ENVIRONMENTAL ASSESSMENT REPORT ON BAMBERMYCINS (FLAVOMYCIN®) FOR FEEDLOT CATTLE

This section of the New Animal Drug Application follows the format as prescribed in 21 CFR 25.31a(a).

1. Date: March 1993

2. Name of applicant:

Sponsor:	Agent:
Hoechst-Roussel Agri-Vet Co.	Hoechst-Roussel Agri-Vet Co.
P.O. Box 2500	P.O. Box 2500
Route 202-206 N	Rt. 202-206 N
Somerville, New Jersey 08876	Somerville, New Jersey 08876

In the United States, Hoechst-Roussel Agri-Vet Company will be the distributor of the product and will control the premix manufacture.

3. Address:

Hoechst-Roussel Agri-Vet Co.
P.O. Box 2500
Route 202-206
Somerville, New Jersey 08876-1258

4. Description of the proposed action:

Purpose of the action. This new animal drug application is submitted for action by the Food and Drug Administration to permit the use of bambermycins (Flavomycin®) for increased rate of weight gain and improved feed efficiency in feedlot cattle.

Bambermycins is the active ingredient in Flavomycin®. Flavomycin® will be marketed as a premix (Type A Medicated Article) which will be incorporated into cattle feeds. Bambermycins has been approved for increased rate of weight gain and improved feed efficiency in feedlot cattle when fed at 10-20 mg bambermycins/hd/day.

Populations: The intended use of Flavomycin® is for cattle (steers and heifers) in feedlots. Flavomycin® will be fed continuously to steers and heifers via the feed. Studies have been conducted to demonstrate the safety of use of the product in the diets of feedlot cattle (Freedom of Information Summary - Bambermycins for Feedlot Cattle, 1993, Section 4. Target Animal Safety).

The feedlot cattle industry is concentrated in eight states in the United States: Texas, Nebraska, Kansas, Iowa, Colorado, Oklahoma, California and Arizona. In Texas, Nebraska and Kansas cattle in feedlots represent seventy percent (70%) of the cattle on feed.

The use of the premix Flavomycin®, in feeds will be limited to feed manufacturers and cattle feedlots who use the new drug in feeds which they manufacture for feedlot cattle (steers and heifers).

The use of the new animal drug will be limited to use in final feeds for feedlot cattle (steers and heifers) under the approval of this new drug application. The feeds will not contain any other drug substance. Feeds containing bambermycins will be fed continuously to feedlot cattle (steers and heifers) being fed for slaughter.

Flavomycin® will be used as a partial replacement for existing agents intended for the same purpose. The approval of this application is projected to result in partial exposure of 0.8 million feedlot cattle. It is the industry practice to incorporate a growth promotant agent in final feeds fed to feedlot cattle. Flavomycin® will provide an alternative means for increasing rate of weight gain and for improving feed efficiency.

Mode of Administration: Oral (mixed into complete feedlot cattle feeds).

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

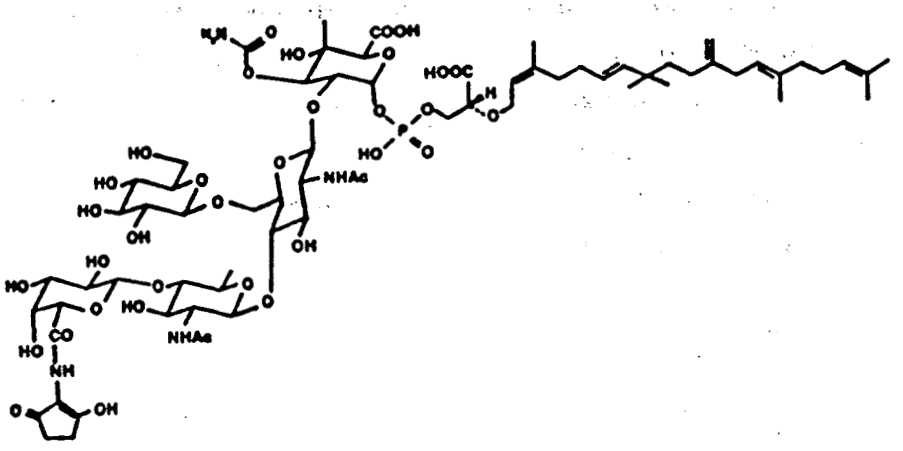
CHEMICAL/PHYSICAL PROPERTIES

The new drug is known as Flavomycin® (bambermycins) Growth Promotant Antibiotic - Type A Medicated Article.

Generic Name: Bambermycins

Chemical Abstract Service Registry No. 11015-37-5.

Bambermycins is a phosphorus-containing glycolipid which is obtained in the form of a colorless amorphous powder. The complete structure of this compound has not been elucidated. The major structural formula of bambermycins is:



Molecular Weight: 1700.

Molecular Formula: $C_{69}H_{107}N_4O_{36}P$

(C,48.5%; H,7.3%; O,37.3T; N,5.1%; P,1.8%)

Solubility: Bambermycins is soluble in water but not polar organic solvents.

Solvent	Solubility at 25°C (g/100 ml)
Water	25
Methanol	6.4
Ethanol	0.05
Acetone	0.01
Chloroform	0.01
Benzene	0.01

PRODUCT DESCRIPTION

Bambermycins is sold as Flavomycin® premix which is incorporated into the feed of feedlot cattle. Bambermycins is the active ingredient in the flavomycin premix and is produced in a dried mycelial biomass form by a fermentation process. The Flavomycin premix is sold in three concentrations: 2, 4 and 10 g bambermycins/lb of premix. In addition to the dried mycelial

biomass the Flavomycin premix may also contain diluents such as rice hulls, calcium carbonate, soybean oil and mineral oil.

ORIGIN OF BAMBERMYCINS

Bambermycins is formed by a group of grey-green streptomyces registered with the American Type Culture Collection (ATCC), comprising *Streptomyces bambergiensis* (ATCC 13879), *Strep. ghanaensis* (ATCC 14762), *Strep. geysiriensis* (ATCC 15503), and *Strep. ederensis* (ATCC 15304) and variants and mutants.
Bambermycins is produced by fermentation. The entire mycelium is dried and used in the production of the feed additive Flavomycin®.

COMPOSITION OF THE MYCELIUM

Analysis of several mycelia batches containing bambermycins yielded the following average values (on a dry matter basis): Dry matter: 96.5%

Crude protein	33.1%	Lysine	0.58%
Crude ash	13.8%	Histidine	0.38%
Crude fiber	0.97%	Arginine	1.41%
Crude fat	3.97%	Aspartic acid	2.51%
Phosphorus	0.61%	Threonine	1.15%
Sodium	1.47%	Serine	1.07%
Potassium	1.26%	Glutamic acid	3.55%
Calcium	2.99%	Proline	0.88%
Arsenic	0.00002%	Glycine	1.77%
Lead	0.0015%	Alanine	2.33%
Chromium	0.0003%	Valine	1.48%
Iron	0.033%	Methionine	1.89%
Cobalt	0.0002%	Isoleucine	0.81%
Copper	0.0017%	Leucine	1.62%
Manganese	0.0032%	Tyrosine	0.89%
Mercury	0.00001%	Phenylalanine	0.89%
Zinc	0.0079%	Cystine	0.41%

MICROBIOLOGICAL SPECTRUM

Bambermycins *in vitro* is predominantly effective against gram-positive pathogenic bacteria; in streptococci, inhibitory values in the range of 0.001 mcg/ml can be shown; and at .05 mcg/ml in staphylococci. Bambermycins is less effective against gram-negative pathogenic microorganisms with the exception of pasteurella and brucella.

MODE OF ACTION

The beneficial effects (increased weight gain and improved feed efficiency) of an antibiotic such as bambermycins are mediated through their effects on bacteria. In gram-positive bacteria, studies have shown that cell wall precursors accumulate in the presence of bambermycins; therefore, the mode of action against bacteria is inhibition of the synthesis of the bacterial cell wall.

The inhibiting effect of bambermycins against certain gram-negative bacteria that carry R factor has been shown by Watanabe[1] and others[2,3,4] to be related to the presence of sex pili. The presence of sex pili causes these bacterial to be sensitive to bambermycins when they would not otherwise be sensitive[1,2,5].

6. Introduction of substances into the environment:

Based on the use of this product, bambermycins could potentially be introduced into the following environments:

- o The environment adjacent to the fermentation plant.
- o The environment adjacent to the premix blending facility.
- o Cattle feedlots where the residues may be found in animal waste.
- o Agricultural lands where waste products from the feedlots are used as fertilizer.

Introduction of substances from the manufacturing site.

The manufacturing site for bambermycins, the active ingredient in the Flavomycin® premix, is designed to have minimal environmental impact. Bambermycins is produced by a fermentation process with a dried mycelial biomass being the final product. The dried bambermycins mycelial biomass is fermented at Hoechst AG, Frankfurt, West Germany. Hoechst AG is in compliance with all applicable emissions requirements including occupational requirements at

the federal, state and local levels (Appendix 1).

Introduction of substances from the premix blending location.

Flavomycin® premix is manufactured using operations such as mixing and packaging. This blending operation is designed to have minimal environmental impact. There are no hazardous solid wastes generated during the formulation of feed premix. Some non-hazardous solid waste is generated and will include; filters from dust collectors, used packaging components from raw materials such as paper bags and fiber drums, floor sweepings, and returned goods. Unused returned good are accepted by the St. Louis plant and are either reworked or landfilled at permitted facilities. This procedure restricts the potential introduction of the drug substances into the environment. Aqueous liquid waste may contain raw material residues, but is discharged into the Metropolitan St. Louis Sewer District for appropriate treatment. Any atmospheric emissions and disposal practices for other waste from the premix blending site for Flavomycin® complies with appropriate statues, regulations and permits. Merck and Co, St. Louis, MO is in compliance with all applicable emissions requirements including occupational requirements at the federal state and local levels (Appendix 2).

Introduction of Substances from the Feed Mixing Locations.

Virtually all feed mixing would be done by feedlot companies that use Flavomycin® premix. The feed mixing locations must comply with current Good Manufacturing Practices for medicated feeds. With the required manufacturing controls for feed, inventory accountability and quality assurance procedures the potential for release of bambermycins into the environment at these locations would be negligible. There are no special types of manufacturing or occupational controls required by the feed mixing locations to reduce the potential release of bambermycins into the environment.

Introduction of Substances from the Use Site.

Most feedlot cattle are fed in the states of Texas, Colorado, Kansas, Nebraska, Oklahoma, Iowa, California and Arizona. Flavomycin® would be marketed directly to these feedlot companies. Any Flavomycin® entering the environment will be via cattle manure and will be introduced into soil by use of cattle manure as fertilizer (see preliminary study, Appendix 3).

Degradation studies in four soil types, one of which contained cattle manure, demonstrated that bambermycins degraded with time. From bioassay analysis, the half-life of bambermycins ranged from 13.3 to 28.0 days for the four soil types. By day 55 of the study, degradation of bambermycins ranged from 72.0 to 98.5 percent for the four soil types. Therefore, environmental exposure at the use site would be negligible from manure from cattle consuming bambermycins because of random dispersion on the land and because of rapid degradation in the soil (Appendix 4).

ESTIMATE OF QUANTITIES ENTERING ENVIRONMENT

Bambermycins is essentially not metabolized in the gastrointestinal tract and is excreted as the intact antibiotic in the cattle feces. This calculation assumes a feedlot of one acre in area, populated by 217 hd. of cattle. These 217 hd. are fed bambermycins at the rate of 20 mg/hd/day for 140 days. It is assumed that the daily excreta from the animals will be a total of 27.2 kg of waste per animal. Thus, each 27.2 kg of waste will contain 20 mg bambermycins (0.735 ppm)[6,7].

Concentration in water run-off from feedlot:

During the feeding period there will be 2 inches of rainfall. Two inches of rainfall weighs 205,500 kg/acre. The total amount of bambermycins excreted in 140 days by 100 animals equals:

217 animals x 20 mg/animal x 140 days = 608 grams

Bambermycins is soluble in water, therefore it is theoretically possible to have all of the residue in the run-off. The maximum concentration of bambermycins in the run-off assuming no degradation equals:

$$\frac{\text{608 grams}}{\text{205,500 kg of water}} = \text{2.96 mg/kg (2.96 ppm)}$$

Concentration in soil due to fertilization with waste from treated cattle.

The following assumptions can be made:

- o No degradation in the manure before applying to the soil.
- o Manure is added to the soil at the rate of 20.0 metric tons per acre. Amount of bambermycins in 20 metric tons equals 14.705 grams.

  (20 mg bambermycins/27.2 kg manure per day) X 20,000 kg per acre = 14.705 gm bambermycins in 20 metric tons manure or 0.735 mg/kg manure.

- o The manure will be incorporated into the top 6" of soil (weight of the top 6" of soil in one acre equals 909,000 kg).

  **The amount of bambermycins in the top six (6) inches of soil would equal:

Drug conc. = in soil (mg/kg)	Drug conc. in manure (mg/kg)	X	Kg manure applied to soil / acre of soil	X	acre of soil / kgs in top 6" of soil

Drug conc. = 0.735 ppm in soil	X	20,000 kg manure / 1 acre	X	acre / 9.09×10^5 kg	=	.016 mg/kg (16 ppb)

As indicated by the above calculations, the amount of bambermycins (assuming no degradation) that would be released into the soil and water run-off is extremely small.

Toxic substances. There is no pollution of the environment in the manufacture, processing, and use of the new animal drug with heavy metal, pesticides, or radiation (Appendices 1 and 2).

7. Fate of emitted substances in the environment:

The primary manner in which bambermycins would be introduced into the environment is through cattle manure collected from a cattle feedlot and applied to agricultural crop land. Any active bambermycins released into the environment is rapidly degraded (Appendix 4).
No other biologically active or hazardous components are contained in the dried mycelial biomass. Additionally, bambermycins should not have adverse effects even when fed at levels up to 1,000 times the recommended dose (Freedom of Information Summary - Bambermycins for Feedlot Cattle, 1993). The low level of bambermycins (10-20 mg/hd/day) being fed to feedlot cattle results in low levels of residues in cattle manure (0.735 ppm).

Any Flavomycin® entering the environment will be via cattle manure and will be introduced into soil by use of cattle manure as fertilizer.

The rate at which bambermycins undergoes degradation was investigated in four different soil types. Degradation studies involving the four soil types, one of which contained cattle manure, demonstrated that bambermycins degraded with time. The bambermycins concentration was monitored on days 0, 6, 13, 20, 27, 33, 41, 48 and 55 using a microbiological assay method.

From the bioassay analysis, the half-life of bambermycins ranged from 13.3 to 28.0 days for the four soil types. By day 55 of the study, degradation of bambermycins ranged from 72.0 to 98.5 percent for the four soil types. Therefore, environmental exposure at the use site would be negligible from manure from cattle consuming bambermycins because of random dispersion on the land and because of rapid degradation in the soil (Appendix 4).

8. Environmental effects of released substances:

Given the information developed in Items 6 and 7 above, it can be predicted that there will be no negative effects on animals, humans, other organisms, and no effects at the ecosystem-level.

9. Use of resources and energy:

Natural resources. Manufacturing Flavomycin® premix will require an amount of energy similar to that used to produce and package any conventional fermentation product. The disposal of

waste wash water and materials from the manufacturing process will not require the use of unusual amounts of natural resources. No irreversible and irretrievable commitment of resources will be involved if the proposed action would be implemented.

Energy. The indirect effect of approval of this NADA will be a saving of energy by reducing the amount of feed needed to finish cattle (steers and heifers) in the feedlot.

Environmental impact of the manufacturing process.

1. An outline of the manufacture of the product is included in (section 5) of the NADA. The synthesis of the new drug substance is contained within the manufacturing facility.

2. The article will be manufactured in GERMANY. Pre-mix operations will be conducted within the United States, and such operations will be in full compliance with federal, state, and local emission requirements. The pre-mixing operation is expected to be contained and there is no waste products produced.

3. The sponsor of this new animal drug application certifies that any emissions resulting from the manufacture of the article will be in full compliance with the appropriate regulations of the country of manufacture. Pre-mix operations will be in full compliance with federal, state, and local emission requirements (Appendices 1 and 2).

10. Mitigation measures:

In light of the data presented above, no mitigation measures are necessary. The use of Flavomycin® premix for feedlot cattle will not have any adverse effects on human health or the environment. No mitigation measures are necessary for Flavomycin® premix.

There are no known significant adverse environmental effects related to the manufacture and use of the new animal drug. The drug has been produced for use in cattle, poultry and swine in over 25 countries, and over nearly 25 years without reported adverse environmental effects.

11. Alternatives to the proposed action:

The only alternative to approval of the New Animal Drug Application, is non-approval. This

would mean that the feedlot cattle industry would not have the choice of use of this drug.

This drug will have the effect of providing an alternative means for increasing rate of weight gain and for improving feed efficiency in feedlot cattle.

No objections have been raised by an agency, organization, or individual. The drug has a history of safe manufacture and use in many countries including the United States. It has been authorized by the government of Germany for manufacture, and has been authorized for use in European Economic Community countries since 1968. Bambermycins has been used without incident for broiler chickens, turkeys and swine in the United States since 1975.

It is the sponsor's position that this action will not require the preparation of an environmental impact statement. It is the sponsor's belief that there is no significant risk associated with the proposed action. We have demonstrated in the application the usefulness of bambermycins in increasing rate of weight gain and in improving feed efficiency in feedlot cattle (steers and heifers). The significant benefits of approval of this NADA far outweigh the potential risks. This new animal drug application contains analytical methods for bambermycins in tissues and soil. It is concluded that the use of Flavomycin® premix for feedlot cattle will not have any adverse effect on human health or the environment. Therefore, alternatives to the proposed action do not need to be considered.

12. List of preparers:

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13. Certification

The undersigned petitioner certifies the information furnished in this Environmental Impact Analysis Report to be true, accurate and complete to the best of his knowledge.

DATE: 3-8-93

Lawrence E. Deetz, Ph.D.

Lawrence E. Deetz, Ph.D.
Research Nutritionist

14. References:

[1]Host cell changes induced by R. factors and other sex factors. T. Watanabe, Y. Ogata, K. Sugawara, K. Oda, T. Saito, Y. Yokoyama. 6th Miles Internat'l Symposium on Molecular Biology (June 1972).

[2]Die Wirkung von Flavomycin auf episomal resistente Keime. G. Lebek, Abl. Vet. Med. 19: 532 (1972).

[3]The effect of Actinomycin D and Flavomycin on *E. coli* R+ strains. H. Brana, J. Hubacek and J. Konig. Folia Microbiol 18: 257-262 (1973).

[4]Inhibitory effect of Flavomycin as a feed additive on R factors in *E. coli* strains isolated from pig weanlings. A. Sokol, V. Kremery, F. Federic, V. Rajtar, J. Janouskova. Eighth international Congress of Chemotherapy (1973).

[5] Additional antibiotic inhibitors of peptidoglycan synthesis. P.E. Linnet, J. L. Strominger, Antimicrob. Agents Chemotherapy 4 (3): 231-236 (1973).

[6]The Feedlot. I. A. Dyer and C. C. O'Mary, Lea & Febiger, p. 154 (1972).

[7]"1977 Agricultural Engineers Yearbook." American Society of Agricultural Engineers, St. Joseph, MO., p 503 (1977).

15. Appendices:

1. Environmental Assessment from Hoechst Aktiengesellschaft, producer of bambermycins.
2. Flavomycin Feed Premix Environmental Assessment Supplement from Merck & Co., Inc.
3. Faecal excretion of Flavomycin in beef cattle, Trial report No. B 506 (preliminary study).
4. Bambermycins Biodegradation in Soils, SLI Report No. 92-4-4234, and Bioassay for Bambermycins Biodegradation in Soils, SLI Supplemental Report No. 93-2-4640.