ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT

GALLIMYCIN (ERYTHROMYCIN) INJECTION 200 mg/mL

1. Date:
2. Applicant: SANOFI ANIMAL HEALTH, INC.
3. Address: 7101 College Blvd., Overland Park, KS 66210
4. Description of Proposed Action:

This Environmental Assessment (EA) has been prepared as a required portion of a supplemental new animal drug application (NADA) for GALLIMYCIN (Erythromycin) Injection 200 mg/mL. This product is intended for over-the-counter use as an intramuscular antibiotic injection for cattle. The approvals requested for this product are 1.) to increase the dosage level from 2 mg/lb. animal body weight to 4 mg/lb. animal body weight to comply with the findings of the National Academy of Science/National Research Council, Drug Efficacy Study Implementation (NAS/NRC/DESI); and 2.) to change the zero tolerance (21 CFR 522.820) to 0.1 ppm in edible tissues of cattle.

The subject new animal drug will be manufactured, packaged and labeled at Boehringer Ingelheim Animal Health, St. Joseph, MO, the approved contract manufacturing facility which currently manufactures the existing erythromycin product. Erythromycin base is manufactured by Abbott Laboratories, North Chicago, Illinois.

The use pattern for the subject drug is expected to remain unchanged. It is currently used by laymen for the treatment of bovine respiratory disease (shipping fever complex and bacterial pneumonia) associated with *Pasteurella multocida*, staphylococcal and streptococcal organisms susceptible to erythromycin. Use of this product occurs in and around cattle feed lots, individual farms and other locations where cattle are held and/or moved. These areas are primarily rural in nature and comprise an otherwise non-specific terrestrial environment. The primary disease for which this drug is used is usually distinguishable from other bovine diseases by clinical signs. Affected animals exhibit depression, anorexia, serous to purulent nasal discharge, cough, fever,

increased pulse rate and rapid, shallow respiration. These symptoms are readily recognizable by laymen accustomed to handling cattle. Affected cattle are generally isolated if possible and treatment is given on the basis of individual animal need. Entire herds of animals are not expected to be given the drug on the basis of symptoms in one or even several animals because of the added cost and time to treat healthy animals in a very cost conscious environment. In addition, the product labeling specifically indicates the product is to be used only in animals exhibiting clinical signs of disease.

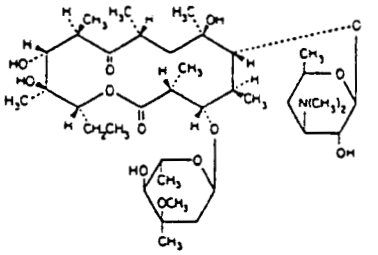
5. Identification of Chemical Substances that are the Subject of the Proposed Action:

Erythromycin

Trade Name(s) and Common or Generic Names: Gallimycin (Erythromycin)

Chemical Name: Erythromycin

Structural Formula:



Empirical Formula: $C_{37}H_{67}NO_{13}$
Molecular Weight: 733.94

TSCA Code Designation: A774-4728

Erythromycin base is a white or slightly yellow, crystalline powder which is odorless or practically odorless. Erythromycin is a structurally complex member of the macrolide group of antibiotics. It consists of two sugars, desosamine and cladinose, which are attached to erythronolide, a macrocyclic lactone. It is produced by fermentation by a strain of *Streptomyces erythreus*, a soil borne organism. Three erythromycins are produced during fermentation, designated *A*, *B* and *C*, with *A* being the major and most important component. Erythromycins *A* and *B* contain the same sugar moieties but differ in position 12 of the aglycone (erythronolide), *A* having a hydroxyl substituent. Component *C* differs by the presence of mycarose instead of cladinose.

The inert ingredients in this injectable product are primarily anhydrous alcohol, ethyl acetate and polyethylene glycol, with smaller quantities of polysorbate 80 and tromethamine. Considerable information is available in the published literature regarding each of these substances.

Anhydrous alcohol

Trade Name(s): Ethanol, ethyl alcohol

Empirical Formula: C_2H_6O

Molecular Weight: 46.07

CAS No.: 64-17-5

Can be manufactured in a variety of ways such as: fermentation of starch, sugar and other carbohydrates; sulfite waste liquors; hydrolysis of ethyl sulfate; oxidation of methane. It is a clear, colorless, very mobile, flammable liquid with pleasant odor and burning taste. It absorbs water very rapidly from air. Is miscible with water and many organic liquids. Oral LD_{50} in rats is 13.0 mL/kg.

Ethyl alcohol is used in alcoholic beverages, as a solvent in laboratories and has many other industrial applications including broad usage in the pharmaceutical industry. It is frequently used as a topical anti-infective and antiseptic.

Ethyl acetate

Trade Name(s): Acetic acid ethyl ester, vinegar naphtha

Empirical Formula: $C_4H_8O_2$

Molecular Weight: 88.10

CAS No.: 141-78-6

Is manufactured by the slow distillation of a mixture of acetic acid, ethyl alcohol, and sulfuric acid. Is a clear, volatile, flammable liquid with a characteristic fruity odor and pleasant taste when diluted. It is slowly decomposed by moisture, then undergoes an acid reaction. Ethyl acetate absorbs up to 3.3% w/w water, is miscible with alcohol, acetone, chloroform and ether. It forms azeotropic mixtures with water and alcohol. Oral LD_{50} in rats is 11.3 mL/kg.

Ethyl acetate is used as an artificial fruit essence and solvent for many substances such as nitrocellulose, varnish, lacquers, artificial leather, photographic films, perfumes, textiles and many other applications.

Polyethylene glycol

Trade Name(s): PEG, Carbowax, Pluracol E, Poly-G

Empirical Formula: Liquid and solid polymers

$H(OCH_2CH_2)_nOH$ where n is ≥ 4. Average value of n for PEG 400 is between 8.2 and 9.1.

Molecular Weight: Range 380-420

CAS NO.: 25322-68-3

Is a clear, viscous, slightly hygroscopic liquid with a slight characteristic odor. Soluble in many organic solvents. Readily soluble in aromatic hydrocarbons and slightly soluble in aliphatic hydrocarbons. It does not hydrolyze or deteriorate on storage, will not support mold growth and is of very low toxicity.

Polyethylene glycols are used as water-soluble lubricants for rubber molds, textile fibers, and metal-forming operations. Is extensively used in food, food packaging, cosmetics, pharmaceuticals and has numerous other industrial applications.

Polysorbate 80

Trade Name(s): Tween 80, Sorbate, Monitan, Olothorb

Empirical Formula: A complex structure consisting of an oleate ester of sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides.

CAS No.: 9005-65-6

An amber colored, viscous liquid; very soluble in water, soluble in alcohol, cottonseed oil, corn oil, ethyl acetate, methanol and toluene. It is insoluble in mineral oil.

Polysorbate 80 is widely used as an emulsifier and dispersing agent for pharmaceutical products, pesticides and as a defoamer and emulsifier in food products.

Tromethamine

Trade Name(s): Tris buffer, Tris, Tham, trisamine, trometamol, Tromethane

Empirical Formula: $C_4H_{11}NO_3$

Molecular Weight: 121.14

Can be prepared by reduction or catalytic hydrogenation of the corresponding nitrogen compound. Is a crystalline substance and a weak monacidic base. Aqueous solutions do not absorb CO_2 from the air. Is soluble in water, ethylene glycol, methanol, anhydrous ethanol, dimethyl formamide, acetone, ethyl acetate, olive oil, cyclohexane, chloroform, and slightly soluble in carbon tetrachloride.

It is used in the synthesis of surface-active agents, vulcanizing accelerators, pharmaceuticals, cosmetics, leather dressings, textile specialties, polishes, cleaning compounds and many other applications.

6. Introduction of Substances into the Environment:

a. Through Manufacture:

This new animal drug containing erythromycin is now being produced, and has been produced for a number of years, at the manufacturing site given in Section 4 using the currently approved formulation. Portions of the materials listed in Section 5 may be released from the manufacturing sites into the environment as a result of the proposed action in the form of air emissions, liquid waste streams and solid waste. However, since the proposed action contemplates no changes in the formulation and since the product has been manufactured at these sites for several years, no additional environmental introductions are expected as a result of the proposed action. A Material Safety Data Sheet has been prepared for erythromycin (Appendix 1) and is available to employees at both sites.

Production Sites

1. Abbott Laboratories

   Bulk Drug: Erythromycin Base

   Abbott Laboratories is the supplier of the bulk drug only, and currently produces erythromycin for use in other animal drugs as well as in human drugs.

   An environmental assessment prepared by Abbott Laboratories for the site of bulk drug production is included in the following pages.

ENVIRONMENTAL IMPACT ASSESSMENT

Date: 2/10/87
Name of Applicant: Abbott Laboratories
Address: 14th & Sheridan Rd.
North Chicago, IL 60064

1496N

Product: Erythromycin Base

1. Description of the proposed action:

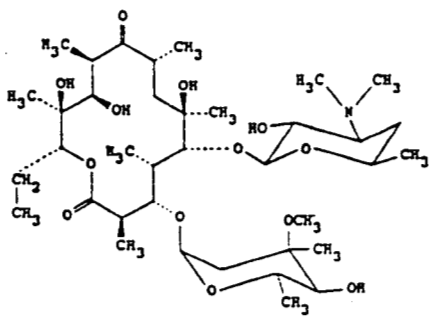
Abbott Laboratories is submitting environmental assessment data for the manufacture of erythromycin base bulk powder at its North Chicago manufacturing facilities located in Lake County, Illinois. Erythromycin base is an effective broad spectrum antibiotic used to treat various bacterial infections in humans and animals. Bulk erythromycin base is intended for use in the manufacture of finished unit dose products including tablets, oral suspensions, injectables and as the base molecule for manufacturing erythromycin salts.

The erythromycin base bulk powder will be utilized by business units within Abbott Laboratories and other pharmaceutical manufacturing concerns for the production of erythromycin based products for sale to the medical community. Erythromycin products are manufactured for topical, oral, and intravenous treatment of bacterial infection sites in both humans and animals. Wastes expected from the production and use of erythromycin base bulk powder will be primarily off-spec products and returned goods. Facilities currently receiving antibiotic wastes are EPA approved nonhazardous sanitary landfill facilities located in rural Northern Illinois and Southern Wisconsin.

2. Identification of chemical substances that are the subject of the proposed action:

Erythromycin Base:	CAS RN 114-07-8, C37H67NO3, MW 733.92
Other Nomenclature:	Erythromycin A, Abomycetin, EMU, Erythrocin, Erymysin, and Ilotycin

Description: Erythromycin - (Merck Index, 10th Edition, No. 3624) Antibiotic substance produced by a strain of Streptomyces erythreus. There are three erythromycins produced during fermentation designated A, B, and C. Ery A is the major and the most important component. Erythromycin readily forms salts with acids and has a solubility in water of 2 mg/mL. This antibacterial base molecule is used to produce: erythromycin estolate, erythromycin stearate, erythromycin ethylsuccinate, and erythromycin lactobionate. The structural formula is presented below.



erythromycin A

3. Introduction of substances into the environment:

Erythromycin base is manufactured by propagating Streptomyces erythreus in a defined fermentation growth medium followed by harvesting of the fermentation beer, extracting and crystallizing the antibiotic, and drying the resulting erythromycin base bulk powder. Chemical substances utilized during the manufacturing process are primarily acids, bases, and solvents. Waste solvents are recovered by distillation and reused or drummed for thermal destruction at an EPA approved incinerator or secondary fuels program. Acids, bases, and washwaters from equipment preparation and clean-up are sewered and treated by Abbott Laboratories' on-site wastewater treatment facility. Spent fermentation beer is recovered, concentrated, and sold as an animal feed supplement. Waste filter cake from antibiotic recovery operations is disposed of at EPA approved nonhazardous landfill sites.

Abbott Laboratories' North Chicago, IL facility is subject to environmental laws and regulations enforced by the U.S. Environmental Protection Agency, the Illinois Environmental Protection Agency, and the North Shore Sanitary District, Gurnee, IL. Abbott Laboratories believes it is in compliance with environmental laws and regulations applicable to this proposed action.

Abbott Laboratories' North Chicago, Illinois facility is subject to the U.S. Occupational and Safety Health Act of 1970 and specifically the safety and health standards promulgated and enforced by the Occupational Safety and Health Administration, U.S. Department of Labor. The facility is also subject to the Illinois Chemical Safety Act and the Illinois Toxic Substances Disclosure to Employees Act. Abbott Laboratories believes it is in compliance with these occupational, safety and health laws and their standards and provisions as they are currently interpreted and enforced with respect to this proposed action.

4. Fate of emitted substances in the environment:

Wastewaters generated during the erythromycin base production process are treated by Abbott Laboratories' activated sludge wastewater treatment facility. Oxygen demand, suspended solids, and nutrients responsible for eutrophication of receiving water bodies are effectively removed by the Abbott treatment system and further polished by an advanced tertiary level municipal wastewater treatment facility (POTW). All solids wastes discharged from the erythromycin process are analyzed and permitted for land disposal in accordance with EPA rules and regulations. Air emissions are controlled as required by regulation at each source by EPA permit. With installation of pollution control technology in the erythromycin production areas and management of generated wastes to minimize volume and hazard to personnel, nearby communities and the environment, Abbott Laboratories does not expect any adverse effect on public health or the environment due to the production of erythromycin base.

5. Environmental effects of released substances:

The manufacture of erythromycin base powder will have no effect on the maintenance of environmental quality and enhancement of long-term productivity. Abbott Laboratories' erythromycin base powder will be used as an effective antibacterial and precursor for the production of erythromycin salts. Erythromycin base is degradable and will not accumulate in the environment. EPA approved methodology will be followed in disposing of wastes and wastewaters resulting from the manufacturing process.

6. Use of resources and energy:

This action will not curtail any beneficial uses of the environment. No irreversible or irretrievable commitment of resources would be involved in the proposed action should it be implemented. The raw materials and energy consumed in the production of erythromycin base bulk powder will, of course, be converted, and will not be available for other uses. In this respect, erythromycin base bulk powder must compete with other beneficial products for available resources.

7. Mitigation measures:

Wastes generated from the erythromycin base manufacturing process which are amenable to biological degradation, will be degraded, and will not accumulate in the environment. All nonbiodegradable wastes generated at the erythromycin manufacturing site will be disposed of by recycling, reclamation/resale, incineration, chemical/physical treatment, and/or land disposal.

8. Alternatives to the proposed action:

The National Environmental Policy Act requires the responsible agency to "study, develop, and describe appropriate courses of action in any proposal which involves unresolved conflicts concerning alternative uses of available resources." We do not believe that this situation applies in the case of erythromycin base bulk powder manufacturing. There are no unresolved conflicts for available resources, and there do not appear to be any adverse environmental effects.

9. List of Preparers:

Richard E. Green - Environmental Engineer, Abbott Laboratories
M.S. Environmental Sciences

10. Certification:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of the environmental assessment.

Date: 2/10/87

Signature: Richard E. Green

Title: ENV. ENGINEER

Pheasant Run Landfill
19414 60th Street
Bristol, Wisconsin 53104
414/857-7956

A Waste Management Company

March 28, 1986

Richard G. Shuff, P.E. Chief
Residuals Management and Land Disposal Section
Wisconsin Department of Natural Resources
P.O. Box 7921
Madison, WI 53707

RE: Acceptance of Special Wastes at Pheasant Run Landfill

Dear Mr. Shuff:

Condition #6 of the Pheasant Run Landfill Plan of Operation approval dated April 29, 1983 requires WDNR approval for disposal of any significant quantities of industrial process waste. In compliance with this condition we request WDNR approval to accept the following for disposal:

1. Approximately 1500 cubic yards per year of Wastewater Treatment Plant grit and screenings. Profile #E70494 (copy enclosed).

2. Approximately 40,000 cubic yards per year of coal cinders and fly ash. Profile #E07169 (copy enclosed).

3. Approximately 30 cubic yards per day of wastewater sludge filter cake. Profile #E07171 (copy enclosed).

4. Approximately 1200 cubic yards per month of Gibberllin filter cake. Profile #E07173 (copy enclosed).

5. Approximately 1500 cubic yards per year of Erythromycin filter cake. Profile #E07170 (copy enclosed).

6. Approximately 4000 cubic yards per year of general pharmaceutical wastes. Profile #Y136616 (copy enclosed).

We would appreciate a timely response to this request. Should you have any questions, please feel free to contact Bill Yach at (414) 425-3550.

Sincerely,

Harold P. Cahill
Regional Engineering Mgr.
Environmental Management

WEY/wey
Enclosure
copy to: Ken Hein, WDNR - SED
George Meinholz - WMI
Mike Infusinno - WMI
Robert Vallis - WMI
Bill Yach - WMI

EXHIBIT "A"

SUPPLEMENTAL INFORMATION DOCUMENT: NUMBER 9-109-86

This Document supplements, and is part of, that certain "Waste Transportation and Disposal Agreement", (hereinafter "the Agreement"), entered into by and between ABBOTT LABORATORIES (hereinafter "the Generator") and Chemical Waste Management (hereinafter "CWM"), on 1/6/83. The provisions of this Document shall be incorporated into the Agreement.

1. DESCRIPTION OF WASTE PRODUCTS. The "Waste Products", to which the Agreement refers, are as described in the "Generator's Waste Material Profile Sheet," Code Designations RVD F01536 attached hereto and made part hereof.

Containers are to be provided by according to the following specifications:

DOT approved containers to be properly labeled according to EPA regulations.

2. TENDER OF WASTE PRODUCTS. Generator shall tender or deliver the above Waste Products to CWM as follows:

(a) Quantity of Waste Products to be Tendered Over Term:

(1) Estimated

(2) Guaranteed (If applicable)
Not applicable

(b) Maximum/Minimum quantity of Waste Products Per Tender
(If tendered installments)
Not applicable

(c) Place of Tender

ABBOTT LABORATORIES
1400 N. Sheridan Rd.
North Chicago, IL 60064

(d) Time and Frequency of Tender
To be mutually agreed upon between Generator and Chemical Waste Management.

(e) Manner of Tender (Including notification to CWM)
To be mutually agreed upon between Generator and Chemical Waste Management.

3. WORK RULES/PROCEDURES AT GENERATOR'S PREMISES. Any specific rules or procedures required by Generator for workers on its premises must be noted here, or attached hereto and ititialed by both parties.

4. LOADING AND TRANSPORTATION. The Waste Products are to be loaded (or Stowed) on vehicles (or vessels) be Generator and transported to the Storage Facility/Disposal Facility (circle one) by CWM. If the Waste Products are first transported to a Storage Facility, they will be reloaded (or stowed) on vehicles (or vessels) by _____, and transported to the Disposal Facility by _____. If CWM is to provide transportation, the following special transportation requirements (if any) shall apply, pursuant to the Generator's direction:

(a) Vehicles or Vessels.

(b) Routes.
To be determined by hauler

(c) Hours of Transportation.
To be determined by hauler

5. STORAGE FACILITY. CWM shall store the Waste Products at the following storage facility for a period not to exceed ____ days, from which facility the Waste Products will then be removed to the Disposal Facility:

(a) Name/Address of Storage Facility:
Not applicable

(b) Name/Address of Facility Permittee:
Not applicable

(c) Permit Number(s)/Initiation and Termination Date(s):
Not applicable

(d) Permitting Authority(ies):
Not applicable

6. DISPOSAL FACILITY. CWM shall dispose of the above Waste Products at the following disposal facility (of facilities):

(a) Name/Address of Facility (Facilities):
Solvent Resource Recovery, Inc. (SRR)
P.O. Box 453, 4301 Infirmary Road
West Carrollton OH 45449

(b) Name/Address of Facility Permittee:
Same as (a) above

(c) Permit Number(s)/Initiation and Termination Date(s):
OHD093945293

(d) Permitting Authority(ies):
Ohio EPA

7. DISPOSAL METHOD: CWM shall utilize one or more of the following methods for the disposal of the Waste Products: Reclamation

8. EMERGENCY SERVICES: CWM shall provide emergency transportation, storage or disposal services, with respect to the above Waste Products, pursuant to the following: Not applicable (unless otherwise attached hereto by Generator).

9. RECLAMATION AND/OR SALE OF WASTE PRODUCTS. CWM is authorized to reclaim, recover and sell, distribute or use the Waste Products, their components or residues, as follows:

Not applicable

10. COMPENSATION. The Generator shall compensate CWM as follows:

(a) For Transportation, Storage and Disposal of Waste Products.
Not applicable

(b) For Transportation and Disposal of Waste Products.

DISPOSAL: $.30 per gallon - See attached price sheets for surcharges.

TRANSPORTATION: $1,450.00 per load

Plus applicable taxes & fees.

Generator will be allowed one hour(s) loading time at their facility with anytime thereafter being considered demurrage and charged at the rate of $75.00 per hour.

(c) For Disposal of Waste Products Only.
Not applicable

The fees set forth are subject to change at anytime during the term hereof upon Disposer providing Generator with at least thirty (30) days' advance written notice.

(d) Emergency Services.
Not applicable

(e) Measurement of Waste Products. Waste Products shall be measured by CWM for the purpose of computing fees hereunder, at the time and place, and in the manner, as follows:

Per the amount listed on the manifest. Amount is subject to physical verification by CWM personnel. Discrepancies will be resolved prior to final acceptance.

(f) Generator's Billing Address. CWM shall submit its statements to:

ABBOTT LABORATORIES
1400 N. Sheridan Rd.
North Chicago, IL 60064

(g) CWM Billing Address. CWM will issue its billings from the following:

SOLVENT RESOURCE RECOVERY, INC. (SRR)
P.O. Box 453, 4301 Infirmary Road
West Carrollton OH 45449

11. TERM. The term of the Agreement, with respect to the Waste Products covered in this Document, shall be as follows: (If provision is to be made for termination without cause, upon written notice by either party, insert such provisions below the Term of the Agreement.)

The term of this agreement will be in effect from the date signed below to the decision expiration date of 9/4/87.

12. LAW TO GOVERN. The Agreement and the Supplemental Information Document shall be goverened and construed in accordance with the laws of the State of Ohio.

13. MISCELLANEOUS CONDITIONS.

See attachments.

By their signatures hereto, the parties agree that this Supplemental Inormation Document shall be considered an attachment to, and part of, that certain "Waste Transportation and Disposal Agreement" identified above.

DATE: 9/5/86

ABBOTT LABORATORIES

BY: R.C. Jones

TITLE: Vice President

CHEMICAL WASTE MANAGEMENT, INC.

BY: Andrew J. Flanagan per pk
Andrew J. Flanagan

TITLE: Sales Manager-Northern Region

sm/ts/srr/alsip

ATTACHMENT

Line 1 - ADDITIONAL CHARGES:

Greater than 12 inches of non-pumpable solids up to 24 inches will have an additional charge of $110.00 per drum. Over 24 inches of non-pumpable solids there will be a flat $300.00 per drum charge.

Line 2 - ADDITIONAL CHARGES:

The above price includes disposal of non-pumpable solids up to 3 inches. Drums with greater than 3 inches up to 12 inches will have an additional charge of $50.00 per drum. Over 12 inches up to 24 inches will be charged $110.00 per drum. Drums over 24 inches of solids will be rejected for recovery.

Line 3 -

Due to the impending November 8, 1986 landfill ban on F001, F002, F003, F004, F005 liquids and the absence of complete regulation qualifying the ban on these items, your waste will be subject to review for applicability to these regulations. Should your material be impacted by these regulations, revisions will be sent to you when we have them.

Line 4 -

Foreign materials not relative to the stream must be kept out of the drum. Examples: Gloves, cups, cans, rags. If foreign material is not kept out, the drums will be rejected.

PRICE LIST

EFFECTIVE SEPTEMBER 9, 1986

Organic Liquid Disposal

Non-Halogenated Solvents with 12,000 BTU/lbs minimum & 2.2 total Halogen max.

Bulk $.30/gallon
Drum $80.00/drum

Surcharges apply for OFF spec material

Flammable Waters

Water processable within plant limits

Bulk $1.25/gallon
Drums $130.00/drum

Qualified stream by stream

Organic Solids Disposal

Materials mixable into fuel program

$300.00/per drum

Waste Oil

Same pricing as Organic Liquid Disposal

Recycling Charges

Quoted of individual streams. Minimum batch size of 40 drums or 2,000 gallons.

Recycable Chlorinated Solvents (disposal)
(Methylene chloride, 1,1,1 Trichlorethane, Trichlorethylene, Freon, Perchlorethylene)

Subject of Purity & yield, verification of material actually delivered.

charge of $45.00/drum
(Qualified streams by streams) No charge to credit on Bulk
0 - .35/gallon

$150.00 Minimum charge per waste stream.

Surcharges

Drums for Toll Recycling

Drums with greater than 3 inches up to 12 inches will have an additional charge of $50.00 per drum. Over 12 inches up to 24 inches will be charged $110.00 per drum. Drums over 24 inches of solids will be rejected for recovery. (subject to organic liquid disposal charges).

Drums for Disposal

Greater than 12 inches of non pumpable solids up to 24 inches will have an additional charge of $110.00 per drum. Over 24 inches of non pumpable solids there will be a flat $300.00 per drum charge.

Surcharge

Foreign materials not relative to the stream must be kept out of the drum. Example: Gloves, cups, cans, rags. If foreign material is not kept out the drums their will be a $100.00 per drum charge for foreign material disposal.

Overpack Surcharges

Add $80.00/drum for Handling

BTU's Surcharges

11333 BTU's per lbs. to 12,000 BTU per lbs - add .30/gal
$15.00/drum

10000 BTU's per lbs. to 11332 BTU's per lbs. - add .44/gal
$20.00/drum

6666 BTU's per lbs. to 9999 BTU's per lbs. - add 1.00/gal
$30.00/drum

Water with Flashpoint Surcharge

$1.25 per gallon in Bulk or any Freewater on loads.

Halogens Surcharges:

Charge for:	Bulk	Drums
2.3 - 3.2	.30	$50.00
3.3 - 4.2	.50	$50.00
4.3 - 5.2	.75	$50.00
5.3 - 6.2	1.00	$100.00
6.3 - 7.2	1.25	$100.00
7.3 - 8.2	1.50	$100.00
8.3 - 9.2	1.75	$100.00
9.3 - 10.2	2.00	$100.00
10.3 - 15.2		$150.00
15.3 - 20.2		$200.00
20.3 - 25.2		$250.00
25.3 - 30.2		$300.00
30.3 - 35.2		$350.00
35.3 - 40.2		$400.00

OVER 10.2% MUST RECEIVE PRICING FROM SALES OFFICE - ON BULK SHIPMENTS

All prices FOB SRR - W. Carrollton: Terms - net 30 days
Prices subject to change upon 15 days written notice.

Restrictions:

Benzene max. 0.5%
Phenol max. 5.0%
pH Range 4-10
PCB non-detectable
No Pesticides and/or Herbicides
No plastic drums
No plastic lined drums
No pallets

Waste Management, Inc.

GENERATOR'S WASTE MATERIAL PROFILE SHEET

WASTE PROFILE SHEET CODE: RVD (TSDF) F01536

GENERAL INFORMATION

GENERATOR NAME: ABBOTT LABORATORIES

FACILITY ADDRESS: 1400 N. SHERIDAN, NORTH CHICAGO ILL 60064

TRANSPORTER: CHEM WASTE

TRANSPORTER PHONE: 312-396-1060

GENERATOR USEPA I.D.: ILD055409940

GENERATOR STATE I.D.:

TECHNICAL CONTACT: RICHARD GREEN TITLE: ENV ENG PHONE: 312 937 4421

NAME OF WASTE: WASTE SOLVENT

PROCESS GENERATING WASTE: MANUFACTURING - PHARM (SPENT SOLV.)

B PHYSICAL CHARACTERISTICS OF WASTE

COLOR: yellow, brown

ODOR: ☐ NONE ☒ MILD ☐ STRONG DESCRIBE:

PHYSICAL STATE @ 70°F: ☐ SOLID ☐ SEMI-SOLID ☒ LIQUID ☐ POWDER

LAYERS: ☐ MULTILAYERED ☐ BI-LAYERED ☒ SINGLE PHASED

FREE LIQUIDS: ☒ YES ☐ NO VOLUME 99 %

pH: ☐ < 2 ☐ 2-4 ☐ 4.1-6.0 ☒ 7 ☐ 7.1-10 ☐ 10.1-12.5 ☐ > 12.5 ☐ EXACT ☐ N/A

SPECIFIC GRAVITY: ☐ < .8 ☒ .8-1.0 ☐ 1.1-1.2 ☐ EXACT ☐ 1.3-1.4 ☐ 1.5-1.7 ☐ > 1.7

FLASH POINT: ☐ < 70°F ☐ 70°F-100°F ☒ 101°F-139°F ☐ 140°F-200°F ☐ > 200°F ☐ NO FLASH ☐ EXACT ☐ CLOSED CUP ☐ OPEN CUP

C CHEMICAL COMPOSITION (TOTALS MUST ADD TO 100%)

ORGANIC LIQUIDS	99 %
WATER	1 %
	%
	%
	%
	%
	%
	%
	%
	%

D METALS ☐ TOTAL (PPM) ☐ EPA EXTRACTION PROCEDURE (mg/L)

ARSENIC (As)	—	SELENIUM (Se)	—
BARIUM (Ba)	—	SILVER (Ag)	—
CADMIUM (Cd)	—	COPPER (Cu)	—
CHROMIUM (Cr)	—	NICKEL (Ni)	—
MERCURY (Hg)	—	ZINC (Zn)	—
LEAD (Pb)	—	THALLIUM (Tl)	—
CHROMIUM-HEX (Cr + 6)	—		

E OTHER COMPONENTS - TOTAL (PPM)

CYANIDES	—	PCB'S	—
SULFIDES	—	PHENOLICS	—

F SHIPPING INFORMATION

D.O.T. HAZARDOUS MATERIAL? ☒ YES ☐ NO

PROPER SHIPPING NAME: WASTE FLAMMABLE LIQUID, N.O.S.

HAZARD CLASS: FLAMMABLE MATERIAL I.D. NO. 1993 R.Q.

METHOD OF SHIPMENT: ☒ BULK LIQUID ☐ BULK SOLID ☐ DRUM (TYPE/SIZE)

ANTICIPATED VOLUME: 100000 GALS. CUBIC YARDS OTHER

PER: ☐ ONE TIME ☐ WEEK ☐ MONTH ☐ QUARTER ☒ YEAR ☐

G HAZARDOUS CHARACTERISTICS

REACTIVITY: ☒ NONE ☐ PYROPHORIC ☐ SHOCK SENSITIVE ☐ EXPLOSIVE ☐ WATER REACTIVE ☐ OTHER

OTHER HAZARDOUS CHARACTERISTICS: ☒ NONE ☐ RADIOACTIVE ☐ ETIOLOGICAL ☐ PESTICIDE MANUFACTURING WASTE ☐ OTHER

USEPA HAZARDOUS WASTE? ☒ YES ☐ NO

USEPA HAZARDOUS CODE(S): D001 F001 F002 F003 F005

STATE HAZARDOUS WASTE? ☒ YES ☐ NO

STATE CODE(S):

SPECIAL HANDLING INFORMATION:

☐ ADDITIONAL PAGE(S) ATTACHED

I HEREBY CERTIFY THAT ALL INFORMATION SUBMITTED IN THIS AND ALL ATTACHED DOCUMENTS IS COMPLETE AND ACCURATE, AND THAT ALL KNOWN OR SUSPECTED HAZARDS HAVE BEEN DISCLOSED.

AUTHORIZED SIGNATURE TITLE DATE

2. Boehringer Ingelheim Animal Health

Formulation: Finished Product

Boehringer Ingelheim presently receives and utilizes the bulk drug produced by Abbott Laboratories and is the currently approved manufacturer of the finished drug product, Gallimycin (Erythromycin) Injection 200 mg/mL.

An environmental assessment prepared by Boehringer Ingelheim for the site of finished drug product manufacture is included in the following pages.

ENVIRONMENTAL ASSESSMENT

Ref: 21 CFR 25.31a(b)(4) Environmental Assessment

1) DATE: March 31, 1992

2) NAME:

Sponsor: Sanofi Animal Health, Inc.

Manufacturer: Boehringer Ingelheim Animal Health, Inc. (BIAHI)
Establishment Registration #1910185

3) ADDRESS:

Sponsor: 7101 College Blvd., Suite 610, Overland Park, KS 66210

Manufacturer: 2621 North Belt Highway, St. Joseph, Missouri 64506

4) DESCRIPTION OF PROPOSED ACTION:

The subject of this Environmental Assessment is Gallimycin/Erythromycin Injection* 200 mg/mL, NADA 12-123. The drug product is produced at Boehringer Ingelheim Animal Health, Inc., a parenteral production facility in St. Joseph, Missouri. BIAHI is currently approved as an alternate manufacturing site under NADA 12-123.

*[The drug product will be referred to hereafter as Gallimycin Injection.]

Gallimycin Injection will be produced at a concentration of 200 mg of erythromycin per mL and packaged in 100-, 250-, and 500-mL sterile containers. The product will be labeled for use in beef cattle for the treatment of bovine respiratory disease caused by organisms susceptible to erythromycin.

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

The product will be compounded, using erythromycin and excipients, by BIAHI at our main plant location identified in parts 2) and 3) above. The BIAHI facilities are located on 67 acres bordered on the East, Northeast and Southeast by commercial zones and on the West, Northwest and Southwest by residential zones. The facility is supplied with all municipal utilities and sewer systems. General pharmaceutical facilities and staff are described in our current Drug Master File.

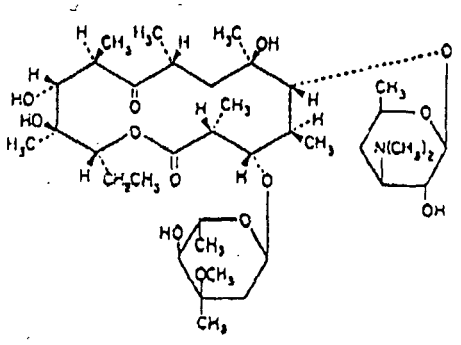
a) Statement of Formula:

	per mL
Erythromycin base USP [Maximum 10% excess]	210 mg/mL
Ethanol anhydrous USP	221 mg/mL
Tromethamine USP	1 mg/mL
Ethyl Acetate NF	253 mg/mL
Polysorbate 80 NF [as Tween 80]	21 mg/mL
Polyethylene Glycol 400 NF	277 mg/mL

b) Active Ingredient:

Erythromycin base, USP XXII, p. 519.
CAS: 114-07-8
Mol. wt.: 733.94

Structural Formula:



$C_{37}H_{67}NO_{13}$

Physical State: White, crystalline powder.
Purity: Contains not less than 850 mcg of $C_{37}H_{67}NO_{13}$ per mg, calculated on the anhydrous basis.

c) Excipients:

i) Ethanol anhydrous, USP XXII, p. 35 [Alcohol Dehydrated USP].
CAS: 64-17-5
Mol. wt.: 46.07
Formula: C_2H_6O

Physical State: Clear, colorless, mobile, volatile liquid.
Purity: Contains not less than 99.2 percent, by weight, corresponding to not less than 99.5 percent, by volume, at 15.56°, of C_2H_5OH.

ii) Tromethamine, USP XXII, p. 1429.
CAS: 77-86-1
Mol. wt.: 121.14
Formula: $C_4H_{11}NO_3$

Physical State: White, crystalline powder, having a slight, characteristic odor.
Purity: Contains not less than 99.0 percent and not more than 101.0 percent of $C_4H_{11}NO_3$, calculated on the dried basis.

iii) Ethyl Acetate, NF XVII, p. 1929.
CAS: 141-78-6
Mol. wt.: 88.11
Formula: $C_4H_8O_2$
Physical State: Transparent, colorless liquid, having a fragrant, refreshing, slightly acetous odor, and a peculiar, acetous, burning taste.
Purity: Contains not less than 99.0 percent and not more than 100.5 percent of $C_4H_8O_2$.

iv) Polysorbate 80 NF [Tween 80], NF XVII, p. 1968.
CAS: 9005-65-6
Mol. wt.: 1304.63
Formula: $C_{64}H_{119}O_{26}$
Physical State: Amber-colored, oily liquid having a faint, characteristic odor and a warm, somewhat bitter taste.
Purity: Polysorbate 80 is an oleate ester of sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides.

v) Polyethylene Glycol 400, NF XVII, p. 1961.
CAS: 25322-68-3
Mol. wt.: Nominal average 400 with viscosity range of 6.8 to 8.0 centistokes.
Formula: $H(OCH_2CH_2)nOH$
Physical State: Clear, colorless liquid.
Purity: The average molecular weight is not less than 95 percent of the labeled nominal molecular weight.

The active drug will be contained in a sterile solution.

6) INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT FOR THE SITE OF PRODUCTION:

a) List the substances expected to be emitted:

The substances that are available to be released are erythromycin, ethanol anhydrous, tromethamine, ethyl acetate, polysorbate 80 and polyethylene glycol 400.

The highly soluble nature of the ingredients in this product and the use of polyethylene glycol 400 as a solvent assure that these substances will be present in dilute concentrations and at levels that have historically been used in parenteral products.

A typical batch production loss of 2.5% is historically seen. Based on the anticipated annual production of this product with 2.5% production loss, the estimated yearly production of effluent for this product would be:

Erythromycin base USP	395.0 Kg
Ethanol anhydrous USP	415.0 Kg
Tromethamine USP	2.5 Kg
Ethyl Acetate NF	472.5 Kg
Polysorbate 80 NF	40.0 Kg
Polyethylene Glycol 400 NF	520.0 Kg
Water used in clean-up	5000 gallons

Waste water is discharged directly into a municipal sewer.

Air emissions would not be expected to be measurable. Air emissions would be possible only during weighing operations; prior to this procedure all materials are enclosed in sealed containers and after weighing all materials are charged into a mixing tank and dissolved. During the weighing procedures, air is filtered and the retained material is disposed of in accordance with our current hazardous waste disposal procedures.

Energy in the form of electricity and gas will be utilized directly and indirectly in the manufacture of this product. These resources are not recoverable.

b) Controls exercised to modify emissions:

Wastewater containing the above emissions goes, in its entirety, into the BIAHI plant sewer and directly to the St. Joseph Municipal Water Pollution Control - Sewage Treatment Plant (WPCSTP).

Solid waste is collected and disposed of by a commercial hauler in the St. Joseph Sanitary Landfill, Route #4, St. Joseph, Missouri, which operates under the St. Joseph City code. Solid waste that would be generated by production of this product would include minimal empty fiberboard and plastic containers, supplied by raw material vendors. In addition, the generation of minimal solid wastes, as identified in the weighing procedure above, would also be disposed of in this fashion.

Air emissions are not anticipated in the manufacture of this product.

c) Applicable emission requirements and permits obtained (including occupational) at the Federal, State and local level:

Attached as APPENDIX I is BIAHI's WASTEWATER DISCHARGE PERMIT, issued by the City of St. Joseph, Missouri, Department of Public Works Water Pollution Control.

This permit includes the maximum permissible substance concentrations allowable for discharge into the City's wastewater treatment works. BIAHI complies with all conditions of this permit and at no time discharges wastewater in violation of the City's current Sewers and Sewage Disposal Ordinance.

Attached as APPENDIX II is BIAHI's OCCUPATIONAL LICENSE as issued by the City of St. Joseph, Missouri. BIAHI certifies that no waste water from our plant is discharged into open bodies of water, i.e., rivers, streams, lakes or land area. As discussed above all such emission goes into the St. Joseph, Missouri municipal water treatment system. Therefore, it is our judgment that the National Pollutant Discharge Elimination System (NPDES) is not applicable to BIAHI.

d) Statement certifying compliance with all applicable emission requirements.

The methods and practices employed in the manufacturing, processing, holding and labeling of the subject product and diluent will comply with all city, state, county, and federal environmental regulations. A certification statement is provided in APPENDIX III. BIAHI has manufactured Sanofi's Gallimycin/Erythromycin Injection 200 mg/mL for over five years and has experienced no problems with emissions associated with its production.

e) Effect approval will have upon compliance with current emissions requirements at the production site:

Approval of this NADA will not impact upon the ability of BIAHI to conform to all applicable city and county regulations. We certify that BIAHI's reserve capacity to dispose of such resulting emission, within applicable emission requirements, is sufficient to assure that no problems with emission disposal will occur in the future.

f) All procedures used in manufacturing the final product are conducted in a safe and responsible manner and in accord with: 1) BIAHI Chemical Hazard Communication Program. This program establishes Standard Operating Procedures enabling BIAHI to conform with Federal Regulations as set forth in 29 CFR Part 1910, as administered by the Occupational Safety and Health Administration, Department of Labor; and 2) BIAHI SAFETY POLICY, 11.02 SPPM - Policies. This policy document is an implementation document to monitor internal compliance with BIAHI safety policies to provide safe working conditions for BIAHI employees. Copies of the applicable Material Safety Data Sheets are made available to the workers.

7 - 11) Documentation for items 7-11 of the Environmental Assessment format in 21 CFR 25.31a is not required for this type of application.

12) LIST OF PREPARERS:

BOEHRINGER INGELHEIM ANIMAL HEALTH, INC.

1. Norman K. Jungk - Director, Regulatory Affairs

   Qualifications:

   Received AB degree 1950 and an MA degree in 1951 from the University of Kansas, Lawrence, with a major in microbiology and minor in biochemistry. Advanced academic training at the University of Minnesota from 1951 - 1953. He has been employed since 1953 in the animal and human health products manufacturing industry in various technical positions in the laboratory and at management levels. He joined BIAHI in 1970 as Director of Quality Control and is currently Director of Regulatory Affairs.

2. Jack A. Zupan, Ph.D. - Director, Pharmaceutical Development

   Qualifications:

   Received B.S. in Chemistry in 1972 from the University of Missouri - Kansas City, Kansas City, Missouri; M.S. in Medicinal Chemistry in 1974 and Ph.D. in Medicinal Chemistry in 1976 from the University of Kansas, Lawrence, Kansas. He joined BIAHI in 1980 as Assistant Manager, Organic Synthesis, and is currently Director, Pharmaceutical Development.

3. Susan A. Herald - Administrator, Regulatory Affairs

   Qualifications:

   Received B.A. in English in 1973 from Missouri Western State College. Joined BIAHI Regulatory Affairs Department in 1972 and is currently Administrator, Regulatory Affairs.

13) CERTIFICATION:

I hereby certify that the information contained in this Environmental Assessment is true, accurate, and complete to the best knowledge of myself and the firm.

Susan A. Herald
Susan A. Herald
Administrator, Regulatory Affairs

3-31-92
Date

APPENDIX I

APPENDIX I

City of St. Joseph, Missouri
Department of Public Works
Water Pollution Control

WASTEWATER DISCHARGE PERMIT

Permit No. 3

In accordance with all terms and conditions of the City of St. Joseph's current "Sewer and Sewage Disposal" Ordinance and also with any applicable provisions of federal or state law or regulations;

Permission is Hereby Granted To Boehringer Ingelheim Animal Health, Inc.

Classified by SIC No. 2836-Biological Products, Except Diagnostic Substances, 2834-Pharmaceutical Preparations.

For the contribution of wastewater into the City of St. Joseph, Missouri's lines at 2621 North Belt Highway, St. Joseph, Missouri 64502.

This permit is granted in accordance with the application filed on August 10, 1988 in the office of the Superintendent of Public Works Operations and in conformity with plans, specifications and other data submitted to the Superintendent of Public Works Operations in support of the above application, all of which are filed with and considered as part of this permit, together with following named conditions and requirements.

Effective this 15th day of May, 1990

To Expire this 14th day of May, 1993

Superintendent of Public Works Operations

No wastewater or pollutant shall be discharged which will directly or indirectly interfere with the operation or performance of the City of St. Joseph's treatment works (POTW). No wastewater shall be discharged in violation of the City's current "Sewers and Sewage Disposal" Ordinance.

Wastes containing any of the following substances in solution or in suspension in concentrations exceeding maximum permissible concentrations shall not be discharged to the city's treatment works.

Substance	Maximum Permissible Concentration	
Arsenic as As	0.045	Mg/L
Boron as B	2.50	Mg/L
Cadmium as Cd	0.018	Mg/L
Chlorinated Organic Compounds	0.02	Mg/L
Chloroform	0.50	Mg/L
Chromium (Hexavalent) as Cr*	2.25	Mg/L
Chromium (Total) as Cr*	3.24	Mg/L
Copper as Cu	1.50	Mg/L
Cyanide as CN	0.01	Mg/L
Ethylbenzene	1.50	Mg/L
Lead as Pb	0.75	Mg/L
Manganese as Mn	14.0	Mg/L
Mercury as Hg	0.15	Mg/L
Methylene Chloride	0.50	Mg/L
Nickel as Ni	0.23	Mg/L
Phenolic Organic Compounds	0.005	Mg/L
Silver as Ag	0.044	Mg/L
Sulfate as SO4	750.0	Mg/L
Sulfides as S	15.0	Mg/L
Toluene	1.30	Mg/L
Vinyl Chloride	0.003	Mg/L
Zinc as Zn	0.34	Mg/L

* The concentration is given as a maximum. In no case can the combination of trivalent and hexavalent chromium exceed the limit for total chromium.

Addendum I

Monitoring Schedule:

Boehringer Ingelheim Animal Health, Inc. will submit to the Director during the months of June and December unless required more frequently by a National Categorical Pretreatment Standard or the Director, a report containing the results of sampling and analysis identifying the nature and concentration of regulated pollutants in the discharge of each regulated process. The method for measuring the pollutants in the discharge, are outlined in the current "Sewers and Sewage Disposal" Ordinance. Specific monitoring requirements shall include those pollutants listed in this permit unless otherwise noted below.

Addendum II

Compliance Schedule:

NOT APPLICABLE! will proceed to conform with the following compliance schedule as submitted in their Wastewater Contribution Permit Application.

NOT APPLICABLE TO YOUR COMPANY!

Addendum III

Conditions of Permit

This wastewater contribution permit shall be subject to all provisions of the City's current "Sewers and Sewage Disposal" and "Sewage Treatment and Sewer User Charges" Ordinances. This Wastewater Contribution Permit shall be subject to the provisions of Section 23-78 of the City's current "Sewers and Sewage Disposal" Ordinance.

Additional conditions of this permit are listed below:

The permittee will submit a Certification Statement, estimated average daily and maximum flow measurements, written authorization (if applicable), and copies of the lab reports on Attachment A with the respective company official signatory. The information will be submitted twice a year with the June and December Semi-Annual Compliance Reports.

Permit No. 149
2

A T T A C H M E N T A

Directions

1. Indicate with an X what form of business your industry is:

   Corporation ____ Partnership ____ Proprietorship ____

2. If a Corporation has annual sales greater then $25 Mill. in 2nd-quarter 1980 dollars OR employs more than 250 people, then the facility manager may sign the certification statement.

   Numer of Employees _____ Annual Sales _____
   (1980 2nd-Quarter Dollars)

OR

3. Your Industry may elect to authorize a person or position at the facility to sign the certification statement. State the name and position of the authorized representative:

   Name _____

   Job Title _____

(Attach a copy of the written authorization signed by a corporation officer, general partner, or proprietor.)

4. State the estimated daily averate and maximum flows of the facility:

   Daily Average Flow _____

   Daily Maximum Flow _____

5. Have the authorized party sign the certification statement.

6. Attach copies of the independent lab reports and written authorization (if applicable).

7. Mail to:

   ATTN: Forest G. Parker
   Water Pollution Control
   3500 Highway 759
   St. Joseph, MO 64504

8. Call (816) 238-6031 if have any questions.

Attachment A
Page 2

Statement of Certification

I certify under penalty of law that this document and all attachments were prepared under my direction or supervision in accordance with a system designed to assure that qualified personnel properly gather and evaluate the information submitted. Based on my inquiry of the person or persons who manage the system, or those persons directly responsible for gathering the information, the information submitted is, to the best of knowledge and belief, true, accurate, and complete. I am aware that there are significant penalties for submitting false information, including the possibility of fine and imprisonment for knowing violations.

Signature of Company Official _____

Job Title _____

Company Address _____

Mailing Address _____

Street Address _____

City _____ State _____ Zip _____

This is to certify that this attachment has been completed and filed in a timely manner in accord with this APPENDIX.

N. K. Jungk
Norman K. Jungk
Director, Regulatory Affairs

Sept 27 1990
Date

OCCUPATIONAL LICENSE

City of St. Joseph, Missouri

BOEHRINGER INGELHEIM
ANIMAL HEALTH INC
2621 N BELT HWY
ST JOSEPH,MO 64506

91004425
LICENSE NUMBER

13-194
MANUFACTURER CODE

Pursuant to City Ordinances and Conditioned Upon Payment of the Required Fee or Tax Due, Subject to Audit and Zoning Requirements, License is Hereby Granted for the Term and Purpose Stated.

VALIDATION NO. 6/25/91 THIS LICENSE IS NOT TRANSFERABLE JUNE 30, 1992
THIS LICENSE EXPIRES

POST IN A CONSPICUOUS PLACE
AT LOCATION LICENSED

Not Valid Unless Countersigned By Authorized Personnel

Boehringer Ingelheim

COMPLIANCE STATEMENT:

Manufacturing operations for the Subject NADA will be carried out at the Boehringer Ingelheim Animal Health, Inc. (BIAHI) main plant location, 2621 North Belt Highway, St. Joseph, Missouri 64506. The BIAHI facilities are located on 67 acres bordered on the East, Northeast and Southeast by commercial zones and on the West, Northwest and Southwest by residential zones. The facility is supplied with all municipal utilities and sewer system. General pharmaceutical facilities and staff are described in the Drug Master File.

Waste materials resulting from manufacturing operations conducted at the St. Joseph, Missouri plant are handled in compliance with:

1) The Code of Federal Regulations Title 40 as administered by the Environmental Protection Agency, Washington, DC;

2) The Code of State Regulations Title 10 for Missouri as administered by the Missouri Department of Natural Resources, Jefferson City, MO;

3) Applicable city regulations as administered by the City of St. Joseph, MO.

See APPENDIX I for BIAHI's WASTEWATER DISCHARGE PERMIT, issued by the City of St. Joseph, Missouri, Department of Public Works Water Pollution Control.

This permit includes the maximum permissible substance concentrations allowable for discharge into the City's wastewater treatment works. BIAHI complies with all conditions of this permit and at no time discharges wastewater in violation of the city's current Sewers and Sewage Disposal Ordinance.

See APPENDIX II for BIAHI's OCCUPATIONAL LICENSE as issued by the City of St. Joseph, Missouri.

BIAHI certifies that no waste water from our plant is discharged into open bodies of water, i.e., rivers, streams, lakes or land area. As discussed above all such emission goes into the St. Joseph, Missouri municipal water treatment system. Therefore, it is our judgment that the National Pollutant Discharge Elimination System (NPDES) is not applicable to BIAHI.

BIAHI certifies that said facility in St. Joseph, Missouri is in compliance with all Federal, State and City emission requirements including those set forth as follows:

1) Missouri Solid Waste Management Law (of 1988) as implemented by the MSWML Regulation 10CSR-80.

2) Missouri Hazardous Waste Management Law (of 1988) as implemented by the MHWML Regulation 10CSR-25.

All procedures used in manufacturing the final product are conducted in a safe and responsible manner and in accord with: 1) BIAHI Chemical Hazard Communication Program. This program establishes Standard Operating Procedures enabling BIAHI to conform with Federal Regulations as set forth in 29 CFR Part 1910, as administered by the Occupational Safety and Health Administration, Department of Labor; and 2) BIAHI SAFETY POLICY, 11.02 SPPM - Policies. This policy document is an implementation document to monitor internal compliance with BIAHI safety policies to provide safe working conditions for BIAHI employees.

The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the firm or agency responsible for preparation of the environmental assessment.

N K Jungk

Norman K. Jungk
Director, Regulatory Affairs

Feb 24 1992
Date:

b. Through Use (Environmental Burden)

Erythromycin injection will be administered to cattle by intramuscular injection at a level of 4 mg/pound body weight (8.8 mg/kg body weight) once daily for 1 to 4 days. The product is used primarily when animals are stressed, such as during or immediately after shipment from one location to another. This suggests that large commercial feed lots would be the sites of worst case environmental concentrations and exposures to erythromycin.

Cattle generally enter these facilities weighing approximately 300 kg and are moved to market after finishing - a duration of approximately 136 days (Feedstuffs, 1988). Using 300 kg as an average weight for a recently shipped, treatment candidate animal, the amount of erythromycin given a single animal at the proposed new dosage is: 300 kg X 8.8 mg/kg = 2640 mg/animal/day. Over a four day treatment period the total dose administered is, therefore, 10560 mg.

The nutritional intake of an average 300 kg feedlot animal is approximately 65 pounds of water and 14 pounds of dry matter per day (NAS/NRC, 1984). Using these values, an estimated average of 52 pounds (24 kg) of waste per animal is produced per day. The normal drug treatment regimen is four days and the drug is essentially eliminated within six more days (ten day overall period).

When injected intramuscularly at a dose of 4 mg/lb body weight, erythromycin has a plasma half-life of about 5 hours and a maximum blood concentration of approximately 3 mcg/mL. At 6-7 hours after administration the highest concentrations are detected in the liver followed by kidney at 9-10 hours and fat at 10-11 hours. This agrees with information in literature which indicates erythromycin is readily concentrated in the liver and greater than 60% of the dose is eliminated from the animal in bile (Huber, 1977; Kurylowicz, 1976). However, as a worst case scenario the

assumption is made that 100% of the drug is excreted intact by cattle during this ten-day period of time.

The concentration of erythromycin in the manure of one treated 300 kg animal is shown in the following calculation:

$$\frac{2640 \text{ mg} \times 4 \text{ days}}{24 \text{ kg waste/day} \times 10 \text{ days}} = 44 \text{ mg erythromycin/kg animal waste} = 44 \text{ ppm}$$

Manure is typically not removed from the feed lot more than once per feedout period, so the expected concentration of erythromycin residues in feedlot manure can be calculated. These calculations assume uniform mixing of the dose into the total amount of manure eliminated by one animal during the feedout period.

Over 136 days an average finished weight animal (455 kg) excretes 7,727 kg waste; therefore, the total amount of erythromycin in one animal's waste:

As is basis: $\frac{10560 \text{ mg}}{7{,}727 \text{ kg waste}} = 1.4 \text{ mg/kg waste} = 1.4 \text{ ppm}$

Dry matter basis: (waste is 80% water) $\frac{10560 \text{ mg}}{1{,}545 \text{ kg}} = 6.8 \text{ mg/kg} = 6.8 \text{ ppm}$

This concentration of erythromycin is diluted by 50% by the waste contribution of each untreated animal cohabitating with each treated animal during the ten day period in which erythromycin is being excreted by the treated animal. Residue concentrations are diluted further by the waste contributions of treated and untreated animals for the remaining 126 days of the feed out period.

Feedlot Runoff

Feedlots normally allot an area of 200 square feet per animal (Dyer and O'Mary, 1972). Projecting that an average of two inches of rain will fall on this area over a 136 day feedout period, and assuming a worst case scenario where all erythromycin residues in manure are washed out by this rainfall and all rainfall runs off,

the concentration of erythromycin (ery) in runoff is calculated as follows:

200 sq. ft. space/animal X 2 inch rainfall X 1 ft./12" X 28.317 L/cu. ft. = 943.9 L runoff water/200 sq. ft. space

$$\frac{\text{10560 mg ery}}{\text{943.9 L water}} = 11.2 \text{ mg /liter} = 11.2 \text{ ppm ery in runoff water}$$

Manure as Fertilizer

Feedlot manure is spread onto fields at an average rate of 20 tons manure/acre (18,182 kg/acre) (Dyer and O'Mary, 1972). The amount of erythromycin residue per acre contributed by spreading manure is calculated as follows:

Avg. ery/kg manure (dry matter basis) = 6.8 mg/kg

18,182 kg/acre X 6.8 mg/kg = 123,638 mg = .124 kg/acre

Assuming that manure is mixed into the top 6" of soil and this amount of soil weighs 9.09×10^5 kg/acre (Goring and Hamaker, 1972) the concentration of erythromycin in agricultural soil is calculated as follows:

$$123{,}638 \text{ mg ery}/9.09 \times 10^5 \text{ kg soil} \times \frac{100 \text{ mcg}}{1 \text{ mg}} = 136.4 \text{ mcg/kg soil} = 136.4 \text{ ppb}$$

Since approval of this supplemental application is requested for cattle only, sheep and swine will be removed from the label as approved species. This represents an average reduction of erythromycin in the environment of 264 mg/animal/day for swine (60 kg body weight X 4.4 mg/kg) and 88 mg/animal/day for sheep (20 mg body weight X 4.4 mg/kg).

7. Fate of Emitted Substances in the Environment:

The fate of erythromycin in the environment is influenced by chemical parameters. A review of existing literature was performed and several studies were conducted by the sponsor to elucidate these influences. These studies were conducted in accordance with the guidelines published in FDA's Environmental Assessment Technical Assistance Handbook.

The chloroform/water partition coefficient for erythromycin is 12,587 X 10^4 at pH 7.4, indicating a high affinity for lipid, non-polar solvents (Burton and Schanker, 1974). According to literature (Merck, 1989) the solubility of erythromycin in water is approximately 2 mg/mL, which is relatively high in view of the chloroform/water coefficient. It is freely soluble in alcohols, acetone, chloroform, acetonitrile and ethyl acetate; moderately soluble in ether, ethylene dichloride and amylacetate. It has a basic reaction and readily forms salts with acids, and has a dissociation constant of 8.8.

The sorption and desorption of erythromycin were investigated with three different soil types: silty clay loam, loam, sandy loam (Appendix 2). Buffer solutions were necessary to adjust the replicate solutions to pH levels above and below that of the test article dissociation constant because the pK of erythromycin was too close to the pH range of the soil and acid hydrolysis of erythromycin in acidic soils had to be limited. Mean sorption percentages for erythromycin in silty clay loam, loam, and sandy loam at pH 8 and pH 9.5 were 83% and 81%, 49% and 47%, and 29% and 25%, respectively. Mean desorption percentages for erythromycin in the three soils at two pH levels were 22% and 38%, 45% and 71%, and 63% and 84%, respectively. The sorption/desorption tests demonstrate the mobility of erythromycin is dependent on the soil type in that erythromycin is relatively mobile in loam and sandy loam soils and immobile in the silty clay loam soil. Distribution coefficients (k_{OC}) were 256 (loam), 145 (sandy loam), and 8724 (silty clay loam).

Clay is defined as an earthy material consisting essentially of hydrated silicates of aluminum. The hydrated nature of clay would allow non-

covalent associations between the hydroxyl groups of erythromycin and the hydrated surfaces of the clay. Erythromycin contains five electron-rich hydroxyl groups which may serve as association sites for cations. Erythromycin is adsorbed only in microquantities by vermiculite and kaolinite, in high quantities in montmorillonite and in moderate amounts by illite. Assay studies of erythromycin in soils have shown that the detection level is 1 mcg/mL. The ability to recover erythromycin from soil samples is directly related to soil clay and silt content. Recovery of erythromycin in samples containing 40% silt and clay was only 36%, while in soils consisting of 96% sand, recovery was 76% (Pinck et al., 1962), which agrees quite well with data obtained from the sponsor's study. Migration of erythromycin through soils with high clay content is therefore expected to be neglible. Similarly, the impact of rainfall runoff in moving erythromycin out of clay soils and into other soil types or into aqueous environments will also be negligible. However, erythromycin residue in other soil types are more freely available for soil migration and transport via runoff, and would therefore be expected to become more widely distributed in the environment.

Aerobic biodegradation of erythromycin was studied in three soil types and the results are shown in Table 1. The patterns of CO_2 production for the soils are shown in Figures 1, 2, and 3.

TABLE 1

Half Lives for Conversion of Erythromycin to CO_2 by Soil in Days

Type of Soil = Sandy Clay Loam	Silty Clay	Silty Loam
$t_{1/2}$ = >64 days	>64 days	>64 days

Soils amended with erythromycin did not yield CO_2 production in excess of the 50% $THCO_2$ threshold value within a 64 day time frame. These negative results do not necessarily mean erythromycin will not biodegrade because as shown in Figure 1, under sandy clay loam conditions degradation may require a longer period of time. In all

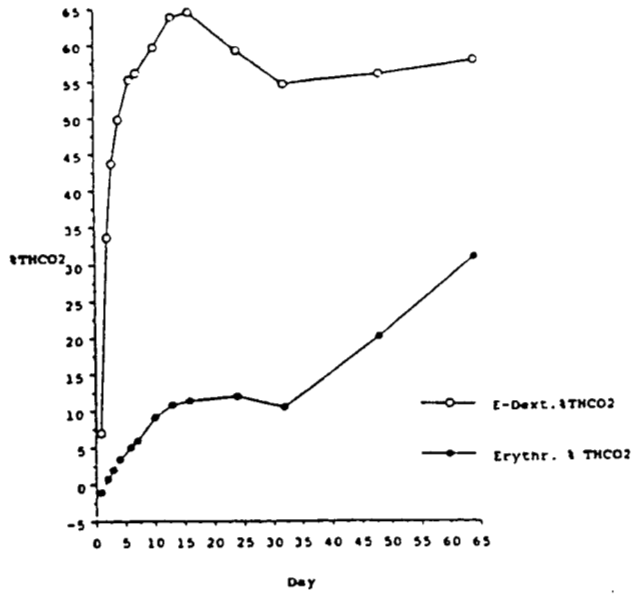


FIGURE 1

Percent of THCO2 Production for Erythromycin and Dextrose During the 64-Day Soil Biodegradation Test

SANDY CLAY LOAM SOIL

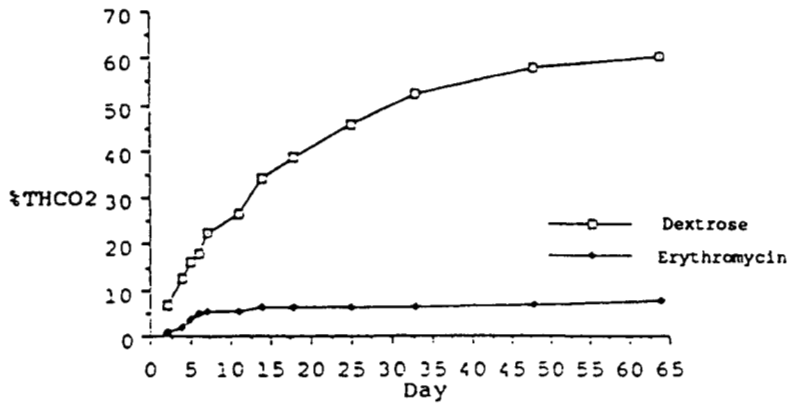


FIGURE 2

Percent of THCO2 Production for Erythromycin and Dextrose During the 64-Day Soil Biodegradation Test

SILTY CLAY SOIL

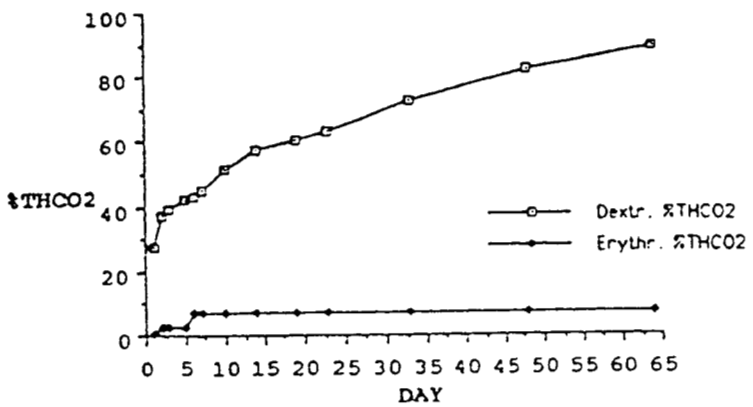


FIGURE 3

Percent of THCO2 Production for Erythromycin and Dextrose During the 64-Day Soil Biodegradation Test

SILTY LOAM SOIL

soils erythromycin underwent partial substrate mineralization by approximately day 32.

In an additional test, a bacteriological plate count was performed at the termination of the soil study which indicated a viable microbial population in erythromycin amended soil, dextrose amended soil, and in the control soil with values of 7.17 X 10^6 CFU/mL, 5.84 X 10^6 CFU/mL and 6.22 X 10^6 CFU/mL, respectively (Summaries of aerobic degradation studies are found in Appendices 3, 4, 5). Therefore, soil is neither rendered sterile by erythromycin nor is bacterial growth inhibited, and erythromycin apparently continues to be slowly degraded by the bacteria.

In aqueous solubilility studies performed by the sponsor (Appendix 6) the solubility of erythromycin in soft blended water at 22 $\pm$ 2°C was determined to be 2.29 mg/mL. However, in hard water this decreased to approximately 1.97 mg/mL. The concentration appeared to peak at approximately 24 hours and then began to decrease due to formation of the dihydrochloride salt, which is known to be water insoluble. Erythromycin as base would not be expected to distribute widely.

In the octanol/water partition study (Appendix 7) it was determined that erythromycin dissociates at pH<9.0. Therefore, due to this dissociation and due, in part, to the limited sensitivity of the analytical method the octanol/water partition coefficient was not obtainable in this study. However, Hansch and Leo (1979) determined the erythromycin partition coefficient to be 300, with a log K value of 2.48. According to these values, erythromycin would not be expected to significantly bioaccumulate (OECD, 1981).

In additional studies by the sponsor the density and relative density of erythromycin were determined to be 1.137 g/mL and 1.138 g/mL, respectively, at 25°C (Appendix 8). Since this density is greater than that of water (0.99707 at 25°C), erythromycin residues in run off will tend to settle in an aqueous environment.

Once erythromycin reaches the aqueous environment, it is subject to degradation by hydrolysis. Erythromycin hydrolysis has been studied

(Appendix 9), with degradation found to be pH dependent as shown in Table 2.

TABLE 2

Half Life of Hydrolysis of Erythromycin in Days @ 25°C.

pH	t1/2 (days)
5	0.8
7	63
9	35

Neutral solutions of erythromycin are stable for several months at 5°C but are otherwise temperature sensitive with fairly rapid degradation of erythromycin taking place at temperatures of 40°C. Data in the scientific literature indicate that loss of activity is very rapid below pH 5 (Garrod et al., 1973).

Wastes (urine and feces) from cattle are on the alkaline side of the pH range. As noted in Table 2, when the pH moves away from neutral either to the acid or alkaline side, the half life of erythromycin decreases considerably.

8. Environmental Effects of Released Substances:

Katae (1982) states that in vivo studies in which erythromycin was administered orally to fish showed the drug was readily absorbed and distributed to blood and tissues within 1 hour of administration. Peak levels were reached in 1-3 hours. The LD_{50} was 72000 g/kg body weight. Conversely, Nusbaum and Shotts (1981) stated erythromycin was poorly absorbed by catfish when added to water at concentrations of 4-32 mg/mL and reported that significant antibiotic degradation in water was observed. Jensen, et al. (1981) reported that aqueous solutions of 2 mg/L of erythromycin phosphate had no deleterious effect on fertilization or activation of salmon eggs. These reported values are greatly in excess of the calculated concentrations of erythromycin in runoff water. Therefore, although the density studies show erythromycin

residues will settle in an aqueous environment, the effects of these residues on fish would appear to be negligible.

In a study by Poels, et al. (1984) it was reported that erythromycin, when used at concentrations normally used in practice, had no inhibitory effect on the anaerobic digestion of piggery waste. Considering this with results of the bacteriological soil plate count, erythromycin residues will have no impact on normal bacteriological breakdown of manure or upon normally occurring soil bacteria. Further, erythromycin appears to have little inhibiting effect on the ability of enzymes in soils to mobilize the organic sulfur fraction. Strickland, et al. (1984) performed studies with erythromycin to determine if it shows any inhibitory effect on release of soluble organic sulfur in soils which had been previously immobilized into a nonsalt-extractable form. This study showed there was no effect.

Erythromycin is generally bacteriostatic rather than bactericidal, affecting both Gram-positive and negative bacteria. The sensitivity of bacteria to erythromycin is shown in Table 3.

TABLE 3

Sensitivity of Bacteria to Erythromycin

Gram-positive Bacteria	MIC mcg/mL	Gram-negative Bacteria	MIC mcg/mL
Str. pneumoniae	0.01-0.2	*N. gonorrhoeae*	0.04-0.4
Str. pyogenes	0.02-0.2	*N. meningitidis*	0.2-1.6
Str. viridans	0.02-3.1	*H. influenzae*	0.4-3.1
Str. faecalis	0.6-3.1	*B. pertussis*	0.2
Staph. aureus	0.01-1.6	*Brucella abortus*	10
Staph. albus	0.2-3 1	*Brucella melitensis*	0-3
C. diptheriae	0.2-3.1	*E. coli*	8-300
Cl. tetani	0.2-0.6	*Shigella spp.*	100-200
Cl. welchii	0.1-0.2	*Salmonella spp.*	100-200
Myco. kansasii	0.5-2.0	*Kl. aerogenes*	>100
Myco. scrofulaceum	0.5-16.0	*Kl. pneumoniae*	>100
Myco. fortuitum	R	*Proteus spp.*	>100
		Ps. aeruginosa	>100

(Garrod, Lambert, O'Grady, Waterworth, 4th Ed., 1973)

As shown, erythromycin is active against a wide range of bacteria at concentrations as low as 0.01 mcg/mL. In the previous example for treating feedlot cattle, the concentration of drug in animal waste after treating one animal is 1.4 mcg/g, which is generally higher than the MIC values shown above; however, after this material is incorporated into soil as fertilizer the concentration of erythromycin is greatly decreased. This, coupled with the fact that erythromycin degrades in the environment, means there will be little, if any, bacteriostatic activity remaining in the environment.

Further, erythromycin has been used as a medicant in animal feeds and in injectable form in humans and various animal species for well over twenty years with no reported bioaccumulation or effect on plants or animals.

9. Use of Resources and Energy:

The energy sources employed for the manufacturing and packaging of this product are not retrievable. These sources include gas, oil and electricity. Effects, if any, upon endangered or threatened species, or upon property listed in or eligible for listing in the National Register of Historic Places, will be minimal as a result of this action. Approval of this application will bring the dosage strength in line with the recommended NAS/NRC DESI review requirements for therapeutic blood levels. Therefore, beef production is improved because of a reduction in disease and mortality. There will be no increased demand on natural resources, such as land, energy, or water caused by the use of erythromycin.

10. Mitigation Measures:

This drug is for use in cattle requiring therapy for conditions listed on the product label. Since use of the product involves added expense to cattle raisers, the product is not expected to be used indiscriminately, and the labeling specifically states that animals are to be treated only when showing clinical signs of illness.

The manufacturers of the bulk drug substance and finished drug products are pharmaceutical plants regularly engaged in the manufacture of products for the betterment of animal health. These facilities are therefore operated with emphasis on close control of all manufacturing phases. In addition, both companies utilize comprehensive occupational health and safety programs, and assure protection for individuals handling erythromycin.

11. Alternatives to the Proposed Action:

There are no known or potential adverse environmental effects which could result from the proposed action; therefore, alternatives have not been considered.

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13. Certification:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of this Environmental Assessment.

Date: May 1, 1992

Signature: Paul W. Carr, P.E.

Regulatory Consultant
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