Approval Date: June 29, 1994

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 034-254

B. Sponsor

The Upjohn Company
Agricultural Division
Kalamazoo, MI 49001(As listed in 21 CFR 510.600(c))

C. Proprietary Name

MGA® 100/200 Premix MGA® 500 Liquid Premix

D. Established Name

melengestrol acetate

E. Dosage Form

Liquid

F. Dispensing Status

OTC

G. Dosage Regimen

0.25 to 0.5 mg melengestrol per head per day

H. Route of Administration

Oral via the feed

I. Indication

For increased rate of weight gain, improved feed efficiency and suppression of estrus (heat) in heifers fed for slaughter

J. Effect of Supplement

This supplement provides for the removal of the requirement for a 48-hour drug withdrawal period prior to slaughter for heifers fed melengestrol acetate.

II. EFFECTIVENESS

This supplement for the removal of the required 48 hour withdrawal period prior to slaughter does not affect the efficacy information contained in the current NADAs.

III. TARGET ANIMAL SAFETY

This supplement for the removal of the required 48 hour withdrawal period prior to slaughter does not affect the target animal safety information contained in the current NADAs.

IV. HUMAN FOOD SAFETY

A. Tolerance

The human food safety studies defining the toxicity of melengestrol acetate (MGA) are contained in NADAs 034-254 and 039-402, and a detailed summary of these studies has been published (Lauderdale et al., 1977. J. Toxicol. & Environ. Health 3:5-33). Based on a reevaluation of these studies, it was determined that the endpoint of toxicological concern is hormonal activity. It was concluded that residues of parent MGA at or below 25 ppb in edible tissues of treated animals will not elicit a hormonal response.

Therefore, a tolerance of 25 ppb is established for residues of the parent compound, MGA, in edible tissues of treated animals. This tolerance corresponds to the limit of sensitivity of the regulatory method. For monitoring purposes, fat is the target tissue.

B. Study to establish the withdrawal period

The following study was conducted to quantitate melengestrol acetate, at zero time withdrawal, in fat of heifers fed melengestrol acetate at 0.5 mg/head daily under commercial feeding conditions in the United States of America.

1. Investigator

   L.F. Krzeminski
   The Upjohn Company
   Kalamazoo,MI

2. Animals: A total of 259 feedlot, mixed breed beef heifers were utilized; seven heifers from each of 25 commercial feedlots where melengestrol acetate was delivered to feed via a conventional commercial supplement and seven heifers from each of 12 commercial feedlots where melengestrol acetate was delivered to feed via a micro-ingredient delivery machine (micro-machine). The feedlots were located in the states of TX, OK, CO, KS, IA, SD, MO, IN, OR and WA.

3. Route of administration: Oral: melengestrol acetate was provided in feed in a manner practiced at each feedlot. Both conventional supplements and micromachines were utilized.

4. Dose and duration of administration: Prior to initiation of the study, cattle were fed melengestrol acetate at 0.25 to 0.45 mg/head daily during the finishing phase consistent with the commercial practice of each feedlot. At the initiation of the study (14 days prior to slaughter), the daily dose of melengestrol acetate was increased to 0.5 mg/head daily, the highest approved dose, and remained at this dose until slaughter.

5. Slaughter time: Cattle were slaughtered at zero time withdrawal which was defined as the interval from last feeding of melengestrol acetate to slaughter. These intervals ranged from 0.5 to 27.5 hours among the 37 groups of cattle. Of the 37 groups of cattle, 27/37 were slaughtered at less than 10 hours after last feeding, 8/37 were slaughtered between 11 and 16 hours after last feeding and 2/37 were slaughtered at 18 and 27.5 hours after last feeding.

6. Tissue residues: At the time of slaughter approximately 1 lb. of perirenal (kidney) fat (target tissue) was collected from each heifer, individually packaged and shipped to The Upjohn Company for determination of melengestrol acetate (marker residue) concentration using the procedure described in JAOAC 59:507515: 1976. The lowest level of reliable measurement of this procedure has been determined to be 10 ppb.

   All 84 samples from cattle fed melengestrol acetate delivered via a micro-machine had residues below 10 ppb. Assay values were obtained from 174 of 175 fat samples (1 of 175 fat samples was not assayed) obtained from heifers administered melengestrol acetate from a conventional feed supplement. Of the 174 samples 139 contained melengestrol acetate residue below 10 ppb; the remaining 35 samples contained residues of melengestrol acetate between 10. 1 and 18.6 ppb.

   A statistical analysis of the data was conducted to determine the 99th percentile with 95% confidence at 12 hours withdrawal (practical zero). The value was found to be less than 25 ppb.

7. Conclusions: This study demonstrates that cattle fed melengestrol acetate at 0.5 mg/head daily (the highest approved dose) and slaughtered at a zero time withdrawal have residues of melengestrol acetate in fat well below the tolerance of 25 ppb.

C. Regulatory methods

The official AOAC method (JAOAC 59:507-515:1976), sensitive to 10 ppb, is used as the regulatory method for tissue residues of melengestrol acetate.

V. AGENCY CONCLUSIONS

Under the Center's supplement approval policy (21 CFR 514.106(b)(2)), this is a Category II change providing for the removal of the requirement for a 48-hour withdrawal period prior to slaughter for heifers fed MGA. This supplement evoked a re-evaluation of the toxicity data contained in NADAs 034-254 and 039-402.

Adequate data were submitted for MGA which permitted the Agency to conclude that a withdrawal period is not necessary for heifers fed MGA.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for food producing animals does not qualify for marketing exclusivity because the supplemental application does not contain new clinical or field investigations (other than bioequivalence or residue studies) and new human food safety studies (other than bioequivalence or residue studies) essential to the approval and conducted or sponsored by the applicant.

VI. ATTACHMENTS

Four (4) pages of labeling are attached as follows:

1. Label for MGA ® 100 Premix (Type A medicated article)
2. Label for MGA ® 200 Premix (Type A medicated article)
3. Label for MGA ® 500 Liquid Premix (Type A medicated article)
4. Blue Bird label for dry Type B supplement containing MGA
5. Blue Bird label for liquid Type B supplement containing MGA

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

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.