

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 012-123

B. Sponsor

Sanofi Animal Health, Inc.
7101 College Blvd., Suite 610
Overland Park, KS 66210

C. Proprietary Name

GALLIMYCIN (Erythromycin)INJECTION, 200 mg/mL

D. Established Name

erythromycin

E. Pharmacological Category

Anticoccidial, antimicrobial, antiparasitic, etc.

F. Dosage Form

Sterile solution

G. How Supplied

Size and Description of container

H. Dispensing Status

OTC

I. Route of Administration

Intramuscular injection only

J. Indication

Indicated for bovine respiratory disease (shipping fever complex and bacterial pneumonia) associated with *Pasteurella multocida* susceptible to erythromycin.

K. Effect of Supplement

One supplemental application is a Category II change in dosage which was initiated in order to bring the drug product into compliance with the National Academy of Science/National Research Council- Drug. Efficacy Study Implementation (NAS/NRC/DESI) recommendations. The other supplemental application is a

Category II change in tolerance for drug residues from zero to 0.1 ppm for beef tissues.

II. EFFECTIVENESS

NADA 012-123 was originally approved as safe for use as labeled on March 22, 1960. The drug was the subject of National Academy of Sciences/National Research Council/Drug Efficacy Study Implementation (NAS/NRC/DESI) reports which were published in the **FEDERAL REGISTER** of August 18, 1970: The Academy evaluated these products as probably effective in the treatment of certain diseases in cattle, sheep, swine, horses, dogs, cats, chickens, and turkeys. The Academy stated:

- a. Each disease claim should be properly qualified "appropriate for use (name of disease) caused by pathogens sensitive to (name of drug)", and if the disease claim cannot be so qualified the claim must be dropped.
- b. Claims made regarding "for prevention of" or "to prevent" should be replaced with "as an aid in the control of" or "to aid in the control of."
- c. The dosage in large animals and frequency of administration in all species need to be documented - the dosage should be expressed on the basis of milligrams of erythromycin per pound of body weight.
- d. The resistance statement and statements claiming more effectiveness than other microbial agents need to be deleted.
- e. Certain items in the labeling need revision, including withdrawal times, cautions, misleading association of sensitivity statement and certain diseases and the recommended use as an aid in curtailing weight losses due to handling and transporting cattle.
- f. Directions for use should provide for administering the preparation with sterile equipment.
- g. Directions for lay use are inadequate.

The Food and Drug Administration concurs with the Academy's findings; interpreting the phrase "...cannot be so qualified ..." in paragraph (a.) to mean "...is not supported by adequate data..." FDA then proceeded to review all available data relating to the effectiveness of products subject to NADA 012-123 to determine which label claims were supported by the requisite proof of effectiveness. That review resulted in a letter dated January 21, 1976, addressed to the firm, in which the agency stated that it had concluded that data supported effectiveness for the/ treatment of bovine respiratory disease only.

Thereafter, the sponsor complied with the evaluation of NAS/NRC and the FDA's conclusions in the following manner:

1. The disease claim has been qualified as to the causative pathogen which is susceptible to erythromycin. All other disease claims and several animal species have been deleted from the indications for use.
2. The labeled indications have been revised to read, "For the treatment of bovine respiratory disease (shipping fever complex and bacterial pneumonia)..." instead of "Is indicated for prompt and effective treatment of conditions resulting from infections caused by organisms..."
3. The dosage and frequency of administration in cattle has been documented. On January 21, 1976, the Center for Veterinary Medicine determined the efficacy portion of the application to be complete by virtue of the fact that bioavailability and comparability data submitted adequately demonstrated that sufficient drug levels were maintained at a dosage of 4 mg per pound body weight administered daily for up to 5 days.
4. The labeling has been revised to delete the resistance statement and statements claiming more effectiveness.
5. The labeling has been revised to include appropriate withdrawal times and cautions, and to delete the other items mentioned above.
6. The directions for use have been revised to include the precautions to administer the preparation with sterile equipment.
7. Adequate directions for lay use for administering this drug by the intramuscular route are included.

III. TARGET ANIMAL SAFETY

NADA 012-123 was originally approved as safe on March 22, 1960. Safety of this product is also substantiated by the absence of any adverse effects reported in three new studies: a bioequivalency study, and the treatment periods of a milk residue study and a tissue residue study.

During these three studies, 24 animals were given two separate injections 14 days apart, five animals were given three consecutive daily injections and 18 animals were given five consecutive daily injections. The injections were given intramuscularly in the leg or neck at a dose of 4 mg/lb. body weight. Transient reactions such as injection site swelling were observed over a few days following these injections, but no evidence of hemorrhage, fibrosis, or necrosis was externally observable.

Gross histopathological examination was made of tissues at and surrounding the injection site following intramuscular injections to 18 cattle of 6.5 ml to 8.8 mL/site of GALLIMYCIN INJECTION. These animals were each given a single daily injection for five days. Three animals per time period were then sacrificed at 6, 12, 18, 24, 36, and 48 hours post-last dose (injection #5). Injection site #3 was excised for examination. Gross inspection revealed that injection site lesions were variable in size with approximate average dimensions of 1.25 cm diameter X 2.9 cm deep. Injection site lesions were characterized by a central core of muscle tissue, tan-gray to gray in color and surrounding this central area of discoloration was a dark red zone of more normal appearing muscle with obvious areas of hemorrhage.

Histopathological examination revealed a central core of acutely necrotic muscle fibers. Surrounding this central core was a zone of muscle fibers in various stages of degeneration characterized by mineralization of the sarcoplasm. Livers and kidneys were examined grossly and histopathologically with no unusual or unexpected observations reported.

Results of these studies indicate that a cautionary label statement concerning the trimming of cattle tissues during the dressing process is necessary based on the withdrawal period for the product.

IV. HUMAN FOOD SAFETY

A. Name and Address of Investigator

Bio-Labs, Inc.
132 Las Cruces Ave.
Las Cruces, New Mexico 88001
Dr. John H. Kinzell

B. Tissue Residue Depletion Studies

A single tissue residue depletion study was conducted in cattle to determine the residues of erythromycin following the administration of GALLIMYCIN INJECTION. The dosage regimen was: intramuscular injection at 4 mg/lb. of body weight for five consecutive days. Residue determinations were made at 6, 12, 18, 24, 36 and 48 hours post last-dose. Three animals were sacrificed at each time period and tissues were excised for erythromycin assay.

Table 3. ERYTHROMYCIN RESIDUES IN TISSUES (PPM)

Hours Post

Injection	Kidney	Liver
6	1.90 (+ 0.39)*	6.13 (+ 4.36)
12	2.90 (+ 1.05)	3.88 (+ 3.14)
18	1.03 (+ 0.54)	4.31 (+ 2.68)
24	0.89 (+ 0.81)	0.82 (+ 0.69)
36	0.18 (+ 0.07)	0.12 (+ 0.02)
48	0.17 (+ 0.05)	0.13 (+ 0.08)

*standard deviation

Residues at the injection site depleted slowly. However, using a conservative 30-hour half-life, residue at the injection site will deplete to a consumption adjusted tolerance of 1.0 ppm within 6 days. Muscle remote from the injection site was less than 0.075 ppm at 48 hours. A withdrawal period was calculated by a statistical procedure based on the kidney depletion data from this study. Using the 99% statistical tolerance limit with 95%

confidence procedure on the residue depletion data for erythromycin in edible tissues, it was determined that a 6-day withdrawal period for cattle treated with up to 4 mg per pound body weight would be acceptable (less than 0.1 ppm erythromycin).

Temporary tissue irritation follows injection. To avoid excessive trim, cattle should not be slaughtered within 21 days of last injection.

Regulatory Method for Tissue Residues

The regulatory analytical method for detection of residues of erythromycin is a microbiological test using *Micrococcus luteus* suspension. This method has been approved by the Food and Drug Administration and was fully validated by the research laboratory. The method is capable of measuring residues of erythromycin at the tolerance level of 0.1 part per million for edible tissues. The supplemental application providing for the revision of the tolerance from "zero" to 0.1 ppm reflects the change in FDA policy regarding the concept of residue tolerance. No new toxicity data were used to revise the tolerance because 0.1 part per million is equivalent to the tolerance level that would have been established when the drug was originally approved (March 22, 1960). Furthermore, this tolerance is consistent with data supporting the published tolerance of 0.1 ppm in uncooked edible tissues of swine.

Under the-zero tolerance concept, no detectable residues of a new animal drug were permissible in edible tissues of treated food animals when tissues were assayed using available analytical methods. However, as analytical technologies advanced, methodologies became increasingly sensitive and capable of measuring progressively smaller amounts of drug residues in tissues. Thus, residues which were not detectable using older, less sensitive methods (i.e., zero residues) began to be found using the more advanced analytical methods. Therefore, FDA adopted the concept of maximum negligible, or permissible, residues which reflect the lower level of quantitative sensitivity of the official regulatory analytical method. For erythromycin, this level is 0.1 part per million.

The validated regulatory analytical method for detection of erythromycin residues is filed in the Food Additives Analytical Manual on display in FDA's Freedom of Information Public Room (Room 12A-30), 5600 Fishers Lane, Rockville, MD 20857.

V. AGENCY CONCLUSIONS

The DESI finalization supplemental NADA satisfies the requirement of section 512 of the Act and demonstrates that GALLIMYCIN INJECTION, 200 mg/mL, when used in accordance with its proposed conditions of use, is safe and effective for the labeled indications. The approval provides for use of GALLIMYCIN INJECTION, 200 mg/mL for the treatment of bovine respiratory disease (shipping fever complex and bacterial pneumonia) associated with *Pasteurella multocida* susceptible to erythromycin.

The "probably effective" finding of the NAS/NRC/DESI regarding Erythromycin which was published in the FEDERAL REGISTER of August 18, 1970 was subsequently reviewed by FDA, resulting in a January 21, 1976 letter to Sanofi. NADA 012-123 was upgraded to "effective" status with respect to the claim noted in the previous paragraph. The firm submitted revised labeling to conform to the letter and, therefore, this supplemental NADA complies with the NAS/NRC/DESI evaluation and FDA's conclusions.

GALLIMYCIN INJECTION, 200mg/mL for use in food-producing animals is currently on the market as an over-the-counter product. When the NADA was reviewed under NAS/NRC/DESI program, it was an over the-counter product and this marketing status remains unchanged. Therefore, the Center for Veterinary Medicine has concluded that this product should retain over-the-counter marketing status.

Additionally, the supplemental application providing for revision of the tolerance from "zero" to 0.1 ppm for cattle is acceptable and is approved.

Under the Center's supplemental approval policy (21 CFR 514.106(b) (2) these are Category II changes. The approval of these changes are not expected to have any adverse effect on the safety of this new animal drug and, therefore, did not require a re-evaluation of the human food or target animal safety data in the parent application.

Under the Generic Animal Drug and Patent Term Restoration Act of 1988, these approvals do not qualify for an exclusivity period under section 512(c)(2)(F)(iii) of the Federal, Food, Drug, and Cosmetic Act (21 U.S.C.360b(c) (2) (F) (iii)) because the supplemental applications do not contain reports of new clinical or field investigations (other than bioequivalence or residue studies) and in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) essential to the approvals and conducted or sponsored by the applicant.

VI. ATTACHMENTS

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

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