Approval Date: April 5, 1990

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 110-315

B. Sponsor

Ivy Laboratories, Inc.
8857 Bond Street
Overland Park, KS 66214

C. Proprietary Name

CALF-oid

D. Established Name

progesterone plus estradiol benzoate

E. Dosage Form

implantation

F. Dispensing Status

OTC

G. Dosage Regimen

The implant consists of four individual pellets packaged in a plastic cartridge and each pellet contains 25 mg progesterone and 2.5 mg estradiol benzoate

H. Route of Administration

subcutaneous implantation in the ear

I. Indication

For increased rate of weight gain.

J. Effect of Supplement

This supplement provides for the use of CALF-oid in suckling beef calves (at least 45 days of age) up to 400 lbs. of bodyweight.

II. EFFECTIVENESS

A. Pivotal Studies

The supplemental new animal application for CALF-oid contains four adequate and well controlled studies demonstrating the effectiveness of the new animal drug for the indication for use as given in item I. above.

The pivotal studies are dose titration studies in which the parameters measured are the same parameters as are measured in clinical (field) studies. The four pivotal studies were conducted in Georgia, North Carolina, Texas and Colorado using a uniform protocol so that the results of the studies could be pooled and summarized.

Investigators:

John Stuedeman, PhD, Watkinsville, GA
Roger McCraw, PhD, Plymouth, NC
Bill Clymer, PhD, Amarillo, TX
John Vetterling, PhD, Fort Collins, CO

The purpose of the studies was to determine the dose response for CALF-oid implants on average daily gain (ADG) of suckling beef calves. The test animals were mostly crossbred animals of English breeds. The calves weighed approximately 250 pounds when the studies were initiated. A total of 446 calves (250 heifers and 196 steers) were used in these studies.

Calves in each study were randomly assigned to one of five treatment groups. One treatment group remained as non-implanted controls, while each of the other groups received one of the following subcutaneous ear implants: one, two, four or eight pellets where each pellet contained 25 mg progesterone and 2.5 mg estradiol benzoate. Calves were pastured with their dams for the following 112 days.

The ADG for each study is shown in Table 1. The studies were pooled by Analysis of Variance to determine the significance of the number of pellets on ADG. The least square means for ADG are presented in Table 2. There was a significant ($P << 0.03$) dose effect on ADG with the optimum effect at a dosage of four pellets (100 mg progesterone/10 mg estradiol benzoate). ADG of calves implanted with the four pellet dose showed an increase of 0.13 pounds (8.2% improvement; $P << .0013$) over the untreated controls for the 112 day period.

These data are sufficient to support the claim and dosage as outlined in Section I above.

No adverse reactions that affected animal safety were reported during the effectiveness studies described above. Since only ruminating beef calves were used in the studies, CALF-oid is not be used in veal calves.

Table 1. Summary of Dose Response (Average Daily Gain) in Calf Studies

Location	**0 pellets/ dose**	**1 pellet/ dose**	**2 pellets/ dose**	**4 pellets/ dose**	**8 pellets/ dose**
Georgia	1.50	1.56	1.59	1.67	1.73
N. Carolina	1.28	1.45	1.44	1.38	1.45
Texas	1.86	1.79	1.84	1.94	1.99
Wyoming	1.75	1.80	1.81	1.86	1.84

Table 2. Least Square Means (ADG)

	0 pellets/ dose	**1 pellet/ dose**	**2 pellets/ dose**	**4 pellets/ dose**	**8 pellets/ dose**
Mean	1.56	1.61	1.65	1.69	1.73
Std. Error	0.03	0.03	0.03	0.03	0.03

III. TARGET ANIMAL SAFETY

A. Pivotal Study

Investigator:

Bill Clymer, PhD
Clymer Research And Consulting
Amarillo, TX

Sixty (20 bulls, steers and heifers) crossbred suckling calves 50 to 78 days of age and weighing 135 to 312 lbs. were randomly assigned to treatment groups and implanted with either zero (T1), 0.5X (T2), 4X (T3), or 8X (T4) of the CALF-oid implant (100 mg progesterone/10 mg estradiol benzoate) on days 0, and 56 of the study. Fifteen calves (five bulls, steers and heifers) were used per treatment group. Calves were maintained on test for 112 days (day of weaning). All animals were observed daily for any clinical or behavioral abnormalities. On days 0, 28, 56, 84 and 112 the calves were individually weighed, received a physical examination, and blood was drawn for hematology and serum chemistries. At the end of the test period, three calves (one bull, heifer, and steer) from each treatment group were randomly selected and subjected to a complete gross pathological examination. The three calves receiving the T4 dose were subjected to a complete histopathological examination.

No adverse clinical or behavioral abnormalities were observed. There were no treatment related adverse conditions observed regarding hematology, clinical chemistry, gross pathology, histopathology except reduced testicular size in the bulls treated at all doses.

CALF-oid labels contain the Caution statement, "Bulling, rectal prolapse, ventral edema and elevated tail-heads have occasionally been reported in calves implanted with progesterone and estradiol benzoate implants." Also, the label restricts the use of CALF-oid in calves intended for reproduction or in calves less than 45 days of age. These data are sufficient to support the safety of the requested dose in suckling beef calves.

IV. HUMAN FOOD SAFETY

A. Safe Concentration of Residues

The increases in hormone levels permitted in muscle above the amount naturally present in untreated animals are 120 ppt for estradiol and 3 ppb for progesterone. The corresponding values for fat tissue based on relative consumption of fat versus muscle are 480 ppt for estradiol and 12 ppb for progesterone. The basis for these

conclusions was discussed in an earlier FOI Summary filed under this NADA for STEER-oid.

B. Residue in Calf Tissue

The human food safety data for this submission relies on data gathered under NADA 110-315 for STEER-oid and under NADA 135-906 for HEIFER-oid (49 FR 29777/8; July 24, 1984). Extensive residue data were submitted on Steer-oid (200 mg progesterone and 20 mg estradiol benzoate) and HEIFER-oid (200 mg progesterone and 20 mg estradiol benzoate) using well validated RIA's to measure hormone levels in tissues.

These data demonstrated that incremental levels of estradiol and progesterone found in edible tissues of steers weighing 500 to 700 lbs. that had been implanted with STEER-oid and heifers weighing more than 400 lbs. that had been implanted with HEIFER-oid were well within the intervals considered safe. Since the largest incremental increase found in the above mentioned studies was only 10.4% of the level permitted for progesterone in fat, similar results, well within the permitted values, would be expected for CALF-oid implants even when the reduced body weight of calves is considered. Based upon the residue data for STEER-oid and HEIFER-oid, CALF-oid is approvable in calves other than veal calves without additional residue data.

C. Analytical Methods for Residues

The Agency's reasons for not requiring regulatory methods for estradiol and progesterone were discussed in an earlier FOI Summary filed under this NADA (47 FR 51108/9; November 12, 1982).

V. AGENCY CONCLUSIONS

Under the Agency's supplemental approval policy (42 FR 64367), this is a Category II change. Adequate data were provided to demonstrate that CALF-oid is safe and effective in suckling beef calves for increased rate of weight gain. Sufficient human food safety data have been submitted under NADA 110-315 for STEER-Oid and under NADA 135-906 for HEIFER-oid to determine that CALF-oid is safe for use in suckling beef calves (at least 45 days of age) weighing up to 400 lbs. body weight.

The Agency concludes that, although regulatory analytical methods for monitoring the residues of animal drugs demonstrated to be carcinogens are ordinarily required under Section 512 (d) (1) (h) of the Act, for these unique steroid hormones, estradiol and progesterone, it is satisfactory to rely upon information provided by research analytical methods together with additional safety information discussed here. Specifically, the Agency concludes that a regulatory method is not needed for CALF-oid implants because the maximum increased exposure, even considering probable misuse of the drug, is demonstrated to be far below those concentrations considered unsafe. FDA has concluded that requiring a regulatory method for estradiol would be inappropriate because doing so would yield a result so unreasonable that it "could not be thoroughly attributed to Congressional design." *United States vs. Rutherford*, 442 U.S. 554, # 545 (1979).

The Agency also concludes that CALF-oid is safe for over-the-counter (OTC) distribution. Directions on labeling and packaging are adequate and ear implantation is a common method of administration of this type product within the cattle industry. Producers who

use this product can be expected to accomplish implantation safely and successfully. Further, there is no special need to recognize a disease condition, the drug is not a "controlled substance," and after implantation there is no need for medical monitoring or evaluation of the treated animal. Accordingly, prescription restriction of this product is not warranted.

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.