FREEDOM OF INFORMATION SUMMARY

Combined use of AVIAX® and STAFAC ® in Chicken Feeds

I. GENERAL INFORMATION:

NADA: 141-114

Sponsor: Pfizer Inc.
812 Springdale Drive
Exton, PA 19341-2803

Generic Names: Semduramicin
Virginiamycin

Trade Names: AVIAX™
STAFAC®

Marketing Status: OTC

II. INDICATIONS FOR USE:

1) For the prevention of coccidiosis caused by *Eimeria tenella*, *E. acervulina*, *E. maxima*, *E. brunetti*, *E. necatrix*, and *E. mivati*/*E. mitis*, and for increased rate of weight gain and improved feed efficiency in broiler chickens;

2) For the prevention of coccidiosis caused by *Eimeria tenella*, *E. acervulina*, *E. maxima*, *E. brunetti*, *E. necatrix*, and *E. mivati*/*E. mitis*, and for increased rate of weight gain in broiler chickens;

3) For the prevention of coccidiosis caused by *Eimeria tenella*, *E. acervulina*, *E. maxima*, *E. brunetti*, *E. necatrix*, and *E. mivati*/*E. mitis*, and for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin in broiler chickens.

III. DOSAGE:

A. Dosage form: This NADA provides for the combined use of these two Type A medicated articles, semduramicin as per 21 CFR §558.555 (b)(1)(i), and virginiamycin as per 21 CFR §558.635 (f)(2)(i), (ii), and (iii). Semduramicin is supplied as a Type A medicated article in a single concentration of 22.7 grams semduramicin activity per pound. Virginiamycin is supplied as Type A medicated articles in concentrations of 20 and 227 grams virginiamycin activity per pound.

B. Route of Administration: Oral, *via* the feed.

C. Recommended Dosage:

Semduramicin	Semduramicin is added to broiler chicken feed at 22.7 g/ton for the prevention of coccidiosis caused by *Eimeria tenella*, *E. acervulina*, *E. maxima*, *E. brunetti*, *E. necatrix*, and *E. mivati*/*E. mitis*.
Virginiamycin	Virginiamycin is added to broiler chicken feed at 5 grams/ton for increased rate of weight gain and improved feed efficiency. Virginiamycin is added to broiler chicken feed at 5 to 15 grams/ton for increased rate of weight gain. Virginiamycin is added to broiler chicken feed at 20 grams/ton for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin.

CAUTION: For broiler chickens only. Do not feed to laying chickens.

IV. 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)).

Semduramicin, as provided by Pfizer Inc., has previously been separately approved for use in broiler chicken feed for the prevention of coccidiosis caused by *Eimeria tenella*, *E. acervulina*, *E. maxima*, *E. brunetti*, *E. necatrix*, and *E. mivati*/*E. mitis* (21 CFR §558.555 (b)(1)(i)). Virginiamycin, as provided by Pfizer Inc., has previously been separately approved for use in broiler chicken feed for 1) increased rate of weight gain and improved feed efficiency (21 CFR §558.635 (f)(2)(ii)), 2) increased rate of weight gain (21 CFR §558.635 (f)(2)(i)), and 3) prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin (21 CFR §558.635 (f)(2)(iii)). Effectiveness for each drug, semduramicin and virginiamycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Pfizer Inc.'s approved NADAs 140-940 and 91-467, respectively. Because semduramicin and virginiamycin each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that semduramicin plus virginiamycin provide appropriate concurrent use for the intended target population. The use of semduramicin plus virginiamycin provides appropriate concurrent use

because these drugs are intended to treat different conditions (semduramicin, coccidiosis; virginiamycin, performance) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial (virginiamycin) contained in this combination animal drug intended for use in Type C medicated feed. Semduramicin is not considered to be an antibacterial animal drug for use in broiler chicken for the purposes of 512(d)(4) of the FFDCA, because semduramicin is approved only for prevention of a protozoal disease in broiler chickens.

V. 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.

Semduramicin, as provided by Pfizer Inc., has previously been separately approved for use in broiler chicken feed for the prevention of coccidiosis caused by *Eimeria tenella*, *E. acervulina*, *E. maxima*, *E. brunetti*, *E. necatrix*, and *E. mivati*/*E. mitis* (21 CFR §558.555 (b)(1)(i)). Virginiamycin, as provided by Pfizer Inc., has previously been separately approved for use in broiler chicken feed for 1) increased rate of weight gain and improved feed efficiency (21 CFR §558.635 (f)(2)(ii)), 2) increased rate of weight gain (21 CFR §558.635 (f)(2)(i)), and 3) prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin (21 CFR §558.635 (f)(2)(iii)). Target animal safety for each drug, semduramicin and virginiamycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Pfizer Inc.'s approved NADAs 140-940 and 91-467, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of semduramicin or virginiamycin 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 141-114.

VI. HUMAN 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 human safety grounds unless one or more of the active ingredients or animal drugs used in the combination at the longest withdrawal for the respective active ingredients or animal drugs in the combination exceeds the established tolerance, or one or more active ingredients or animal drugs in the combination interferes with the method of analysis for another active ingredient or drug in the combination.

A. Toxicity Studies

Safety of this combination product has been established by data in NADAs 91-513 for virginiamycin and in NADA 140-940 for semduramicin.

As part of the approval of this combination product, the human safety data on the individual components was updated. Acceptable Daily Intakes (ADI) of 0.25 mg/kg/day for virginiamycin and 0.18 mg/kg/day for semduramicin are established.

B. Tolerances

A tolerance for residues of virginiamycin in broiler chickens is not required.

A tolerance for semduramicin was not codified for previous approvals. At this time a tolerance of 400 ppb for residues of parent semduramicin in liver and a tolerance of 130 ppb for residues of parent semduramicin in muscle are established. These tolerances are based on data submitted under NADA 140-940 that allowed the calculation of a safe concentration of 369 ppb for muscle and 1108 ppb for liver, and described the ratio of parent semduramicin to total residue in tissues of broiler chickens at zero withdrawal.

C. Residue Non-Interference Study

Residue data supporting the approved individual uses of virginiamycin and semduramicin, each having zero withdrawal times, were submitted in their respective original applications (see Part A, above). Metabolism data on virginiamycin in chickens are included in approved NADAs 91-467 and 91-513. The following study (Study No. 2511S-60-94-035) was conducted at Pfizer, Inc., Lee's Summit, MO and Hazelton Labs, Madison, WI to establish that each drug in the presence of the other does not exceed its established tolerance at zero withdrawal and that the presence of virginiamycin does not interfere with the assay of semduramicin. This study determined non-interference for two-way and three-way drug combination use. Only the two-way (virginiamycin and semduramicin) results will be reported here.

Broiler chickens were fed nonmedicated starter diet from Day 0 through Day 20. From Day 21 through 38, seventy birds (35 males, 35 females) were fed medicated feed containing 20 g/ton (22 ppm) ^{14}C-virginiamycin plus 22.7 g/ton (25 ppm) semduramicin. Fifty birds (25 males, 25 females) acted as control animals and were fed unmedicated feed throughout the test period. All birds were fed unmedicated feed from Day 38 to slaughter. Six test birds (3 males, 3 females) were slaughtered at 0, 6, and 12 hours of withdrawal and livers were collected for analysis. The livers were analyzed by combustion for ^{14}C-virginiamycin and by an established HPLC method for semduramicin.

Mean Virginiamycin and Semduramicin Residues (in ppb) in Liver Collected from Broiler Chickens Treated with Medicated Feed containing 20 g/ton ^{14}C-Virginiamycin and 22.7 g/ton Semduramicin.		
Withdrawal Time in Hours	Virginiamycin (ppb ± SD)	Semduramicin (ppb ± SD)
0	78 ± 9	242 ± 66
6	72 ± 8	79 ± 28
12	65 ± 10	<40 (LOQ)

Samples of control liver were fortified with virginiamycin and semduramicin and then analyzed for semduramicin. The data showed that the presence of virginiamycin does not interfere with the assay of semduramicin. Noninterference testing was not conducted for virginiamycin because a combustion procedure was used to measure virginiamycin residues.

Residues for virginiamycin and semduramicin were below their respective tolerances at zero withdrawal, the established withdrawal periods for each of the drugs, thereby indicating an absence of interference.

D. Regulatory Methods

Regulatory analytical methods for virginiamycin and semduramicin are not required because total residues of the drugs were well below the safe concentrations in edible tissues of chickens that were dosed with ^{14}C-virginiamycin and ^{14}C-semduramicin and sacrificed at a practical zero withdrawal time (6 hours).

VII. AGENCY CONCLUSIONS:

The data submitted in support of this NADA comply with the requirements of Section 512 of the FFDCA and demonstrate that semduramicin (22.7 g/ton) plus virginiamycin (5, 5 to 15, and 20 g/ton) are safe and effective for the claims indicated in Section II of this FOI summary.

As part of the approval of this combination product, the human safety data on the individual components was updated. Acceptable Daily Intakes (ADI) of 0.25 mg/kg/day for virginiamycin and 0.18 mg/kg/day for semduramicin are established. A tolerance of 400 ppb for residues of parent semduramicin in liver and a tolerance of 130 ppb for residues of parent semduramicin in muscle are established. The data demonstrate that residues for virginiamycin and semduramicin were below their respective tolerances at zero withdrawal, the established withdrawal periods for each of the drugs, thereby indicating an absence of interference. Regulatory analytical methods for virginiamycin and semduramicin are not required because total residues of the drugs were well below the safe concentrations in edible tissues of chickens that were dosed with ^{14}C-virginiamycin and ^{14}C-semduramicin and sacrificed at a practical zero withdrawal time (6 hours).

Pursuant to 21 CFR §514.106 (b)(2), this combination NADA approval is regarded as a Category II supplemental change which did not require a reevaluation of safety and efficacy data in the parent NADAs. The drugs are to be fed in Type C medicated feeds, in accordance with Section II and III of the FOI Summary and the Blue Bird labeling that is attached to this document.

Attached labeling: Type C medicated Feed (Blue Bird)