July 12 , 1977

ENVIRONMENTAL ASSESSMENT OF
A REGULATION ENTITLED
GENTAMICIN SULFATE INJECTION
IN DAY-OLD CHICKENS

The environmental assessment for this action has been accomplished on the basis of a complete Environmental Impact Analysis Report. It is concluded that the proposed action will not have a significant impact on the quality of the human environment and that an Environmental Impact Statement is not needed.

Thomas V. Raines

Thomas V. Raines, D.V.M.
Primary Action Officer

Kenneth E. Taylor

Kenneth E. Taylor, D.V.M.
Director,
Environmental Impact Staff

Enclosures:
Environmental Impact Analysis Report
Environmental Assessment Report

Environmental Assessment Report of a
Regulation Entitled Gentamicin Sulfate
Injection in Day-Old Chickens

A. Summary of Action

Schering Corporation is requesting approval for the use of gentamicin sulfate injection for the prevention of early mortality in day-old chickens caused by Escherichia coli, Salmonella typhimurium and Pseudomonas aeruginosa susceptible to gentamicin sulfate. Each day-old chicken is injected subcutaneously in the neck with Garasol to provide 0.2 mg gentamicin in a 0.2 ml. dose. The trade name of the product is Garasol.

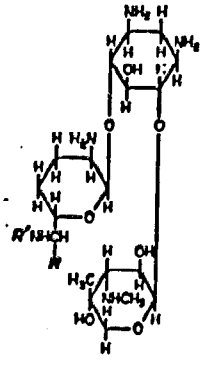
A warning statement precludes its use except in day-old chicks and provides that Garasol injected chicks must not be slaughtered for at least 5-weeks following treatment.

The environmental effects of the proposed action have been considered pursuant to Section 21 CFR 25.1 (b)(9), and it is concluded that there will not be a significant effect on the quality of the human environment and that an Environmental Impact Statement is not required.

This conclusion is based upon data contained in the Environmental Impact Analysis Report and additional related data, all contained in the June 20, 1977 submission. This report is complete in that it lists all the effects likely to occur and is accurate in that it describes the expected environmental impacts within the limits of existing knowledge.

B. Evaluation

The structural formula for gentamicin is:



Gentamicin	R	R'
C_1	CH_3	CH_3
C_2	CH_3	H
C_{1a}	H	H

The molecular weight of gentamicin varies because it is a complex of three components, sulfates of gentamicin C_1, gentamicin C_2 and gentamicin C_{1A} in variable amounts. Generally gentamicin C_1 sulfate is 722, gentamicin C_2 sulfate is 708 and gentamicin C_{1A} sulfate is 694.

Gentamicin sulfate in aqueous solution as a GARASOL Injection for chickens has a pH of 3-5.

Based on available stability, GARASOL Injection for chickens is stable for 24 months.

Gentamicin sulfate is an aminoglycoside antibiotic, derived from a naturally occuring fungus, Micromonospora purpurea, originally isolated from a domestic soil sample. It is highly soluble in water and insoluble in an oil-water system. Upon equilibration in an oil-water system, negligible distribution into the organic (oil) phase occurs.

Gentamicin sulfate is active against both gram positive and gram negative bacteria. Its in vitro activity is documented (In Vitro Activity of Gentamicin Against Bacteria Isolated from Domestic Animals, 1971, Hennessey et al V.M./S.A.C. p.1118-1221).

A one-day old chick receives a single dose of 0.2 mg of gentamicin; therefore, the maximum excretion possible is 0.2 mg/bird. The majority of the drug is excreted in the droppings the first few days of life though extremely small (immeasurable) amounts may be excreted up to 5-weeks.

There is little known about metabolites detected after parenteral administration of gentamicin or other aminoglycosides. It is generally accepted that aminoglycosides are excreted in active form.

In studies done by Waitz and Weinstein, gentamicin serum levels in dogs were assayed by three different methods -- microbiological, radioimmunoassay, and C^{14} radioactive assay. Serum levels determined by the three different methods were identical which indicates no metabolism of gentamicin occurred. Levels of gentamicin in urine determined by radioimmunoassay and microbiological assay were similar

by both assay methods which further confirms lack of metabolites. Reference: Schering P 44400 - attached.

Common practice is to grow chickens on .75 square foot of litter covered floor space per chick, eg. wood shavings, and then spread the manure at a maximum of 5 tons per acre. There would be 300 mg or less of gentamicin per acre. Common practice of plowing or discing the manure into the top 6 inches of soil would distribute the 300 mg of gentamicin into 909,000 kg. of soil. The maximum concentration of gentamicin in soil would be 0.3 mcg/kg (ppb) which is approximately 1000 fold below any detectable level.

Calculations are:

Weight of top 6" soil/acre = approx. 2,000,000 lbs. = 909,000 kg.
M.L. Jackson. Soil Chemical Analyses. Practice-Hall, Inc.; Englewood Cliffs, N.J.

Figuring the worst possible situation, e.g., if there were no litter on the floor to dilute the feces and the drug were not bound to the feces the following calculations are made:

A broiler chicken from 1 day of age to marketing at approximately 8 weeks of age produces approximately 8 pounds of manure; therefore,

5 tons per acre = 10,000 pounds per acre.

$$\frac{10,000 \text{ pounds}}{8 \text{ pounds (manure per bird)}} = 1250 \text{ birds to produce this amount of manure to fertilize 1 acre.}$$

1 bird receives .2 mg. of drug. If it all came out in the feces 1250 birds would produce approximately 250 mg. of gentamicin.

$$\frac{250 \text{ mg gentamicin}}{909,000 \text{ kg soil}} = .275 \text{ mcg (ppb) gentamicin/kg soil}$$

Studies showed that 98% of gentamicin added to the soil was adsorbed, and less than 2% could be extracted.

There is no cumulative adverse effects upon the environment. Ninety eight percent or more of an applied concentration of gentamicin was immediately adsorbed to soil colloids. The adsorbed gentamicin is not extractable by routine assay and did not show evidence of antibacterial activity against highly sensitive bacteria. Over a period of 31-days, the percent of free gentamicin recovered from non-sterilized and presterilized soil samples was reduced by 43% and 37% respectively.

The use of this product would not affect animal waste excreted. The excreted drug quantity (1000 fold below any detectable level) would not be expected to have any adverse effect upon any aspect of the environment including land, water supplies, wild life, plants and man.

Garasol is utilized in human medicine. Therefore, data were submitted on the transfer of drug resistance among bacteria exposed to gentamicin sulfate. The firm's data on the effect of Garasol injection on the antibiotic sensitivity patterns of E. coli isolates of chicks were evaluated. Treatment of chicks as recommended with Garasol Injection did not result in increased resistance to any of the 6 antibiotics against which it was tested. These were gentamicin, tetracycline, neomycin, kanamycin, dihydrostreptomycin and penicillin. The Agency, therefore, concludes that under the proposed use that Garasol is safe. It does not select for or promote coliform resistance to antibacterials. (See attached data in E.I.A.R. and Dr. Joseph Gainer's evaluation of these data).

The Bureau of Foods has evaluated 90-day rat and dog toxicity data, and they conclude that the no effect level in both rat and dog is 60 mg/kg of body weight. (see also attached F.O.I. Summary). The proposed action is not expected to adversely affect, human, plant, or animal populations at levels of exposure likely to be encountered. The highest level of exposure from gentamicin in soil is 0.3 mcg./kg (ppb) is 1000 fold below the detectable level.

The following is cited:

Sensitivity of Environmental Microorganisms to Antimicrobial agents by P. Van Dijck and H. Van De Voorde published in Appl. Environmental Microbiology, 332-36 March 1976. In this paper sensitivity of different microorganisms considered as typical representatives of microflora of soil and water were tested against gentamicin and 22 other antibacterials. Dilutions were made to 1 mcg./ml. for the sensitivity testing. Practically, dilutions to 1 and 0.1 mcg/ml are performed but the firm could not locate any dilution factor below. Dr. Van Dijck states that 1 mcg/ml is 10-100 times lower than the MICs of strains with ecological importance.

It is recognized that:

Toxicity of gentamicin to algae, fish or soil organisms such as earthworms was not determined. Phytotoxicity was not determined.

Such determinations are not considered necessary since gentamicin will not come in contact with aquatic organisms, soil invertebrates or plants. Calculated possible gentamicin concentration in the soil is 0.3 mcg/kg (0.3 ppb). In sensitivity testing by tube dilution methodology, it is impractical to dilute to ppb. Concentrations by tube dilution sensitivity testing may reach 1 mcg/ml which is in ppm.

The new drug substance is manufactured in Puerto Rico. A small portion of the raw materials used in the manufacturing of gentamicin sulfate will be ultimately discharged into the ecosphere. The air discharge consists mainly of carbon dioxide with minute traces of chloroform. Remaining liquids and soilds are degradable and are returned to the environment. The liquids are barged 40 miles to the ocean under an Interim Barging Permit No. II-PR-104 which covers Spent Broth Wastes from the Environmental Protection Agency. The solids are disposed of by dumping in a sanitary land fill in an approved manner. The organic portion of the bioproducts are ultimately returned to the natural pool of carbon dioxide and ammonia. This is in compliance with appropriate emission certifications for boilers and the fermenters as covered by the Approved Envrionmental Quality Board (Puerto Rico) Annual Inspection (1976). Manufacture of the final dosage form involves no impact on the environment. No pollutants result from preparation of the dosage form.

It is estimated that the production of gentamicin sulfate in Puerto Rico for this product -- GARASOL Injection for Chickens -- will consume about 0.6% of the fuel used at that manufacture site per year. The small portion of manufactured gentamicin destined to become this marketed product is in this respect considered of insignificant proportion and will not require additional energy beyond that presently allocated.

The firm is in compliance with the November 1976 fermentation regulations. The manufacturing process for gentamicin sulfate involves only Puerto Rico. The firm is in compliance with the document published in the Federal Register, Vol. 41, No. 223, November 17, 1976 -- Part 439 - Pharmaceutical Manufacturing Point Source Category pertaining to Fermentation Products.

There are no known public objections to the use of gentamicin sulfate injection in day-old chicks.

Considerable overall benefits will accrue from the use of gentamicin sulfate injection in exchange for little or no local effects due to manufacture of the product. The injection of gentamicin sulfate in day-old chickens causes better livability (see attached FOI Summary) and thus makes more chicken protein available as a source of human food. In the long run this means feeding of larger numbers of people without increasing the environmental burden resulting in the production of feed and energy.

The drug is highly active against the claimed bacterial infections (see attached FOI Summary).

The data submitted are sufficient to permit the determination of potential impacts. We have concluded from the data that an Environmental Impact Statement is not required.