ENVIRONMENTAL ASSESSMENT

NADA

REVALOR^{R}-S (trenbolone acetate and estradiol) Cattle Ear Implant

1. DATE: March, 1988

2. APPLICANT:

Sponsor	Agent
Roussel-Uclaf Division Agroveterinary 163 Avenue Gambetta 75020, Paris, France	Hoechst-Roussel Agri-Vet Co. Route 202/206 No. Somerville, New Jersey 08876

In the United States, Hoechst-Roussel Agri-Vet Co. will be the distributor of the product.

3. ADDRESS:

Hoechst-Roussel Agri-Vet Co.
Route 202/206 No.
Somerville, N.J. 08876

4. DESCRIPTION OF THE PROPOSED ACTION

A new animal drug application has been approved by the Food and Drug Administration for the use of a cattle ear implant, REVALOR^{R}-S, which contains the active ingredients, trenbolone acetate and estradiol. The ear implant improves average daily gain and efficiency of feed conversion in feedlot steers. This ear implant is for use in feedlot steers at a dosage of 140 mg. trenbolone acetate and 28 mg. estradiol per animal. The ear implant will be manufactured by Roussel-Uclaf, Compiegne, France and shipped to the United States for distribution by Hoechst-Roussel Agri-Vet Co., Somerville, N.J. The use of this product is limited to growing finishing feedlot steers that are being grown for slaughter. REVALOR^{R}-S will be used as a partial replacement for existing agents intended for the same purpose. Because it is industry practice to implant cattle when they arrive at the feedlot, the overall use of anabolic implants is not expected to increase with the approval of this product. REVALOR^{R}-S will compete with other anabolic products in the marketplace and its use will simply be in place of another product.

The cartridge containing the ear implants is designed to be used with a special implant gun. Each cartridge contains ten (10) ear implants. Each implant

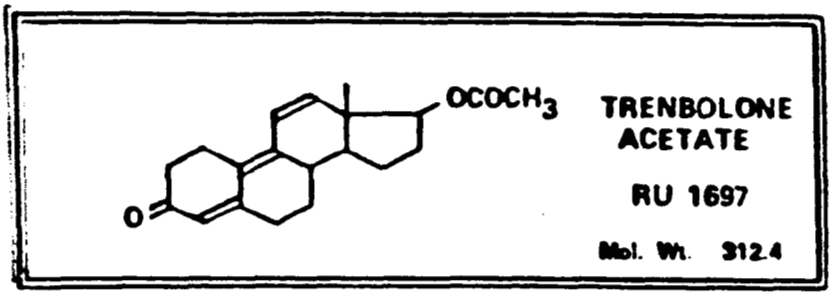
contains a number of pellets which make up the dose of REVALOR^{R}-S. Each pellet contains 20 mg. trenbolone acetate and 4 mg. estradiol. There are seven (7) pellets in each implant for steers.

5. IDENTIFICATION

A. Trenbolone Acetate

Chemical name: 17 b - (acetyloxy) estra-4,9, 11-trien-3-one

Chemical Abstract Service Registry Number: 10161-34-9.
The following is the structural formula:



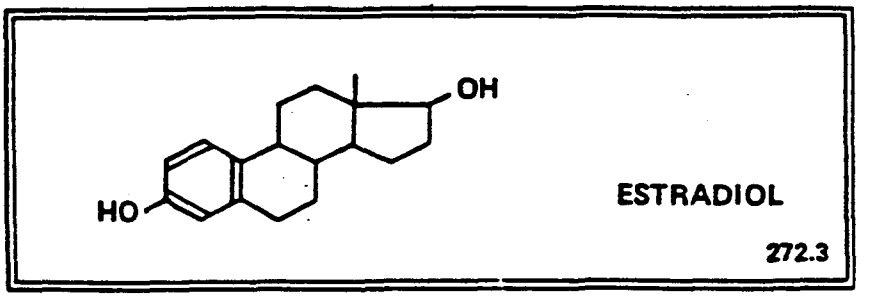
Molecular Formula	$C_{20}H_2O_3$
Molecular Weight	312.39
Code Designation	RU 1697
WHO Number	2916

The principal physical and chemical properties are as follows:

- Pale yellow, crystalline powder
- Melting point: 95 - 97° C
- a D: + 39° to + 43° C (C = 0.5% methanol)
- Dessication loss 1 g/100 g
- E 1% / 1 cm: 920-980 (at 337 mu in ethanol)
- Sulfuric ash 0.2 g/100g
- Vapor pressure: 25° C
  - ps (trenbolone Acetate) = 10^{-9}TORR
  - ps (TBOH - 17-alpha) = $7 \cdot 10^{-10}$TORR
  - ps (TBOH - 17-beta) = $8 \cdot 10^{-11}$TORR
- Water solubility:
  - Trenbolone acetate - 17-21 mg/1
  - 17-alpha Trenbolone - 40-42 mg/1
  - 17-beta Trenbolone - 340-380 mg/1

B. Estradiol

Molecular Formula: $C_{18}H_{24}O_2$
Molecular Weight: 272.37
Chemical Name: Estra-1, 3, 5(10) triene-3, 17b-diol
CAS: 50-28-2
Structural Formula:



6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

A. Substances expected to be emitted at the sites of production.

This approval allows the use of the active drugs (trenbolone acetate and estradiol) as produced in the Roussel-Uclaf facility, 63480 Vertolaye, France and the formulated product as produced at USIPHAR, a subsidiary of Roussel-Uclaf, Route de Choisy-au-Bac, 60205, Compiegne, France. The finished product will be imported, distributed, and sold "over the counter" in the United States. The packages as prepared in France are not intended to be opened until immediately before use at the farm or feedlot. The cartridges contain a pre-measured dose of the drug, avoiding any direct handling or spillage of the drug product. Unused dosages can be retained in the original cartridge until used.

a. Emissions to the atmosphere

The manufacturing of the REVALOR^R-S implants does not result in emissions of pollutants to the atmosphere. The ventilation systems for these manufacturing operations are designed to filter any dust from air exhausted to the atmosphere from all areas of production. In the manufacturing areas employees wear protective clothing, gloves, and dust masks to protect themselves from any contamination of trenbolone acetate or estradiol.

b. Waste Waters

There are essentially no waste water pollutants produced in the manufacturing process. The handling of any possible pollutants are certified by the manufacturer to be in full compliance with the

appropriate regulations of the country of manufacture (see Environmental Assessment from NADA 138-612; FINAPLIX (trenbolone acetate) - 52 FR 24994 - July 2, 1987).

c. Solid and liquid wastes

Solid wastes including packaging materials or implant debris are removed from the plant site and transported to a landfill for disposal by burial or to an incineration facility for burning, as appropriate. Solvent washes of the implants and manufacturing equipment are returned to a recovery facility for reuse or to an incineration facility for burning, as appropriate.

2. Applicable Federal, State and Local Emission Requirements

The sponsor for this new animal drug application certifies that any emissions resulting from the manufacture of trenbolone acetate and estradiol will be in full compliance with the appropriate regulations of the country of France (also see the Environmental Assessment for NADA 138-612- FINAPLIX - 52 FR 24994 - July 2, 1987).

3. Statement of Compliance with Said Requirements

Based on the statements in (1) and (2) above, disposal practices for any wastes resulting from the manufacture of REVALOR^{R}-S will comply with the applicable environmental regulations, including those pertaining to the workplace.

Approval of REVALOR^{R}-S implants for use in steers will have no conceivable effect upon compliance with current emissions or disposal requirements at the production sites.

B. Substances Introduced into the Environment at Sites of Use

1. Metabolism of trenbolone acetate and estradiol in the bovine

The metabolism of trenbolone acetate can be found in the environmental assessment for FINAPLIX (NADA 138-612 - 52 FR 24994 - July 2, 1987). Estradiol (E2b) is the natural estrogen produced by the graafian follicle in the ovaries of all mammals. In the bovine, the primary metabolite (84%) of estradiol is 17 alpha estradiol[1,2,3] which is non-estrogenic. 10% of the estradiol synthesized by the ovary is converted to estrone. 2% of the estradiol synthesized by the ovary is excreted into the urine as free or conjugated E2b. Essentially all of the E2b synthesized is rendered biologically inactive and excreted into the urine. Estradiol is inactivated chemically as 17 alpha estradiol or conjugated with glucuronide or sulfate by the liver prior to excretion.

2. Distribution and Excretion Patterns of Trenbolone Acetate and Estradiol.

The distribution and excretion patterns of trenbolone acetate can be found in the environmental assessment from NADA 138-612 - FINAPLIX (52 FR 24994 - July 2, 1987).

The rate of absorption from an injection site and subsequent rate of excretion of estradiol has been studied[4]. Estradiol was injected intramuscularly and monitored in the plasma and urine for approximately four days. Peak plasma levels were found within two hours after injection and declined rapidly to near detection levels at 30 hours. The urinary excretion pattern was similar to that found in plasma. No detectable levels of estradiol were found in urine 95 hours after injection.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The fate of trenbolone acetate in the environment has been summarized in the Environmental Assessment for FINAPLIX (NADA 138-612; 52 FR 24994 - July 2, 1987).

Since the amount of estradiol released from the implant daily to treated heifers is much lower than that produced by heifers during estrus, studies to determine the fate of excreted compounds are unwarranted. Also, the amount of estrogens excreted by heifers is small compared to the amount excreted by pregnant cows. The relatively large amounts produced by the human body and other mammals also argue against the need for evaluations of the fate of excreted estrogenic substances in the environment.

Currently implanted animals receive estradiol benzoate implants (21 CFR 522.840), zeronal implants (21 CFR 522.2680) and estradiol implants (21 CFR 522.840). REVALOR ^{R}-S implants will compete with such products in the marketplace and it's use generally would be substituted for their use. The overall use of anabolic implants as a result of this proposed action is not expected to increase appreciably.

Since all anabolic estrogens exert a similar physiological effect, it is reasonable to assume that the substitution of the estradiol in REVALOR^{R}-S implants for other estradiol benzoate, estradiol or zeronal containing implants should not appreciably alter the concentration and distribution of such products into the environment.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

The environmental effects of trenbolone acetate are fully documented in the Environmental Assessment for NADA 138-612 -FINAPLIX; 52 FR 24994 - July 2, 1987.

Estradiol and its metabolites are found in the normal physiological environment of both males and females as well as in the human food supply. The physiology, pharmacology, and toxicology of estradiol are well established. Estradiol is synthesized by the gonads and/or adrenals of all mammalian species including the human. There is accumulated evidence that supports a role for estradiol in the development of certain types of cancer, including human cancer. When estradiol is administered to animals in very large doses, estradiol has the potential to cause toxic, including carcinogenic, effects in the exposed animals. The evidence however, also indicates that estradiol is not a direct acting carcinogen but is a permissive carcinogen requiring administration of physiological dose levels over long periods of time in the presence of a true carcinogen before it "permits" tumors. For more additional background information see 46 FR 24694 - May 1, 1981 and 44 FR 1463-Jan. 5, 1979.

Of critical importance in the determination of the safety of estradiol is the fact that estradiol is a naturally occurring and essential hormonal substance. Also, most of this estrogen is cleared from the body and excreted in the urine. Little is known about the effects of excreted estradiol and its metabolites. Since it is endogenous to all mammals there appears to be little reason for concern or to conduct studies to evaluate such effects. The amount of these compounds expected to be excreted as a result of the proposed action is very small compared to the amount of estradiol normally produced in the human body, excreted by normal cattle and compared to the amounts of estradiol present in food.

9. USE OF RESOURCES AND ENERGY

There will be no significant depletion of natural resources or energy associated with the approval of this new animal drug application. Energy requirements for manufacturing REVALOR^{R}-S implants are similar to those which would be used in any conventional human or animal pharmaceutical operation.

The indirect effect of approval of this NADA will be a saving of energy by the improved average daily gain and improved feed efficiency of feedlot steers resulting in the more efficient use of feed resources and a shorter period of time in the feedlot.

10. MITIGATION MEASURES

The proposed action would not be expected to have an adverse effect on human health or the environment. Therefore, no mitigation measures are necessary.

11. ALTERNATIVES TO THE PROPOSED ACTION

The proposed action is not expected to have an adverse effect on human health or the environment. Without the availability of growth promoting products, the

adverse effects on the cattle industry would be increased cost of production and increased depletion of feed supplies through less efficient production.

12. LIST OF PREPARERS

The following employees of Hoechst-Roussel Agri-Vet Co. were responsible for the preparation of this document:

Dr. R. J. Grant, Manager Nutritional Research
Mr. J. W. McCLain, Manager, Regulatory Affairs

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate and complete to the best knowledge of Hoechst-Roussel Agri-Vet Co.

Date: 4/11/88

Robert Grant

Dr. Robert J. Grant, Manager, Nutritional Research

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1. Erichsen, S. and W. Velle. Studies on oestrogens in cattle. Acta Endocrinologica 34:27-32, 1960.

2. Mellin, T. N. and R. E. Erb. Estrogen metabolism and excretion during the bovine estrous cycle. Steroids 7 (6): 589-606, 1966.

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4. Bellows, R. A. Reproductive performance in beef cattle and sheep. W-112 Progress Report, 1971-72, U.S. Range Livestock Experiment Station, Miles City, Montana, July 26, 1972.