Approval Date: May 6, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 046-718

B. Sponsor

Pharmacia & Upjohn Company
Animal Health
7000 Portage Road
Kalamazoo, MI 49001-0199

C. Proprietary Name

MGA® 100/200 Premixes; MGA® 500 Liquid Premix

D. Established Name

melengestrol acetate (MGA)

E. Dosage Form

melengestrol acetate: dry feed supplement, liquid feed supplement;
oxytetracycline: dry feed supplement, complete feed

F. Dispensing Status

OTC

G. Route of Administration

Oral

H. Indication

For increased rate of weight gain, improved feed efficiency, suppression of estrus (heat) and reduction of liver condemnation due to liver abscesses in heifers being fed in confinement for slaughter.

II. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on effectiveness grounds unless the Agency finds that the NADA fails to demonstrate that 1) there is substantial evidence to demonstrate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the combination makes a contribution to the labeled effectiveness, 2) each of the active

ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population, or 3) where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness (21 USC §512(d)(4)(D)).

MGA, as provided by Pharmacia & Upjohn, has previously been separately approved for use in feed for heifers fed in confinement for slaughter for the increased rate of weight gain, improved feed efficiency, and suppression of estrus (21 CFR 558.342 (d)(1)).

Oxytetracycline, as provided by Pfizer, has previously been separately approved for use in feed in growing cattle (over 400 lb) for increased weight gain, improved feed efficiency, and reduction of liver condemnation due to liver abscesses (21 CFR 558.450 (d)(1)(xii)). Effectiveness for each drug, MGA and Over The Counter, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Pharmacia & Upjohn's approved NADA's 34-254 and 39-402, and in approved NADA 8-804, respectively, to which Pharmacia & Upjohn has a right of reference.

Because MGA and Over The Counter each has at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that MGA plus Over The Counter provide appropriate concurrent use for the intended target population. The use of MGA plus Over The Counter provides appropriate concurrent use because these drugs are intended to treat different conditions (MGA, estrus suppression; Over The Counter, liver abscesses) likely to occur simultaneously with sufficient frequency in heifers fed in confinement for slaughter. There is no more than one nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed. MGA is not considered to be an antibacterial animal drug for use in heifers for the purposes of 512(d)(4) of the FFDCA, because MGA is not approved for use in heifers for the diagnosis, cure, mitigation, treatment or prevention of bacterial disease and is not approved for any other use the Center for Veterinary Medicine deems attributable to its antibacterial properties.

III. TARGET ANIMAL SAFETY

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the active ingredients or animal drugs intended for use in combination have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on target animal safety grounds unless there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination or a scientific issue is raised by target animal observations contained in studies submitted to the NADA for the combination and FDA finds that the application fails to establish that such combination active ingredient or animal drug is safe for the target animal.

MGA, as provided by Pharmacia & Upjohn, has previously been separately approved for use in feed for heifers fed in confinement for slaughter for the increased rate of weight gain, improved feed efficiency, and suppression of estrus (21 CFR 558.342 (d)(1)).

Oxytetracycline, as provided by Pfizer, has previously been separately approved for use in feed in growing cattle (over 400 lb) for increased weight gain, improved feed efficiency, and reduction of liver condemnation due to liver abscesses (21 CFR 558.450 (d)(1)(xii)). Target animal safety for each drug, MGA and Over The Counter, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Pharmacia & Upjohn's approved NADA's 34-254 and 39-402, and in approved NADA 8-804, respectively, to which Pharmacia & Upjohn has a right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of MGA or Over The Counter when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination.Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety study(ies) are required for approval of NADA's 46-718 and 46-719.

IV. HUMAN FOOD SAFETY

A. Tolerances:

Tolerances for MGA and Over The Counter are published in the *Code of Federal Regulations*. The tolerance for MGA in edible tissues of cattle under 21CFR 556.380 is 25 ppb in fat with a zero withdrawal period under 21CFR 558.342. The tolerance for Over The Counter in edible tissues of cattle under 21 CFR 556.500 is 2.0 ppm in muscle with a zero withdrawal period under 21 CFR 558.450.

B. Residue Depletion/Non-Interference:

Residue depletion studies completed to support the combination use of MGA and Over The Counter were conducted during a time when MGA had a zero residue clearance with a 48 hour preslaughter drug withdrawal. Since that time, MGA regulations have been revised to reflect a tolerance for MGA in edible tissues of cattle of 25 ppb in fat and a zero day preslaughter withdrawal period. Over The Counter regulations have also been revised to reflect a tolerance for Over The Counter in edible tissues of cattle of 2 ppm in muscle with a zero day preslaughter withdrawal period.

The following studies, were conducted to support the use of the combination of MGA and Over The Counter. Residue depletion studies were conducted using the approved regulatory assays for each drug. The level of sensitivity for the Over The Counter microbiological method is 0.25 ppm, while the level of sensitivity of the GLC method for melengestrol acetate is 25 ppb.

1. In a study conducted by L.F. Krzeminski, R.E. Gosline, A.M. Thornton, and C.J. Subacz, The Upjohn Company, Kalamazoo, Michigan, nine heifers were treated with a combination of MGA and Over The Counter according to the following treatment schedule:

Days on Treatment

Group	**0-5**	**5-115**	**115-Withdrawal**
1 (3 cattle) Over The Counter MGA	75 mg 0.5 mg	75 mg 0.5 mg	2 g 0.5 mg
2 (3 cattle) Over The Counter MGA	2 g 0.5 mg	75 mg 0.5 mg	2 g 0.5 mg
3 (3 cattle) Over The Counter MGA	75 mg 0.5 mg	75 mg 0.5 mg	2 g 0.5 mg

Heifers, in groups of three, were slaughtered after 48, 72 and 96 hours withdrawal. No detectable MGA residues relative to the sensitivity of the assay method (25 ppb) were found in muscle, kidney, fat (target tissue), or bone marrow.

2. In a study conducted by R.E. Kelley, The Upjohn Company, Kalamazoo, Michigan, nine heifers weighing 545 pounds were fed a combination of 0.5MGA and 75 mg Over The Counter according to the following treatment schedule:

Group	**Treatment/Day**	**Withdrawal**
1 (3 cattle)	Control	--
2 (3 cattle)	a. 0.5 mg MGA 0-118 days b. 2.0 g Over The Counter 109-118 days	2
3 (3 cattle)	a. 0.5 mg MGA 1-117 days b. 2 g Over The Counter 0-5 days c. 75 mg Over The Counter 6-107 days d. 2 g Over The Counter 108-117 days	3
4 (3 cattle)	a. 0.5 mg MGA 1-116 days b. 75 mg Over The Counter 1-106 days c. 2 g Over The Counter 107-116 days	4

Treated heifers in groups of three were slaughtered at 48, 72 and 96 hours post-treatment. Muscle, liver, and fat tissues from all animals were negative for the presence of Over The Counter at the three withdrawal times. No Over The Counter residues were detectable in kidney tissues of heifers slaughtered after 48 or 96 hours post-treatment. Muscle, liver, kidney, fat and bone marrow samples were below the sensitivity of the method for MGA at all withdrawal times.

3. In a study conducted by R.E. Kelley, The Upjohn Company, Kalamazoo, Michigan, six heifers weighing 455 pounds were fed a ration containing 0.5mg MGA and 75 mg Over The Counter/head/day for 21 days. Over The Counter and MGA were withdrawn from the ration and three animals were slaughtered after 2 and 3 days, respectively. Liver, kidney, muscle, and fat samples were collected from each animal and assayed for the presence of Over The Counter. Of all sample tissues assayed, one kidney from the 48-hour group showed positive Over The Counter activity of 0.35 ppm. The sample was reassayed the following day with negative response. The initial positive response for the one sample was attributed to laboratory contamination. The above studies showed there were no detectable MGA residues in muscle, kidney, fat (target tissue) or bone marrow.

The above data are adequate to permit the assignment of a zero withdrawal for the combination of MGA and Over The Counter. As noted above, the uses of MGA and Over The Counter alone at the doses proposed in the combination are approved with zero withdrawal. With respect to Over The Counter, that drug was approved with a zero withdrawal period even when its tolerance in edible tissues of cattle was 0.1 ppm. The increased tolerances of 2 ppm in muscle, 6 ppm in liver and 12 ppm in kidney and fat provide additional assurance that residues of Over The Counter, when used in combination with MGA, would not exceed applicable tolerances. The residue data for MGA in these studies are consistent with those for MGA when used alone. Moreover, even in the presence of an exaggerated dose of Over The Counter (i.e., 2 g), no effect on MGA was seen.

C. ***Regulatory Analytical Methods and Assay Non-Interference Studies***:

Practical regulatory analytical methods of analyses for the demonstration of tissue residues of both MGA and Over The Counter may be found in the publication ***AOAC Official Methods of Analysis***.

An assay interference study of melengestrol acetate (MGA) in the presence of residues of oxytetracycline (OTC) in perirenal fat tissue was conducted. A modified form of assay for MGA was used, and the results of the study demonstrated that the assayability of MGA at 25 ppb in bovine perirenal fat tissue is unaffected by the presence of up to 100 ppb Over The Counter.

An assay interference study of Over The Counter in the presence of residues of MGA in perirenal fat was conducted. Bovine perirenal fat was spiked and assayed by the "Green Book" method; the results of the study indicating that the assayability of Over The Counter (1 ppm) is shown to be unaffected by the presence of up to 100 ppb MGA.

V. AGENCY CONCLUSIONS

The data submitted in support of these NADA's comply with the requirements of Section 512 of the FFDCA and demonstrate that MGA (0.25 to 0.50 mg/hd/day) plus

oxytetracycline (75 mg/hd/day) is safe and effective for increased rate of weight gain, improved feed efficiency, suppression of estrus (heat) and reduction of liver condemnation due to liver abscesses in heifers being fed in confinement for slaughter.

Pursuant to 21 CFR 514.106(b)(2), these combination NADA approvals are regarded as Category II changes which did not require a reevaluation of the safety and efficacy data in the parent NADA's (8-804, 34-254, and 39-402).

VI. ATTACHMENTS

MGA® 100, MGA® 200(dry Type A medicated articles)
MGA® 500 (liquid Type A medicated article)
Terramycin® 50 D (dry Type A medicated article)
Heifer Dry Supplement M-0 (Type C medicated feed blue Bird label)
Liquid Heifer Supplement (Type C Blue Bird label)
Cattle Finisher (Type B medicated feed blue bird label)
Cattle Finisher (Type C medicated feed blue bird label)

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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