FENPROSTALENE 0.25 MG/ML INJECTABLE SOLUTION

ENVIRONMENTAL ASSESSMENT

1. Date:

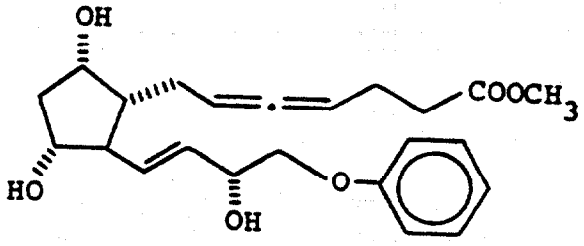
2. Name of Applicant: Syntex Animal Health, Inc.

3. Address: 4800 Westown Parkway
West Des Moines, Iowa 50265

INTRODUCTION

The following is an Environmental Assessment, pursuant to proposed 21 CFR 25.31 a(b)(4), covering the manufacture and veterinary use of an injectable prostaglandin in swine to induce parturition. Fenprostalene, the active ingredient in the new animal drug, is manufactured by Syntex, S.A., Chemical Division, Cuernavaca, Mexico. Pharmaceutical manufacture of the new animal drug will be carried out by Diamond Scientific Co., Des Moines, Iowa.

Fenprostalene, a synthetic prostaglandin and the active ingredient of the drug, is also known as methyl (±)-7-((1R*,2R*,3R*,5S*)-3,5-dihydroxy-2-((E)-(3R*)-3-hydroxy-4-phenoxy-1-butenyl)-cyclopentyl)-4,5-heptadienoate and has a molecular weight of 402.48, with a molecular formula of $C_{23}H_{30}O_6$, a CAS No. 69381-94-8, and the chemical structure shown below:



4. Description of the Proposed Actions:

Syntex Animal Health, Inc., is currently marketing the new animal drug product, fenprostalene, a safe and efficacious feedlot abortifacient and estrus synchronizing agent in beef cattle and non-lactating dairy cattle. Currently, Syntex Animal Health, Inc., proposes to address the use of fenprostalene as a safe and efficacious animal drug product for the induction of parturition in swine.

The drug product will be administered by the subcutaneous injection of a sterile solution of fenprostalene into the swine to be treated.

One dose of fenprostalene causes induction of parturition by approximately 27 hours after treatment. Readministration of the drug is not recommended and not likely to be done.

5. Introduction of Substances into the Environment

a. Identities of the Substances

The identities of the substances expected to enter the environment as a result of this action are as follows:

I. Diamond Scientific Co. - Des Moines Facility

Fenprostalene	
Polyethylene glycol 400	USP/NF
dl-α-tocopherol	USP/NF

II. Cuernavaca Facility

The effluents that are expected to be produced in the manufacture of 1 kg of fenprostalene are listed below.

Acetic acid	1 gal.
Acetone	60 gal.
Ammonium chloride	45 lbs.
Carbon tetrachloride	10 gal.
Celite	14 lbs.
Dichloromethane	600 gal.
Dimethyl acetonide	2 gal.
Dimethylformamide	70 gal.
Dimethylsulfoxide	12 gal.
Ethanol	12 gal.
Ethyl acetate	200 gal.
Ethyl ether	100 gal.
Hexane	200 gal.
Lithium salts	22 lbs.
Methanol	90 gal.
Methoxyethanol	5 gal.
Phosphates	45 lbs.
Polymeric chromium salts	10 lbs.
Potassium chloride	6 lbs.
Potassium cyanide	3 lbs.
Pyran	1 gal.

Pyridine	12 gal.
Silica gel	635 kg.
Sodium acetate	150 lbs.
Sodium bicarbonate	6 lbs.
Sodium bromide	4 lbs.
Sodium chloride	120 lbs.
Sodium hydrogen sulfate	10 lbs.
Sodium potassium tartarate	4 lbs.
Sodium sulfate	210 lbs.
Sodium thiosulfate	2 lbs.
Tetrahydrofuran	70 gal.
Triethylamine hydrochloride	2 lbs.

b. Quantities Discharged at Production Facilities and Manufacturing Controls Employed

I. Diamond Scientific Co. - Manufacture of New Animal Drug

Due to the great cost associated with the manufacture of fenprostalene, the production staff takes extreme care to recover all of the active ingredient that goes into the formulation. Furthermore the amounts of the substances that can be expected to enter the environment as a result of equipment and facilities cleaning are insignificant, and will be disposed of in accordance with local environmental regulations (section 5f).

During the processing and handling of fenprostalene, workers are equipped with appropriate clothing and protective devices which may include the use of rubber gloves, safety goggles, boots, head covers and an appropriate full dress gown. The workforce is furthermore limited in that it excludes pregnant women, those people with a history of upper respiratory tract infections, and asthmatics from working with this substance. Written guidelines describing the applicable safety precautions for the handling of fenprostalene are made available to the personnel which are involved in the process.

II. Cuernavaca Facility - Chemical Manufacturing

The quantities of the effluents produced in the manufacturing process are listed in section 5a II above. These materials are either recycled into the process or disposed of in such a manner as to

minimize any environmental impact. A detailed discussion of the disposal techniques and the controls exercised over these materials follows below.

i. Bulk Solvents

Bulk solvents are recovered whenever possible by a process of filtration, to remove suspended impurities, followed by fractional distillation in the necessary columns. The solvents are then analyzed according to the appropriate specifications and if they comply, are reused in the process. Those inflammable solvents which do not meet specifications are disposed of by incineration in an apparatus especially built for this purpose (i.e., the incineration of liquids). Chlorinated solvents are likewise disposed of by mixing them in small proportions with other inflammable solvents which are then burned. If a large quantity of chlorinated solvents exists, it is kept in drums until it can be mixed and burned.

Those solvents mixed with water are distilled from the solution until the solvent fulfills the specifications of Quality Control. Small quantities remaining in the water are sent via the chemical drain and eliminated in the water treatment plant.

ii. Solid Waste

Solid organic wastes and solid inorganic wastes such as filter aid and chromatography packing materials, when contaminated with organic residues, are incinerated. The ashes are then analyzed for any organic residue and if any is found they are reburned. The ashes once having been analyzed and having demonstrated that there is no residual organic material present, are sent to the municipal solid waste disposal area.

iii. Potentially Toxic Materials

Cyanide compounds are decomposed depending on the nature of the effluents in one of the following ways:

a) The compounds are treated with sodium hydroxide and chlorine gas.

b) The compounds are treated with ammonium bicarbonate, ammonium hydroxide and acetone.

The residues from these processes are disposed of as are other organic residues by incineration.

iv. Materials Contaminated with Biologically Active Materials

Contaminated solvents and organic residues are burned in the incinerator. Other contaminated solvents are likewise incinerated and the ashes analyzed for any organic residues before disposal.

Aqueous wastes which have come into contact with biologically active materials are extracted with toluene until an analysis conducted by the Quality Control Department shows 0% of the active material present. The toluene extract is then burned in the incinerator for liquids.

All degradation products including mother liquors from recrystallizations are burned, following dissolution in an inflammable solvent, in the incinerator for liquids.

v. Aqueous Streams

Aqueous discharges are sent via the chemical drain to a water treatment plant which operates specifically for the industrial plants in the Cuernavaca Industrial Park (CIVAC). The water treatment plant requires that the pH of these waters be between 5 and 9 and that they are free of heavy metals, cyanide, or other toxic materials.

The water streams are neutralized in special tanks and equipment such as potentiometers, chromatographs, and other general Quality Control equipment are available to monitor the aqueous streams before discharge.

vi. Residues

To prevent contamination of the soil, there is a solid incinerator and a liquid burner which can also burn greases and oils soluble in flammable solvents. The Secretary of Health and the Sub-secretary of Environmental Improvement are currently investigating the possibility of assigning special sites to the Cuernavaca industrial area, in which solid products which cannot be sent to the main disposal dump will be discharged.

vii. General Operating Controls

Cuernavaca is a fully equipped chemical manufacturing facility which minimizes the release of effluents into the environment by standard good manufacturing practices. As an example, all small scale reactions that release noxious gases are effected in vessels with extractors. These gaseous emissions on a larger scale are passed through suitable absorbants to eliminate them from the effluent.

The synthesis and storage of fenprostalene are carried out in a building specifically constructed and dedicated to that purpose. All the workers have individual protection equipment that consists of: helmets, goggles, gloves, respirators, shoes, uniforms, interior clothes and apron. They have at their disposal a complete air mask with an autonomous suit. After their work, they are able to bathe and submit all their clothing for washing. Furthermore during the production of those steps which involve biologically active materials, those employees who handle equipment will be required to use surgical gloves while they are in any part of the manufacturing area. The supervisors involved in this process will receive special training in the handling of these materials which will further minimize the chance of any exposure of the staff to hazardous materials.

c. Quantities Discharged at Place of Use

Based on current projections, the quantities of Fenprostalene expected to be used in the manufacture of Fenprostalene Injectable Solution (0.25 mg/ml) during each of the first three years of its production are:

Year 1	Year 2	Year 3
26g	30g	33g

The identification of the other substances in the product are indicated in aI, above, and the quantitative composition of the materials in the formulation may be found in section 2i of NADA 138-903.

Data from Iowa State University and the National Pork Producers Council indicate that there are about 6.9 to 8 million sows in the United States. The national average is 1.8 farrowings per sow per year. There are approximately 20% of the producers that keep the records necessary to use prostaglandins in induced farrowings. Therefore:

7,000,000 sows x 1.8 = 12,600,000 farrowings per year
12,600,000 x 20% = 2,520,000 farrowings with suitable records
2,520,000 / 365 = 6,904 farrowings any given day of the year

This approximates 7000 daily farrowings which would be distributed in large part within the six major states that produce 80% of the pigs in the U.S. Approximately 70% of the operations confine sows prior to farrowing. The remaining 30% allow the animals to farrow under pasture conditions and are unlikely to be treated with fenprostalene because of a lack of the necessary records and the ability to handle the animals in pasture.

Most of the major swine operations have adopted totally confined or semi-confined (housing only from birth to weaning for the sow) managing systems that provide for farrowing about four times yearly in order to more efficiently utilize their farrowing facilities. Therefore, the number of sows treated at any given facility would probably rarely exceed 25% of the numbers within that herd. Dosing of an entire herd or even the majority of the herd at one time would be highly unlikely particularly in the large establishments because of labor and facility limitations.

Treatment of pregnant sows and gilts with fenprostalene solution is accomplished through the administration of a single 0.25 mg dose by subcutaneous injection. Radioisotopic metabolism studies in swine (see section 7 of NADA 138-903) have demonstrated that 70% and 20% of the radiolabel is recovered in the urine and feces, respectively, over a 3 day period of time, for a total recovery of 90%. Of the recovered label, 32% consisted of fenprostalene and its free acid. For the normal 0.25 mg dose, an animal would excrete 0.056 mg (0.25 X .70 X .32) of drug equivalents (primarily the de-esterified fenprostalene free acid) in the urine and 0.016 mg (0.25 X .20 X .32) of drug equivalents in the feces over a 3 day period. The average daily output of urine from a pregnant female weighing 200 Kg would be approximately 25ml/Kg for a total of 5 liters and the average daily fecal output would be approximately 25g/Kg for a total of 5 Kg. These drug metabolites would be distributed over areas that might be fertilized with manure from medicated animals.

Calculations which estimate the concentration of fenprostalene and its metabolites in the soil and water of affected areas follow:

i) <u>Estimation of the Concentration of Fenprostalene in the Feces and Urine of Treated Animals</u>

a. Concentration in excreta for first 3 days:

These calculations are based on the assumption that an adult pregnant sow produces 5 liters of urine and 5 kg of feces per day. Thus 0.056 mg drug equivalents would be shed in 15 liters of urine and an additional 0.016 mg shed in 15 kg of feces.

Urine:

$$\frac{0.056 \text{ drug equivalents}}{15 \text{ liters urine}} = 3.73 \text{ ppb}$$

(Note: specific gravity of urine was taken to be approximately equal to 1)

Feces:

$$\frac{0.016 \text{ mg drug equivalents excreted}}{15 \text{ kg feces}} = 1.06 \text{ ppb.}$$

However, since most (70%) excreta from sows is flushed into a lagoon in swine operations, the amounts contained in urine and feces will be combined and thus calculations would be:

$$\frac{0.056 + 0.016}{30 \text{ kg}} = 2.40 \text{ ppb.}$$

b. A dilution factor is introduced to account for the effect of mixing the medicated excreta with the waste that will be collected in the farrowing house during the animals stay. With 1.8 farrowings/year/sow the unmedicated period amounts to 359 days [365 - (1.8 x 3)]:

$$\frac{\text{6 days of medicated excreta}}{\text{365 days total stay}} = .016 \text{ dilution factor}$$

Therefore the total drug equivalents in the waste per year would be:
2.40 ppb X 1.8 (farrowings/year) X 0.016 = 0.069 ppb or 69 ppt.

ii) Concentration in water run-off from sow's range. Assume the following circumstances:

1. Only 30% of the sows farrow under these circumstances.

2. Each animal will excrete 0.072 mg of drug equivalents from a 0.25 mg dose in the urine and feces.

3. A one acre area could contain as many as 100 sows.

4. Between 2 to 4 inches rainfall, with 2 inches being sufficient to wash away all the drug metabolites.

5. Two inches of rain will weigh 205,500 kg/acre.

6. It is unlikely that fenprostalene will be used in pasture sows due to lack of records and facilities for treatment. However, for the purpose of this report we will assume treatment.

Therefore:

a. Number of doses administered - 100 of 0.25 mg each.

b. Amount dispersed per acre: 0.072 mg drug equivalent per animal x 100 doses = 7.2 mg drug equivalents/acre.

c. Concentration in run-off.

$$\frac{\text{7.2 mg drug/acre}}{\text{205,500 kg water/acre}} = 0.000035 \text{ mg drug/kg water}$$

= 35 ppt of drug metabolites in the run-off from a 1 acre pasture.

This number represents the maximum possible concentration of drug for the circumstances stated. The actual concentration in the runoff would be expected to be much less as the drug equivalents in the feces would be removed for fertilization and not washed into the water system.

iii) Concentration of fenprostalene in soil due to fertilization with medicated materials.

Assume the following circumstances:

1. Drug equivalents from both urine and feces will find their way into excreta to be spread.

2. Addition of urine will not change the weight of manure (i.e., we assume the total amount of drug metabolites (0.072 mg) will be incorporated into the 15 kg of feces with the mass of urine being water and so evaporated).

3. Incorporation rate of manure into soil is 4.5 metric tons per acre.

4. The excreta will be incorporated into the top 6" of the soil of 1 acre of land weighing 909,000 kg.

Therefore:

a.) Concentration of drug equivalents in excreta 0.072 mg drug equivalents/15 kg feces = 0.0048 mg drug equivalents/kg excreta to be spread.

b.) In one metric ton:
(0.0048 mg) x 1000 = 4.80 mg of drug equivalents.

c.) In one acre of spreading therefore there is 4.80 mg x 4.5 metric tons/acre = 21.6 mg/acre.

d.) This indicates a concentration of 21.6 mg/acre = 21.6 mg/909,000 kg = 24 ppt.

This number would indicate the soil concentration if only medicated excreta were to be spread.

e.) We have shown how the medicated excreta is diluted by untreated swine and drug equivalent free waste. We now introduce these dilution factors to give a more accurate estimate of soil contamination.

24 ppt x .016 = 0.384 ppt.

This estimates the maximum concentration of drug metabolites in the soil treated with medicated excreta collected at the end of one year.

As indicated by the above calculations, the amount of fenprostalene metabolites that will be released into the soil and water as a result of the treatment of confined or pastured animals and the subsequent disposal of the waste as described is extremely small. In addition, these calculations assumed no decomposition of the drug and its metabolites upon being excreted. Both fenprostalene and its free acid (the two major metabolites) undergo rapid oxidation and decomposition when exposed to the conditions described, thus further reducing the actual concentration of fenprostalene metabolites in the environment.

The calculations should also be viewed in terms of the total number of animals in the market that the drug is expected to reach. Marketing forecasts indicate that fenprostalene solution will be used in 104,000 to 132,000 farrowings over the next three years. The represents 4 to 5% of the farrowing animals that have records suitable for treatment with the drug. This represents a very small proportion of the entire market.

The extremely small concentrations of drug metabolites in the environment, the wide geographic areas over which they will be spread, the relatively small proportion of swine that will receive the drug product, and the decomposition of metabolites upon exposure to the conditions of the environment all argue for the position that the use of fenprostalene solution will have a negligible effect upon the environment.

d. Physical and Chemical Characteristics of Effluents:

I. Diamond Scientific Facility

The physical and chemical characteristics of all the substances above, except fenprostalene, may be found in the United States Pharmacopeia. The physical and chemical characteristics of fenprostalene may be found in Section 5 of NADA 128-549.

II. Cuernavaca Facility

The physical and chemical characteristics of all the substances listed in section 5aII. can be found in Master File Number 3546 and in Section 5 of NADA 128-549.

e. Duration of Emissions:

Emissions related to manufacture will occur only during actual production runs and during equipment cleaning. The duration of such emissions cannot be precisely ascertained at this time, but will be in compliance with any applicable environmental regulations (see f. below).

f. Citation of Environmental Regulations and Certification of Compliance Thereto:

Diamond Scientific, Syntex Animal Health, Inc. and Syntex S.A. Chemical Division, Cuernavaca hereby certify that the manufacture of Fenprostalene Injectable Solution and the fenprostalene drug substance will comply with all applicable federal, state, and local regulations, as follows:

I. Diamond Scientific Facility

i. Air effluent: No vapors or fumes are generated by the manufacturing process. An Air Pollution Control Permit has been issued to Diamond Scientific, by the City of Des Moines. Reference: Air Pollution Control, Chapter 38, City of Des Moines, Department of Public Health.

ii. Water effluent: No effluent is generated in the manufacturing process with the exception of that resulting from equipment cleaning, which is considered negligible. All

pertinent approvals for Diamond Scientific facilities have been received from the Des Moines Municipal Sewage Treatment Facility. Reference: Chapter 16, Water Quality Commission, Department of Environmental Quality, State of Iowa.

iii. Solids effluent: The great cost of fenprostalene necessitates that all possible material be recovered and incorporated into the formulation. In light of the careful controls employed in the manufacture of Fenprostalene Injectable Solution, only an insignificant amount of material from the process can be expected to be released into the environment. The only other possible solid waste would come from defective packaging material which would be disposed of through normal solid waste collection procedures. The disposal of solids complies with all local waste disposal regulations. Reference: Chapter 25, Solid Waste Commission, Department of Environmental Quality, State of Iowa.

iv. Containers and distribution: No release of the product or its ingredients into the environment should occur because of faulty containers or improper distribution, as both of these are controlled under current GMP's.

II. Cuernavaca Facility

i. Air effluents: Vapors and fumes which are emitted as a result of manufacturing processes are regulated by the Agency For The Prevention and Control of Atmospheric Contamination, Originated by the Emission of Fumes and Dust. The Cuernavaca manufacturing facility complies with those regulations set forth by this regulatory agency.

ii. Water effluents: The release of effluents into the water stream is controlled by the Agency For The Prevention and Control of the Contamination of Water. It is obligatory that all industries comply with the rules set forth by this regulatory agency. Furthermore the water must meet those specifications of the Cuernavaca Industrial Park which specifies a pH between 5 and 9 and an absence of toxic materials and heavy metals.

iii. Containers and shipping: These items are carefully controlled under current Good Manufacturing Practices and there should be no material released into the environment as a result of improper shipping or faulty packaging.

Though Syntex does not exercise direct control over the use of product in the feedlot or range, our calculations and discussions of section 5c argue for the use of Fenprostalene Injectable Solution having negligible environmental consequences.

6. Fate of Emitted Substances in the Environment:

a. Fate of Substances Released as a Result of Production:

The environmental fate of substances emitted as a result of the manufacturing process is subject to the federal, state, and local controls noted above, with which Diamond Scientific and Syntex S.A., Chemical Division certify compliance.

b. Fate of Substances Released as a Result of Use and Disposal:

Syntex Animal Health, Inc. has no direct control over the use and disposal of the product once it has been distributed. The following considerations, however, lead us to conclude that a detailed analysis of environmental fate is not necessary:

i. Local environmental buildup is precluded by a geographically widely dispersed pattern of use, such as the material used for fertilization.

ii. The amounts of materials involved are minute, and are readily broken down in the environment so that no appreciable local buildup can be expected.

7. Effects on the Environment of Released Substances:

No adverse environmental effects are expected as a result of this action for the following reasons:

a. Compliance with all applicable environmental regulations regarding manufacturing, as noted in Section 5 and 6 above.

b. The probable lack of local buildup as noted in Section 6 above.

8. Utilization of Natural Resources and Energy:

The raw materials used in the formulation of the final dosage form are readily available. The production of Fenprostalene Injectable Solution and the energy use involved therein do not cause depletion of any natural resources which are in critically short supply, although the materials are irretrievable once used.

9. Disruptions of the Physical Environment:

No disruption of the physical environment is anticipated other than the usual effects of operating the pharmaceutical and chemical manufacturing facilities which are already in place.

10. Mitigation Measures:

Diamond Scientific and Syntex S.A., Chemical Division, Cuernavaca take all the necessary measures to remain in compliance with the statutes noted in Paragraph 5 above.

11. Alternatives to Proposed Action:

No potential adverse environmental effects have been identified as a result of the proposed action. Therefore alternatives have not been considered.

12. List of Preparers:

Dr. Marvin O. Maul
Syntex Corporation Regulatory Affairs

Dr. R.C. Herschler
Institute of Agriscience
Syntex Research

13. Certification:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of Diamond Scientific, Syntex Animal Health, Inc., Syntex S.A., Chemical Division, Cuernavaca, and Syntex Corporation.

May 25, 1988
(Date)

Anthony Bruckner
(Signature of Responsible Official)
Vice President, Regulatory Affairs

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