Approval Date: August 19, 1994

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 009-576

B. Sponsor

Syntex Animal Health
Division of Syntex Agribusiness, Inc.
3401 Hillview Avenue
Palo Alto, CA 94304

C. Proprietary Name

Synovex® S

D. Established Name

Estradiol benzoate and progesterone

E. Dosage Form

Synovex® S implants consist of eight pellets containing a total of 20 mg estradiol benzoate and 200 mg of progesterone.

F. Dispensing Status

OTC

G. Route of Administration

Synovex® S implants are administered by subcutaneous implantation in the middle one-third of the ear of steers.

H. Indication

For increased rate of weight gain and improved feed efficiency.

I. Effect of Supplement

This supplement provides for reimplantation of Synovex® S at approximately day 70 in steers fed in confinement for slaughter for additional improvement in rate of weight gain.

II. EFFECTIVENESS

Pivotal Studies:
The supplemental new animal drug application for Synovex® S contains data from adequate and well-controlled investigations demonstrating the effectiveness of Synovex® S in improving weight gain in steers fed in confinement for slaughter when reimplanted at day 70. The studies were conducted in major beef producing areas of the

United States using a uniform protocol so that the results of the studies could be pooled and summarized.

Name and Address of Investigators:

Dr. Ronald Hale
Continental Beef Research
Lamar, Colorado

Dr. James J. Sheldon
Reeves Research
Garden City, Kansas

Dr. Daryl G. Meyer
Lucerne Enterprises
Colon, Nebraska

The purpose of the studies was to determine the effect of Synovex® S when reimplanted at day 70 on rate of weight gain and feed efficiency in feedlot steers. At each location, 96 medium-frame beef steers were allocated to three groups on the basis of weight in a randomized complete block design (4 blocks of 3 pens with 8 steers per pen). The animals were blocked on the basis of initial weight. Group 1 (-/-)consisted of non-implanted steers (controls); Group 2 (S/-) steers were administered Synovex S implants on day 1 (beginning of feeding period); Group 3 (S/S) animals were implanted with Synovex S implants on days 1 and 70. Average initial weights of animals at the three locations ranged from 734 to 748 pounds. The animals were slaughtered when visual inspection suggested that approximately 70% would grade USDA Choice. Average daily gain and feed efficiency data are summarized in Table 1 for each of the three studies:

TABLE 1. SUMMARY FROM THREE STUDIES COMPARING THE PERFORMANCE OF FEEDLOT STEERS ON REIMPLANTATION OF Synovex® S

Location

Average Daily Gain (lbs)

Treatment	**Colorado**	**Kansas**	**Nebraska**	**LS Means**
-/-	2.96	2.60	2.88	2.81
S/-	3.32	3.11	3.36	3.26
S/S	3.53	3.16	3.58	3.42

Feed Efficiency (lbs dry matter/lb gain)

Treatment	Colorado	Kansas	Nebraska	LS Means
-/-	6.6	7.8	7.0	7.15
S/-	5.9	5.8	6.3	5.98
S/S	5.8	6.7	6.2	6.22

A randomized complete block design was used for all studies and the data were pooled by analysis of variance to determine the significance of the effect of reimplanting Synovex® S on average daily gain and feed efficiency. Steers implanted with Synovex® S on days 1 and 70 were shown to be better than nonimplanted controls ($P < 0.001$) and better than steers implanted only on day 1 ($P < 0.05$) for average daily gain. Feed efficiency of animals implanted on day 1 or on days 1 and 70 was significantly better than that of non-implanted controls ($P < 0.05$) but no differences were observed between the two implanted groups. These data indicate that the replantation of Synovex® S is effective for increasing weight gain in steers fed in confinement for slaughter. The effects of treatment on carcass parameters (dressing percent, yield grade, quality grade, and marbling score), and on the incidence of liver abscesses were evaluated at slaughter. A reduction in marbling score and percent grading choice was observed for the S/S group. Because of the observed decrease in marbling scores, the following statement is required on the label: Studies have demonstrated that reimplantation of Synovex® S can result in decreased marbling scores when compared to non-implanted steers. No effect of treatment was seen on dressing percent, yield grade, or the incidence of liver abscesses.

III. TARGET ANIMAL SAFETY

Pivotal Studies:

A. Drug Tolerance Study

A drug tolerance study was conducted by Dr. Donald E. Bidlack, Department of Pathology, Syntex Research, 3401 Hillview Avenue, Palo Alto, CA. The purpose of the study was to evaluate the acute effects of exaggerated overdosing on steers. Three mixed beef-breed steers averaging 325 kg were assigned to the study. Two of the steers received 21 consecutive daily subcutaneous injections of 75 mg estradiol benzoate and 75 mg progesterone in sesame oil. This dose was estimated to be approximately 25 times the release rate for estradiol benzoate and progesterone from Synovex® S implants. The control steer received subcutaneous injection of sesame oil (vehicle) for the same period. Observations and laboratory measurements continued for two weeks after the end of dosing. All steers were euthanized and necropsied at study termination. All preserved tissues were examined microscopically.

Changes associated with the treatment regimen were seen in the two steers that received estradiol benzoate and progesterone. Sexual behavior, characterized by posturing (placing the head on the back or rump of another animal) or mounting (as if to breed) was seen in one or both treated steers on study days 10, 30, and/or 35 when cattle were allowed to commingle. Subtle tailhead prominence was present, concurrent with relaxation of the perirectal musculature, in one treated steer. Slight eversion of rectal mucosa or rectal prolapse was present in the treated steers. The condition was observed while the animals were lying down, but it corrected spontaneously when the animals were standing.

Body weight gains, feed consumption, heart rates, and rumen activity were not adversely affected by the treatment regimen. The treated steers gained an average of 64.5 kg during the study while the control steer gained 39 kg. Sporadic swelling of some of the injection sites, considered to be associated with the nature of the sesame oil formulations, was present in all steers, including the control animal.

Other changes were observed clinically, but were considered related to intercurrent conditions and unrelated to the treatment regimen.

Alkaline phosphatase levels were increased in both treated steers beginning with study day 10. In the absence of significant histopathologic changes, the alkaline phosphatase increases were not considered relevant.

No gross histopathologic changes attributable to systemic effects of estradiol benzoate/progesterone were present in any tissues. The local swellings of some of the injection sites were characterized microscopically by mixed leukocytic infiltration and fibrosis. Oil droplets were present in the sections. These changes were considered associated with subcutaneous injections of sesame oil.

B. Drug Safety Study

A target animal safety study was conducted by Dr. James Sheldon, CAVL, Inc., P.O. Box 1296, Casa Grande, AZ. The purpose of the study was to assess the safety to feedlot cattle of Synovex® S when reimplantation occurred. Thirty-six beef-type steers with an initial mean weight of 200.6 kg were allotted to four treatment groups, with each group composed of three replicate pens of three steers (9 steers per treatment group). Steers were implanted with Synovex® S in multiples of the clinically recommended dose. Groups were designated as follows: Group 1 - Sham control; Group 2 - 1X Synovex® S; Group 3 - 3X Synovex® S; Group 4 - 5X Synovex® S. The steers were implanted on study day 1 and reimplanted on study day 63. The cattle were fed a roughage/concentrate ration typical for cattle in confinement. Body weights (fasted) and feed consumption were recorded at approximately monthly intervals and at study termination for this 206-day study. Hematology and serum chemistry determinations were made at the same intervals. The animals were observed daily and the clinical condition of the animals was recorded weekly and when a change in clinical condition was observed. At study termination, gross pathologic examinations were conducted on all animals. Protocol-specified tissues were preserved in 10% formalin and archived.

No Synovex® S treatment-related deaths occurred during the study. One steer died of pneumonia on study day 6 and was replaced (study day 7). There were no clinical abnormalities in steers attributable to Synovex® S treatment. Changes associated with restraint-related injuries were present. Implant retention was satisfactory, but edema and/or abscessation of the implant site occurred in 1 or 2 animals in groups 1, 3, and 4.

There were no clinically significant effects of Synovex® S on hematologic or serum chemistry parameters during the study. No Synovex® S treatment-related effects were observed for body weight gain, dry matter feed intake, or feed efficiency. No gross pathologic changes attributable to Synovex® S treatment were present.

IV. HUMAN FOOD SAFETY

Reimplantation of Synovex® S (Estradiol Benzoate and Progesterone) at 70 Days After Initial Implantation in Steers.

The permitted increments of estradiol concentrations above those concentrations naturally present in untreated steers are: 120 ppt for muscle; 480 ppt for fat; 360 ppt for kidney; and 240 ppt for liver (**21 CFR 556.240**).

The permitted increments of progesterone concentrations above those concentrations naturally present in untreated steers are: 3 ppb for muscle; 12 ppb for fat; 9 ppb for kidney; and 6 ppb for liver (**21 CFR 556.540**).

Syntex Corporation has submitted the following studies in support of reimplantation of Synovex® S implants in steers:

Residue Study in Steers Implanted with a Single Implant:
After a single Synovex® S implant in 58 steers weighing approximately 700 lb, steers were slaughtered and tissues were analyzed for estradiol and progesterone levels after 15, 30, 61, 90, and 120 days. The data indicated that the concentrations of estradiol and progesterone in edible tissues of steers implanted with Synovex® S were well below the permitted levels at all time points (see Table 2 on following page).

TABLE 2. MEAN TISSUE RESIDUE CONCENTRATIONS OF ESTRADIOL17 Beta AND PROGESTERONE AFTER A SINGLE IMPLANTATION OF Synovex® S IN STEERS

Estradiol-17Beta (pg/g)

Treatment Duration (Days)	Fat	Muscle	Liver	Kidney
Control	1.8	0.8	0.9	1.6
15	41.4	9.7	5.4	13.7
30	28.6	8.3	6.7	9.5
61	38.6	7.3	4.5	6.4
90	27.3	4.5	5.4	5.7
120	13.4	2.2	1.4	4.2

Progesterone (ng/g)

Treatment Duration (Days)	Fat	Muscle	Liver	Kidney
Control	2.5	0.3	0.3	0.2
15	3.2	0.2	0.2	0.1
30	3.5	0.2	0.2	0.1
61	3.4	0.4	0.3	0.2
90	3.7	0.4	0.2	0.3
120	2.6	0.6	0.3	0.2

Based on these data, the maximum levels of estradiol and progesterone that would be expected in edible tissues of steers reimplanted with Synovex® S approximately 60 days after the initial implant were estimated. We used observed values at 61 days after a single implant as baseline. The tissue values at 61 days were added to the tissue values at 15 days after the first implant minus the control value. For estradiol, the calculated worst case values after reimplantation with Synovex® S were 78.2 ppt for fat, 16.2 ppt for muscle, 9.0 ppt for liver, and 18.5 ppt for kidney. The allowable concentrations above background are 480 ppt for fat, 120 ppt for muscle, 240 ppt for liver, and 360 ppt for kidney. The ratios of the worst case estradiol concentrations following reimplantation to the maximum concentrations after the initial implant were 1.9, 1.7, 1.3, and 1.4 for fat, muscle, liver, and kidney, respectively. These worst case estimates were supported by a study in which blood levels of estradiol were measured in cattle reimplanted with Synovex® S after 63 days. The worst cast estimates for progesterone levels after reimplantation were all well below the permissible concentrations.

Steer Plasma Hormone Concentrations After Reimplantation:

The plasma study was conducted on steers weighing approximately 450 lb. Nine steers were treated with a Synovex® S implant on study day-1 and day-63. Nine untreated steers served as controls. Blood was collected on days: 1, 2, 4, 7, 14, 21, 28, 42, 63, 64, 66, 69, 76, 83, 90, 104, 125, 140, 168, and 206. Plasma samples were analyzed for estradiol and progesterone.

Highest Mean (peak) Plasma Levels

The results showed that following the first implantation, the highest mean concentration of plasma estradiol was 57.8 pg/mL on day-63 just before reimplantation. The highest mean concentration of estradiol after reimplantation was 99.2 pg/mL on day-104 (approximately 40 days after reimplantation). The ratio of these values was 1.7. Following the first implantation, the highest mean concentration of progesterone was 1186 pg/ml on day-21 and after reimplantation, the highest mean concentration was 1910 pg/ml on day-206 (ratio = 1.6).

Overall Mean Plasma Levels

The overall mean plasma levels of estradiol and progesterone during the two time periods were calculated. For estradiol, the mean plasma level for days 1-63 was 38.2 pg/mL, and the mean plasma level for days 64-125 was 53.5 pg/mL. For progesterone, the mean plasma levels for corresponding days were 766 pg/mL and 995 pg/mL, respectively. Hence, the ratios of the mean plasma levels after the second implant to the first implant yielded 1.4 for estradiol and 1.3 for progesterone.

Area Under the Curve (AUC) Plasma Levels. The AUCs for estradiol and progesterone after the first and the second implant were calculated. For estradiol, the AUC for days 1-63 was 2258, and the AUC for days 64-128 was 3746. The ratio of these AUCs was 1.66. For progesterone, the AUC for days 1-63 was 53858, and the AUC for days 64-128 was 67340. The ratio of these AUCs was 1.25.

As explained above, for edible tissues, the ratios of the calculated worst case values after reimplantation to the maximum concentrations following a single implant were no greater than 2 for both estradiol and progesterone. The data for plasma hormone concentrations are therefore consistent with calculated values for edible tissues. Taken together, these data show that tissue hormone levels would not reach violative levels in steers following reimplantation of Synovex® S 63 days after the initial implant. Since we do not anticipate that the hormone levels resulting from reimplantation after 63 days and 70 days would be significantly different, we conclude that residues of estradiol and progesterone following reimplantation of Synovex® increases above endogenous levels and do not pose any human food safety concern.

V. AGENCY CONCLUSIONS

Adequate data were provided to demonstrate the safe and effective use of Synovex® S when reimplanted at approximately day 70 for additional improvement in rate of weight gain in steers fed in confinement for slaughter.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change providing for the reimplantation of Synovex® S in steers fed in confinement for slaughter. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for food producing animals qualifies for three years of marketing exclusivity beginning on the date of approval because the supplemental application contains reports of new clinical investigations (other than bioequivalence or residue studies) essential to the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the change in the labeling (providing for the reimplantation of Synovex® S at approximately day 70 in steers fed in confinement for slaughter) for which the supplemental application was approved.

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