Date of Approval _____

FREEDOM OF INFORMATION SUMMARY

For the removal of large roundworms (*Ascaridia spp*.) from turkeys, chickens, and large roundworms (*Ascaris summ)* and nodular worms (*Oesophagostomum spp.) from swine.*

Fleming Laboratories
Charlotte, NC 28234

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

NADA Number	10-005
Sponsor:	Fleming Laboratories Charlotte, NC 28234
Generic Name:	Piperazine dihydrochloride Piperazine dipiperazine sulfate
Trade Name:	Wazine®, Pig Wormer
Marketing Status:	OTC
II. INDICATIONS FOR USE:	Chickens, and turkeys: *Ascaridia spp*. Swine: *Ascaris summ* and *Oesophagostomum spp.*
III. A. DOSAGE FORM:	Soluble powder & liquid
B. ROUTE OF ADMINISTRATION:	Oral
C. RECOMMENDED DOSAGES:	Chickens: 50 milligrams per bird under 6 weeks of age; 100 milligrams per bird over 6 weeks of age. Turkeys: 100 milligrams per bird up to 12 weeks of age; 200 milligrams per bird over 12 weeks Swine: 50 milligrams per pound body weight.

IV. ANIMAL EFFECTIVENESS: The drug was the subject of National Academy of Science/National Research Council (NAS/NRC) reports which were published in the FEDERAL REGISTER of February 14, 1969 (34 FR 2213). The Academy evaluated these products as 'effective' for an anthelmintic for dogs, cats, chickens, turkeys, horses, swine, sheep and cattle.

V. ANIMAL SAFETY: No further safety data are required

VI. HUMAN FOOD SAFETY: Generally, NAS/NRC evaluation of a drug is concerned only with the effectiveness and safety of the drug for the treated animal. FDA's approval of this supplemental application providing for DESI-finalization also required that the product carry the proper human food safety warning and caution statements. Therefore, the supplemental application did involve a reaffirmation of the human safety data, establishment of a tolerance and assignment of withdrawal periods.

Piperazine is a low molecular weight secondary amine that is used in human medicine to treat ascariasis (roundworms) and enterobiasis (pinworm). The oral dosage for treating enterobiasis in humans is 65 mg/kg/day for seven consecutive days with a maximum daily dose of 2.5 g. This dosing regimen is routinely repeated two weeks after the first. Extrapolation between the short-term therapeutic use in humans and chronic lifetime exposure can be handled by assuming that a threshold for activity exists and applying a large safety factor to the therapeutic dose.

The residue data in Master File No. 3527, Jefferson Chemical Company, show that, following treatment of food-producing animals with piperazine, relatively high levels of total residues are incurred in tissues. The metabolism data also show that these residues deplete relatively quickly, and there is evidence that piperazine may be metabolized into endogenous substances. Thus, at longer withdrawal times, much of the residue present may be of no toxicological concern. Together, these data indicate that a period of withdrawal prior to slaughter should be observed with the use of piperazine in chickens, turkeys, and swine.

Currently there is no validated analytical method available to measure the depletion of parent piperazine in tissues of food-producing animals. However, the residue studies with radiolabeled piperazine in Master File 3527 indicate that withdrawal periods of two to three weeks should be ample to assure depletion of drug related residues to below levels of concern. Withdrawal times of 14 days for poultry and 21 days for swine are acceptable.

Under 21 CFR 556.1(a)(2), if it is not possible to determine a finite tolerance, but the agency believes that residues will be present in edible tissues, a negligible tolerance is required. Thus, given the available information on piperazine, it is recommended that a tolerance of 0.1 ppm parent piperazine base be established for all edible tissues. Assuming a person consumes 300 g of muscle tissue containing 0.1 ppm of piperazine, they will be exposed to a dose that is 13,000 times lower than the therapeutic dose that is well tolerated in humans. A tolerance of 0.1 ppm piperazine base is established for all tissues of poultry and swine.

VII. AGENCY CONCLUSIONS:

This supplemental NADA satisfied the requirements of section 512 of the Act and demonstrates that Piperazine wormer when used under its proposed conditions of use, is safe and effective for the labeled indications. The approval provides for use of piperazine for use as an anthelmintic in chickens, turkeys and swine.

The 'effective' finding of the NAS/NRC regarding piperazine which was published in the FEDERAL REGISTER of February 14, 1969, was subsequently reviewed by FDA with respect to the claims noted in the paragraph above. The firm submitted revised labeling to conform and, therefore, this supplemental NADA complies with the NAS/NRC evaluation and FDA's conclusions.

When NADA 10-005 was reviewed under NAS/NRC/DESI program, it was an over-the-counter product and this marketing status remains unchanged. Other piperazine products are also currently on the market as over-the-counter products. Therefore the Center for Veterinary Medicine has concluded that this product should retain over-the-counter marketing status.

Under the Center's supplemental approval policy (21 CFR 514. 106(b)(2)), these changes are Category II changes. The approval of these changes is not expected to have any adverse effect on the safety of effectiveness of this new animal drug. However, the new tolerance and withdrawal periods did require a reevaluation of the human food data in the parent application.

VIII. Labeling

Wazine 17
Piperazine Dihydrochloride Powders
Pig Wormer 17
Wazine Soluble
Pig Wormer Soluble