Approval Date: July 9, 1999

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 011-427

B. Sponsor

Syntex, Inc.
3401 Hillview Avenue
Palo Alto, California 94304

C. Proprietary Name

Synovex-H Heifer Finishing Implants

D. Established Name

Estradiol benzoate and testosterone propionate

E. Dosage Form

8 pellets containing 200 mg testosterone propionate and 20 mg estradiol benzoate

Implant complete contents of one cartridge

F. Indication

For improved growth promotion and feed efficiency in heifers weighing 400 lbs or more.

G. Effect of Supplement

Supplemental application to provide for the deletion of the 60-day withdrawal period statement in the labeling for Synovex-H.

II. EFFECTIVENESS

Not affected by this approval.

III. TARGET ANIMAL SAFETY

Not affected by this approval.

IV. HUMAN FOOD SAFETY

Safe levels of Estradiol and Testosterone
Information is available showing that the proposed use of Synovex-H controlled-release implant is safe. Synovex-H contains estradiol benzoate and testosterone propionate, which are rapidly converted in the target animal to the endogenous steroids estradiol 17B and testosterone, respectively. The criteria employed in evaluating these data are

different from the criteria used in evaluating the safety of non-endogenous substances when used in food-producing animals (see 44 FR 17070: March 20, 1979). The present information supports an alternative approach to demonstrating safety by focusing on the levels of these endogenous hormones in edible tissues of treated heifers as compared with the levels found normally in the edible tissues of untreated animals, and the production rate in men, women and children. Estradiol and testosterone are naturally occuring sex steroids synthesized by the gonads and adrenals of all mammalian species. The physiology, pharmacology, and toxicology of these hormones are well established. The accumulated evidence supports a role for estradiol in the development of certain types of cancer seen in humans and animals. FDA scientists have concluded, however, that in the absence of a persistent overstimulation of the hormonal system by residues remaining in the tissues of treated animals, individuals will not be subjected to an unacceptable increased risk of cancer from estradiol or testosterone. For additional background information see 46 FR 24694 (May 1, 1981) and IARC, Sex Hormones II, 1979.

Because these compounds are naturally occurring in people and in food-producing animals, the individual is exposed throughout his lifetime to rather large quantities of these compounds by his own daily synthesis and to much lesser quantities from unmedicated food-producing animals. Therefore, Agency has concluded that no harmful effects will occur in individuals chronically ingesting animal tissues that contain an incremental increase of endogenous steroid equal to 1% or less of the amount produced daily by the segment of the population with the lowest daily production. In the case of estradiol, prepubertal boys synthesize the least; in the case of testosterone, prepubertal girls synthesize the least. The calculated incremental increase permitted in beef muscle above the amount naturally present in untreated animals are 120 ppt for estradiol and 0.64 ppb for testosterone. Based upon relative consumption of other tissues versus muscle, safe incremental levels of 480 ppt and 2.6 ppb for estradiol and testosterone, respectively, are established for fat, 350 ppt and 1.9 ppb for kidney, and 240 ppt and 1.3 ppb for liver.

When the sponsor can demonstrate with a suitable assay that under the proposed conditions of use the concentration of residue of the endogenous sex steroid in treated food-producing animals is such that the actual increase in exposure of people will not exceed the permitted increase, then the compound is shown to be safe.

Residue Study
Tissue samples were obtained by the sponsor from liver, kidney, muscle, and fat of cycling heifers weighing approximately 750 lbs that had been implanted with 8 pellets of Synovex-H (a total of 200 mg testosterone propionate and
20 mg estradiol benzoate) 61 or 30 days prior to slaughter, and from untreated controls. These tissue samples were assayed for concentrations of estradiol-17B and testosterone by RIA methods that have been validated and determined to be acceptable for research purposes. The results of the study are presented below. The number of animals used in each group is in parentheses.

Mean Hormone Concentrations in Control Heifers and Heifers Implanted with

	Estradio1-17B (ppt)			**Testosterone(ppt)**		
	Control	**30 days**	**61 days**	**Control**	**30 days**	**61 days**
muscle	5.54 (n=15)	33.2 (n=20)	10.7 (n=10)	19.6 (n=15)	101.0 (n=20)	46.7 (n=10)
liver	1.54 (n=10)	23.1 (n=10)	3.2 (n=10)	12.9 (n=10)	34.1 (n=10)	15.7 (n=10)
kidney	2.89 (n=15)	23.5 (n=10)	9.8 (n=15)	189.0 (n=15)	450.O (n=10)	228.0 (n=15)
fat	13.4 (n=35)	86.7 (n=20)	49.3 (n=25)	25.9 (n=35)	339.0 (n=20)	142.0 (n=25)

The results of the study were adequate to demonstrate that incremental levels of estradiol and testosterone in edible tissues of heifers implanted with Synovex-H were well within the interval considered safe. Because these values were determined while the animals were still implanted with Synovex-H, the Agency has determined that no withdrawal period after implantation will be necessary to protect the public health.

V. AGENCY CONCLUSIONS

A review of the human food safety data submitted under NADA 11-427 showed that sufficient information has been provided to allow the conclusion that the previous 60-day slaughter withholding statement for Synovex-H may be deleted with no loss in food safety protection for the consulting public.

The Agency also concludes that, although regulatory analytical methods monitoring the residues of animal drugs demonstrated to be carcingoens are ordinarily required under section 512(d)(1)(H) of the Act, in the case of these unique endogenous hormones, estradiol and testosterone, it is satisfactory to rely upon information provided by research analytical methods together with additional safety infomarion discussed here. Specifically, the Agency concludes that a regulatory method is not needed for the assurance of safety of the approved use of Synovex-H implants Because the maximum increased exposure, even considering probably misuse of the drugs, is demonstrated to be far below those concentrations considered unsafe. FDA has concluded that requiring a

regulatory method for estradiol would inappropriate because doing so would yield a result so unreasonable -that it "could not be thoroughly attributed to congressional design." *United States v. Rutherford,* 442 U.S. 544, 545 (1979).

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and demonstrate that Synovex-H implant ,when used under its proposed conditions of use is safe and effective as an aid for improved growth promotion and feed efficiency.

VI. ATTACHMENTS

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

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.