SYNOVEX® ONE FEEDLOT:

Not for use in humans. Keep out of reach of children.

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that SYNOVEX® ONE FEEDLOT, when used according to the label, is safe and effective for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later. Additionally, data demonstrate that residues in food products derived from species treated with SYNOVEX® ONE FEEDLOT will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product can be marketed OTC because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the labeling are reasonably certain to be followed in practice.

B. Exclusivity

This supplemental approval for SYNOVEX® ONE FEEDLOT qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to

SYNOVEX® ONE FEEDLOT for increased rate of weight gain for up to 200 days in growing beef steers and heifers fed in confinement for slaughter in a reimplantation program where SYNOVEX Choice® is the first implant and a SYNOVEX® ONE FEEDLOT implant is administered 60 to 120 days later.

C. Supplemental Applications

This supplemental NADA required a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.