ENVIRONMENTAL ASSESSMENT

Banamine Solution 50 mg/mL for Cattle

1. DATE: June 5, 1996

2. NAME OF APPLICANT: Schering-Plough Animal Health Corporation

3. ADDRESS: P.O. Box 529
Kenilworth, New Jersey 07033
Contact: Mrs. Joyce Yates
Telephone: (908) 629-3387

4. DESCRIPTION OF THE PROPOSED ACTION:

a. Request for Approval

Schering-Plough Animal Health Corporation is submitting an abbreviated Environmental Assessment (EA) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 25.31a(b)(4) for Banamine Solution 50 mg/mL for Cattle (NADA No. 101-479). The drug product will be packaged in 250 mL multi-dose glass vials for use as an injectable solution.

b. Need for Action

The product is currently approved by the Food and Drug Administration for use as an anti-inflammatory/analgesic agent in horses. The applicant is petitioning the Food and Drug Administration for approval of an additional claim for the currently approved formulation to allow the product, Banamine Solution 50 mg/mL, to be used in cattle as adjunctive therapy in the treatment of bovine respiratory disease.

c. Production Locations

The Flunixin-B intermediate for this process, 2-methyl-3-trifluoromethylaniline (MABTF), will be manufactured by Foreign Contract Manufacturer # 1, under Type II VMF# 5223. For this foreign manufacturing site, the appropriate environmental compliance certification is included in **Confidential Appendix 2.**

The drug substance, flunixin meglumine, will be manufactured by Schering-Plough (Avondale) Co. located in Rathdrum, Co. Wicklow, Ireland. For this foreign manufacturing site, the appropriate environmental compliance certification is included in **Confidential Appendix 2**.

Additionally, the drug substance will be provided by the applicant's facility in Union, New Jersey. The facility is operated in accordance with the environmental rules and regulations of the State of New Jersey and the United States. The Union, New Jersey facility is located at 1011 Morris Avenue, Union, New Jersey 07083, in an industrial/commercial zone which is bordered by the Elizabeth River on one side of the site. The terrain in the area is flat and the climate is temperate.

The final product, Banamine Solution 50 mg/mL for Cattle, will be manufactured (processed, packaged, and labeled) by the applicant's facility in Manati, Puerto Rico. This manufacturing site, Schering-Plough Products, Inc., is located on Carretera Estatal 686 in Manati, Puerto Rico 00674. The Schering-Plough Products, Inc. facility is located in the northern coastal region of Puerto Rico, approximately two miles from the Atlantic Ocean. The climate in the region of the facility is tropical. The facility is operated in accordance with the environmental rules and regulations of Puerto Rico and the United States.

d. Location of Use

Through the approval of this action, Banamine Solution 50 mg/mL will be made available for use on cattle. It is expected to be used on cattle throughout the United States.

e. Disposal Sites

Returned or rejected drug product will be collected at the applicant's warehouse facility in Omaha, Nebraska. At this facility, returned goods are handled as solid waste and sent to a licensed disposal facility for incineration. The facility is Environmental Health Systems, 6100 North 60th Street, Lincoln, NE 68507. It is permitted by the Lincoln-Lancaster Health Department under operating permit number 69, which has an indefinite expiration. The facility does not have an EPA identification number.

Any drug product not used by consumers will be disposed of at their farms or veterinary clinics in the U.S. according to procedures set at those facilities. Typically these procedures result in the disposal of waste via a community's solid waste management system which may include landfills, incineration, and recycling, although users may dispose minimal quantities of unused drug in the sewer system.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

Flunixin meglumine

a. Nomenclature

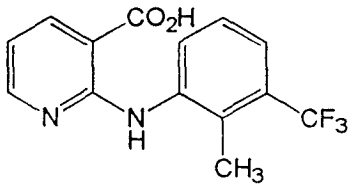
i.	Established Name:	Flunixin meglumine
ii.	Brand/Proprietary Name:	Banamine Solution
iii.	Chemical Name:	2-(2'-methyl-3'-trifluoromethyl-anilino)nicotinic acid, n-methyl

b. CAS Registration #: 6284-40-8

c. Molecular formula: $C_{14}H_{11}F_3N_2O_2 \cdot C_7H_{17}NO_5$

d. Molecular weight: 491.50

e. Structural formula:



• $CH_3NHCH_2(CHOH)_4CH_2OH$

f. Physical Description: Is an odorless fine white powder. It has a melting point of 138°C and is stable under normal conditions.

g. Additives:

In addition to the drug substance, the final dosage consists of the following ingredients:

Substance	CAS #
2,2 Iminodiethanol	111-42-2

Phenol	108-95-2
Disodium edetate	139-33-3
Sodium Formaldehydesulfoxilate	149-44-0
Propylene glycol	57-55-6
Hydrochloric acid	7647-01-0
Water	7732-18-5

h. Impurities:

There are no individual impurities at levels greater than 1% of the active drug substance in the product. The inactive ingredients (additives) are all USP/NF grade.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

SITE OF MANUFACTURE OF INTERMEDIATE DRUG SUBSTANCE

The Flunixin-B intermediate, 2-methyl-3-trifluoromethylaniline (MABTF), will be manufactured by Foreign Contract manufacturer #1. The environmental compliance certificate for this facility is included in **Confidential Appendix 2.**

SITE OF MANUFACTURE OF THE DRUG SUBSTANCE

The drug substance, flunixin meglumine, will be manufactured by Schering-Plough (Avondale) Co. located in Rathdrum, Co. Wicklow, Ireland. For this foreign manufacturing site, the appropriate environmental compliance certification is included in **Confidential Appendix 2**.

Additionally, the drug substance will be provided by the applicant's facility in Union, New Jersey and is addressed below:

a. Substances Expected to be Emitted

This information is provided in **Confidential Appendix 3**.

b. Controls Exercised

i. Air

Negligible amounts of air emissions will be generated during the production of the drug substance, flunixin meglumine. Vapors from the solvents used in the process are recondensed. Any air emissions from drying will be controlled by

dust collectors. All dust collectors connected to a process have a permitted minimum control efficiency of 99% for particulate matter. Any air emissions from the facility will comply with and conform to the permit conditions and all other applicable emission requirements.

ii. Wastewater

Liquid waste will be generated in the manufacture of the drug substance and subsequent cleaning-out of the process equipment. Any liquid waste is pretreated by neutralization prior to discharge to the Joint Meeting of Essex and Union Counties (JMEUC) Treatment Plant. Union's discharge to the JMEUC treatment plant will be in accordance with the JMEUC rules and regulations and the conditions set forth in the facility discharge permit.

The Union facility's wastewater discharge is in compliance and conformance with the facility's discharge permits.

iii. Solid/Hazardous Wastes

Hazardous waste will be generated from the clean-out of the process equipment. The waste generated, mainly methanol (CAS# 67-56-1), is collected and transported to a licensed waste disposal firm for solvent blending. The current facility used is listed below:

Marisol, Inc.
125 Factory Lane
Middlesex, New Jersey 08846

EPA ID #: NJD002454544
Hazardous Waste Facility Permit #: 1211B1HP04
Issuing Authority: New Jersey Department of Environmental Protection (NJDEP)
Expiration Date: Originally 5/4/92, but the permit has been administratively extended by the NJDEP.

Low levels of non-hazardous pharmaceutical waste is expected to be generated during the production of the drug substance and the subsequent cleaning of process equipment. Any non-hazardous waste generated is collected and transported to a licensed waste disposal firm for incineration. The current facility used is:

Long Beach Recycling and Recovery Corporation
70 Water Street
Long Beach, New York 11561

The facility operates under the following conditions:

State ID #: 30-E-03
EPA ID #: NYN100000052
Solid Waste Management Facility Permit #: 1-2809-00088-00008-0
Permitting Authority: New York State Department of Environmental Conservation (NYSDEC)
Expiration Date: February 12, 2001

Waste handling, storage, transport, and disposal comply with and conforms to all applicable requirements.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

Listed below are the laws, rules, and regulations at the federal, state and local level that cover emissions, including occupational requirements, and are applicable to the Schering Corporation facility in Union, New Jersey:

* National Primary and Secondary Air Quality Standards (40 CFR 50)

* National Emission Standards for Hazardous Air Pollutants (40 CFR 61)

* New Jersey Air Pollution Control Regulations (N.J.A.C. 7:27 et. seq.)

* U.S. EPA Pretreatment Regulations (40 CFR 403 and 439)

* Joint Meeting of Essex and Union Counties (JMEUC) Rules and Regulations (December 20, 1989)

* Resource Conservation and Recovery Act of 1976 PL 94-580 as amended

* New Jersey Administrative Code, Title 7, Chapters 14A, 26, and 27

* U.S. Dept. of Labor, Occupational Safety and Health Administration (OSHA), Occupational Safety and Health Standards (29 CFR 1910)

The following permits are applicable to the control of emissions from the micronization of the drug substance at the applicant's facility in Union, New Jersey:

Emission	Authorizing Agency	Permit #	Exp Date
Air	New Jersey Dept. of Environmental Protection (NJDEP)	095068	3/29/96[1]
		082108	2/26/98
		082109	2/02/98
		102308	7/05/96
		082106	2/26/98
		082107	2/26/98
		112320	7/02/00
		115725	3/20/96[1]
Process wastewater	Joint Meeting of Essex and Union (JMEUC)	JM7145	4/14/91[2]

[1] Permits administratively extended by the New Jersey Dept. of Environmental Protection (NJDEP)

[2] Permit extended by the Joint Meeting of Essex and Union (JMEUC) until further notification

The Union facility operates under permit number (ID number) NJD001317601 for the generation, storage, and transportation of hazardous waste. This permit is issued by the U.S. Environmental Protection Agency (EPA) and the NJDEP and expires on December 30, 1996.

The Union, New Jersey facility is in compliance with all emission requirements.

Worker safety is governed by the U.S. Department of Labor, Occupational Safety and Health Administration (OSHA), Occupational Safety and Health Standards (29 CFR 1910). During manufacturing, special gear and equipment is used to protect workers from excessive inhalation of and skin contact with the active substances. Safety glasses, uniforms, latex gloves, and half-face respirators must be worn by workers whenever a particular hazard exists.

A Material Safety Data Sheet (MSDS) for flunixin meglumine is contained in the **Non-Confidential Appendix 1**. Material Safety Data Sheets for all other ingredients are maintained at the applicant's facility in Union, New Jersey.

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The approval of the proposed action and subsequent increase in production will not affect compliance with current emission requirements at the Union, New Jersey facility.

SITE OF MANUFACTURE OF DRUG PRODUCT

The final product will be processed, packaged, and labeled at the applicant's facility in Manati, Puerto Rico. Substances expected to be emitted, controls on these emissions, and compliance with emission requirements are addressed below.

a. Substances Expected to be Emitted

This information is provided in **Confidential Appendix 3.**

b. Controls Exercised

i. Air

The only possible source of air emissions would be the compounding step. Approximately 0.0002 pounds of sodium formaldehydesulfoxilate may be discharged per batch. The remainder of the compounding is conducted under a nitrogen blanket with no flow. There is no significant emission to the atmosphere within the facility nor to the outside environment; therefore, no control equipment is necessary.

ii. Wastewater

Liquid waste may be generated during manufacture. Any wastewater is neutralized at the facility then discharged to the Barceloneta Regional Wastewater Treatment Plant (BRWTP). The BRWTP is operated by the Puerto Rico Aqueduct and Sewer Authority.

iii. Solid/Hazardous Wastes

No hazardous wastes are expected to be generated during manufacture. Small amounts of nonhazardous pharmaceutical wastes are expected to be generated during compounding and packaging of the product. Nonhazardous solid waste is collected and transported to the Toa Alta Municipal Sanitary Landfill.

c. Citation of and Statement of Compliance with Applicable Emission Requirements

Listed below are the laws, rules, and regulations at the federal, state, and local level that cover emissions, including occupational requirements, and are applicable to the Schering Corporation facility in Manati, Puerto Rico.

* National Primary and Secondary Air Quality Standards (40 CFR 50)

* National Emission Standards for Hazardous Air Pollutants (40 CFR 61)

* Puerto Rico Environmental Quality Board's Regulation for the Control of Atmospheric Pollution, August 17, 1971, as amended

* Puerto Rico Environmental Policy Act; Law No.9 of June 18, 1970.

* U.S. EPA Pretreatment Regulations (40 CFR 403 and 439)

* Puerto Rico Environmental Quality Board Water Quality Standards, January 4, 1974

* Facility agreement among Puerto Rico Industrial, Medical, and Environmental Control Facilities Financing Authority and Schering Corporation and the Puerto Rico Aqueduct and Sewer Authority

* Resource Conservation and Recovery Act of 1976 PL 94-580 as amended

* Regulation for the Control of Hazardous and Non-hazardous Solid Waste of the Puerto Rico Environmental Quality Board

* U.S. Dept. of Labor, Occupational Safety and Health Administration (OSHA), Occupational Safety and Health Standards (29 CFR 1910)

The following permits are applicable to the control of emissions from the manufacture of the drug product at the applicant's facility in Manati, Puerto Rico:

Emission	Authorizing Agency	Permit #
Air	Puerto Rico Environmental Quality Board	PFE-47-1290-1306-1-11-0 Expires 1997[1]
Air	Puerto Rico Environmental Quality Board	PFE-47-0692-0853-1- Expires 1997[1]
Process Wastewater	Puerto Rico Aqueducts and Sewers Authority	Pretreatment Permit GDA 91-210-026 Expires 7/13/95[2]
Hazardous Waste	USEPA	ID# PR 090 139536

[1] Expiration date has been extended until submission of the Title V permit application during the first quarter of 1997.

[2] Permit renewal application was submitted on time. New permit expected soon.

Worker safety is governed by the U.S. Department of Labor, Occupational Safety and Health Administration (OSHA), Occupational Safety and Health Standards (29 CFR 1910). During manufacturing, special gear and equipment is used to protect workers from excessive inhalation of and skin contact with the active substances. Safety glasses, uniforms, latex gloves, and half-face respirators must be worn by workers whenever a particular hazard exists.

A Material Safety Data Sheet (MSDS) for flunixin meglumine is contained in the **Non-Confidential Appendix 1**. Material Safety Data Sheets for all other ingredients are maintained at the applicant's facility in Manati, Puerto Rico.

d. Discussion of the effect of Approval on Compliance with Current Emission Requirements

The approval of the proposed action and subsequent increase in production will not affect compliance with current emission requirements at the Manati facility.

EXPECTED INTRODUCTION CONCENTRATIONS FROM USE

The FDA regulations, 21 CFR Part 25.31a(b)(4)(i), state that the applicant should provide an estimate of the maximum yearly market volume of the drug product under review to aid in determining whether approval of the application will result in potentially significant environmental introductions from the use of the product. The maximum yearly market volume (fifth-year production estimate) of the drug product is considered confidential business information and is provided in **Confidential Appendix 3**.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT:

21 CFR Part 25.31a(b)(4)(ii) provides for abbreviation of the EA format for a NADA where the product is intended for the use under prescription or veterinarian's order, or for use in nonfood animals. Thus, format item number 7 information has not been provided.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES:

21 CFR Part 25.31a(b)(4)(ii) provides for abbreviation of the EA format for a NADA where the product is intended for the use under prescription or veterinarian's order, or for use in nonfood animals. Thus, format item number 8 information has not been provided.

9. USE OF RESOURCES AND ENERGY:

21 CFR Part 25.31a(b)(4)(ii) provides for abbreviation of the EA format for a NADA where the product is intended for the use under prescription or veterinarian's order, or for use in nonfood animals. Thus, format item number 9 information has not been provided.

10. MITIGATION MEASURES:

21 CFR Part 25.31a(b)(4)(ii) provides for abbreviation of the EA format for a NADA where the product is intended for the use under prescription or veterinarian's order, or for use in nonfood animals. Thus, format item number 10 information has not been provided.

11. ALTERNATIVES TO THE PROPOSED ACTION:

21 CFR Part 25.31a(b)(4)(ii) provides for abbreviation of the EA format for a

NADA where the product is intended for the use under prescription or veterinarian's order, or for use in nonfood animals. Thus, format item number 11 information has not been provided.

12. LIST OF PREPARERS:

The information contained in this Environmental Assessment was provided by the following individuals:

Schering Corporation

Mr. David A. Schreiber	Regulatory Affairs Manager
Mr. Carlos M. Jimenez-Barber	Environmental Compliance Manager

Foreign Contract Manufacturer #1

Schering-Plough (Avondale) Co.

13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of Schering-Plough Corporation

Appendices 2 and 3 of this document contain information which is considered confidential in nature and is therefore not releasable to the public.

The undersigned official certifies that the EA summary document and Appendix 1 contain non-confidential information and understands that this information will be made available to the public in accordance with 40 CFR Part 1506.6.

Date: 6/5/96 By: J Nusser

Joseph A. Nusser, P.E., Sr. Director
Environmental Projects & Compliance
Schering Laboratories

14. REFERENCES:

This section is not applicable.

15. APPENDICES:

Appendix 1: Material Safety Data Sheet (MSDS) for flunixin meglumine.

Appendix 2: Confidential Information regarding the Environmental Certifications for Foreign Contract Manufacturer #1 and the applicant's Rathdrum, Ireland facility.

Appendix 3: Confidential Business Information as referenced in the EA summary document.

APPENDIX 1

Non-confidential Information

Material Safety Data Sheet (MSDS) for Flunixin Meglumine

Material Safety Data Sheet FLUNIXIN MEGLUMINE	Page: 1 Rev. Date 05/06/96

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

COMPANY CONTACT: Safety & Industrial Hygiene
TELEPHONE NUMBER: (908)298-5044

PRODUCT NAME: FLUNIXIN MEGLUMINE
PRODUCT CODE: SCH 14717
CAS NUMBER: 6284-40-8
CHEMICAL FORMULA: C14 H11 N2 F3 O2 * C7 H17 N O5

SYNONYMS: 2-(2'-METHYL-3'-TRIFLUOROMETHYLANILINO)NICOTINIC ACID, N-METHYL BANAMINE
GLUCAMINE SALT

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT NAME	EXPOSURE LIMITS	CONCENTRATION PERCENT BY WEIGHT
Flunixin meglumine CAS NUMBER: 6284-40-8	PEL None TLV None	

3. HAZARDS IDENTIFICATION

POTENTIAL HEALTH EFFECTS

EYES
Eye irritation. Irritation of mucous membranes.

SKIN
May produce reversible skin irritation.

INGESTION
The effects of ingestion of flunixin meglumine is humans are unknown. The LD 50 in rats of 120 mg/kg. suggests a moderate to high toxicity via the oral route.

INHALATION
Irritation of the respiratory tract and mucous membranes. Prolonged inhalationmay produce pulmonary edema.

4. FIRST AID MEASURES

EYES
Flush with water for at least 15 minutes. Obtain medical attention.

SKIN
Remove contaminated clothing. Thoroughly wash exposed area with soap and water Obtain medical attention.

INGESTION
Give copious amounts of water and induce vomiting, if conscious. Obtain medical attention.

INHALATION
Remove from exposure. If breathing is feeble or ceases, give cardiopulmonary resuscitation. Obtain medical attention.

5. FIRE FIGHTING MEASURES

FLAMMABLE PROPERTIES
FLASH POINT: n/a°F

FIRE AND EXPLOSION HAZARDS
Under normal conditions of use this material does not present a significant fire or explosion hazard. However like most organic compounds it is combustible and may form a dust explosion hazard if widely dispersed in air.

EXTINGUISHING MEDIA
CO2, Dry chemical, Water, Water Spray.

FIRE FIGHTING INSTRUCTIONS
Fight fire from safe distance or protected location. Use water spray to keep exposed containers and equipment cool. Wear full protective equipment including self contained breathing apparatus (SCBA).

6. ACCIDENTAL RELEASE MEASURES

Sweep, scoop, or vacuum up spill. Minimize contact with spilled material. Keep other personnel away from the clean up area. Wear appropriate respiratory protection and protective clothing in the spill area. Notify your supervisor immediately. Clean area with a wet mop. Dispose of spilled material and clean up materials as given in Waste Disposal Methods below.

7. HANDLING AND STORAGE

HANDLING AND STORAGE PRECAUTIONS
Store in double lined plastic in fiberboard or other appropriate container. Store in a cool, dry, well ventilated area.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

ENGINEERING CONTROLS
Provide adequate local exhaust ventilation.

EYE/FACE PROTECTION
Splash goggles/safety glasses. Dust proof goggles.

SKIN PROTECTION
Gloves- Latex or better
Lab coat or uniform

RESPIRATORY PROTECTION
Minimum of half facepiece respirator with HEPA cartridges.
Full facepiece respirator may be substitued for eye protection.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE
Fine white powder.

BASIC PHYSICAL PROPERTIES
MELTING POINT: 138°C
MOLECULAR WEIGHT: 491.50

10. STABILITY AND REACTIVITY

STABILITY: Stable

HAZARDOUS DECOMPOSITION PRODUCTS
Oxides of nitrogen and Hydrogen fluoride

11. TOXICOLOGICAL INFORMATION

MISCELLANEOUS TOXICOLOGICAL INFORMATION
LD 50 oral(rats)=120 mg/kg. Flunixin meglumine is of moderate to high toxicity via the oral route. It is an eye irritant and most likely will also produce irritation of mucous membranes and the upper respiratory tract. In produces slight reversible dermal irritation in test animals. A high degree of toxicity is indicated via the inhalation and oral routes in rats.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE
May cause sensitization.

12. ECOLOGICAL INFORMATION

NO DATA GIVEN

13. DISPOSAL CONSIDERATIONS

While not hazardous waste, material should be disposed in an environmentally sound manner. Incineration is the preferred disposal method.

14. TRANSPORT INFORMATION

PROPER SHIPPING NAME: DOT ORM-A NOS;IATA Other Reg. Substance

HAZARD CLASS: DOT ORM-A;IATA 9
DOT IDENTIFICATION NUMBER: NA1693
DOT SHIPPING LABEL: DOT N/A;IATA miscellaneous
PACKAGING REQUIREMENTS: DOT 173.510;IATA 906

15. REGULATORY INFORMATION

NO DATA GIVEN

16. OTHER INFORMATION

Hazard Rating - HEALTH: 2 Moderate
- FIRE: 1 Slight
- REACTIVITY: 1 Slight
- Other:

SPECIAL HAZARDS: Intended Use- Veterinary Analgesic/Anti-Inflammatory

REFERENCE DOCUMENTATION
OTHER SOLUBILITIES: Ethanol, methanol, DMF,DMSO, Propylene glycol.

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