Date of Approval: November 18, 2005

# FREEDOM OF INFORMATION SUMMARY

## ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-334

EQUIZONE 100
(phenylbutazone)

Powder

Horses

For oral use in horses for the relief of inflammatory conditions associated with the musculoskeletal system

Sponsored by:

A & G Pharmaceuticals, Inc.

**FREEDOM OF INFORMATION SUMMARY**

***1. GENERAL INFORMATION:***

| | |
|---|---|
| a. File Number: | ANADA 200-334 |
| b. Sponsor: | A & G Pharmaceuticals, Inc.<br>1030 West Commodore Blvd.<br>Jackson, NJ 08527<br><br>Drug Labeler Code: 057699 |
| Agent: | James H. Schafer, D.V.M.<br>Schafer Veterinary Consultants, LLC<br>800 Helena Ct.<br>Ft. Collins, CO 80524 |
| c. Established Names: | Phenylbutazone |
| d. Proprietary Name: | EQUIZONE 100 |
| e. Dosage Form: | Powder |
| f. How Supplied: | 2.2 lb (1 kg) jars |
| g. How Dispensed: | Rx |
| h. Amount of Active Ingredients: | Each 10 grams of powder contains 1 gram of phenylbutazone |
| i. Route of Administration: | Oral |
| j. Species/Class: | Horses |
| k. Recommended Dosage: | Administer orally on a small amount of palatable feed 1 to 2 level scoops (using the scoop provided) per 500 pounds of body weight, but not to exceed 4 grams per animal daily. One level scoop contains 10 grams of powder equivalent to 1 gram of phenylbutazone. Use high dose for the first 48 hours, then gradually reduce to a maintenance dose. |
| l. Pharmacological Category: | Non-steroidal anti-inflammatory drug (NSAID) |

| | |
|---|---|
| m. Indications: | For the relief of inflammatory conditions associated with the musculoskeletal system in horses. |
| n. Pioneer Product: | Phenylbutazone Tablets, USP; phenylbutazone; NADA 091-818, Phoenix Scientific, Inc. |

## *2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:*

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

On December 7, 1999, A & G Pharmaceuticals, Inc. was granted approval of a suitability petition (SP 99P-4167/CP 1) that requested a change in dosage form from that of the approved new animal drug. The pioneer product, NADA 091-818, is a tablet, whereas the generic product is a powder. To establish that the different oral dosage forms are bioequivalent and can be used interchangeably, the sponsor conducted an *in vivo* blood-level bioequivalence study comparing the generic product EQUIZONE 100 (phenylbutazone) powder to the reference product Phenylbutazone Tablets, USP. A separate palatability study was conducted to demonstrate that the generic phenylbutazone powder would be consumed when fed with a grain ration at the dose indicated on the product labeling. The studies are summarized below.

### A. Blood-level Bioequivalence Study

**Title of Study:** "A Two-Way Single-Dose Bioequivalence Study with Oral Phenylbutazone in Healthy Horses." (Study No. C-0004)

**Investigator(s):** Colorado Animal Research Enterprises
Fort Collins, CO
(Animal phase)

PPD Development
Middleton, Wisconsin
(Analytical phase)

**General Study Design:**

1. Objective: Assessment of *in vivo* bioequivalence of A & G's formulation of Phenylbutazone Palatable Powder (test product) in horses compared to Phenylbutazone Tablets, USP, NADA 91-818, manufactured by Phoenix Scientific, Inc. of St. Joseph, MO (reference product). This study was conducted in accordance with Good Laboratory Practice Regulations (21 CFR Part 58).

2. Study Animals: Twenty-four domestic breed horses (12 non-pregnant females and 12 gelded males) were randomly assigned in equal numbers to either of two treatment sequences.

3. Treatment Groups: The study was of two-period crossover design. Group I received control product and Group II received test product in Period 1. Fourteen (14) days later, Group I received the test product and Group II received the control product as period 2.

| No. of Horses | Treatment Design | | | |
|---|---|---|---|---|
| | Phenylbutazone Oral Dosage (mg/kg body wt.) | Period 1 | Washout Interval Between Treatments | Period 2 |
| 6 male, 6 female | 8.8 mg/kg | Product A | 14 days | Product B |
| 6 male, 6 female | 8.8 mg/kg | Product B | 14 days | Product A |

Treatment codes A and B were randomly assigned to the drug products as follows:
A = Reference Article (Phenylbutazone Tablets, USP, 1 g/tablet)
B = Test Article (Phenylbutazone powder, 100 mg/g)

4. Dosage Form: A & G's generic Phenylbutazone Powder contains 1 grams of phenylbutazone per 10 grams powder (100 mg/g). The reference product Phenylbutazone Tablets, USP, NADA 91-818, manufactured by Phoenix Scientific, Inc. has a potency of 1 gram phenylbutazone per tablet.

5. Route of Administration: Test powder and control tablets were dispensed into gelatin capsules for oral administration. Horses were fasted for approximately 12 hours pre-dose to approximately 4 hours post-dose. Water was withheld for approximately 4 hours pre-dose and 4 hours post-dose.

6. Dosage(s): 8.8 mg per kg of body weight.

7. Pertinent Parameters Measured:
    a. Clinical Examinations and Observations – Prior to the onset of each period, each horse received a veterinarian-conducted physical examination in accordance with protocol specifications. General animal health status and conditions in the test facility were observed at least twice daily by animal technicians from the time of animal acquisition until the study concluded. Daily observations and body weight measurements did not result in reference or test article related findings.

    b. Analytical methods – Blood samples were collected at scheduled collection times. Plasma was harvested and assayed for phenylbutazone concentration. Individual plasma levels were tabulated and applicable pharmacokinetic parameters were calculated for horses receiving the test and control products.

c. Statistical analysis – Phenylbutazone concentrations in plasma extracted from blood samples were measured at appropriate intervals after treatment Maximum Concentration ($C_{MAX}$), Time to Maximum Concentration ($T_{MAX}$), Area Under the Curve (AUC).

**Results:** Differences in the pharmacokinetic parameters between Test and Reference products were statistically evaluated by means of 90% confidence intervals. Control and test product means for each parameter are provided below, along with the corresponding confidence intervals.

| ***Variable*** | **Test Mean** | **Control Mean** | **Lower CI** | **Upper CI** |
|---|---|---|---|---|
| $Log_e$ (Area Under Curve) | 5.942 | 5.926 | -7.11% | 11.20% |
| $Log_e$ (Maximum Concentration) | 3.516 | 3.449 | 0.71% | 15.09% |
| Time to Maximum Concentration (hours) | 4.425 hrs | 4.492 hrs | -19.96% | 21.48% |

**Adverse Reactions:** No adverse reactions to the test or reference product dosages were noted during this study.

**Conclusions:** Based on a criterion that the 90% confidence interval for the difference between product means be within ±80-125% of the reference product mean (for log transformed data), the test product was found to be bioequivalent to the reference product.

**B. Palatability Study of Phenylbutazone Powder in Horses**

**Type of Study:** Palatability Study

**Investigator:** J. Stanley Brown, D.V.M.
Columbus, NJ

**General Design of the Investigation:**

1. Objective: This clinical study was designed to determine the palatability of A&G Pharmaceutical, Inc.'s phenylbutazone oral powder when administered orally in a palatable grain rations to horses.

2. Study Animals: Fifty-eight (58) male and female Standardbred and Arabian horses approximately 2 to 15 years age at the time of treatment and weighing 750-1250 pounds were included in the study.

3. Dosage Form: A&G Pharmaceuticals, Inc.'s phenylbutazone oral powder, an orally administered product which contains 10% phenylbutazone, was used as the test article for this study.

4. Route of Administration: Oral – The powder was administered in a palatable grain ration.

5. Dosage: A&G Pharmaceuticals, Inc.'s phenylbutazone oral powder was administered at a rate of 2 grams of phenylbutazone per 500 pounds of body weight per day for two days. Half of the daily dose of powder was administered orally by mixing it in 2-3 pounds of their grain ration at each feeding.

6. Pertinent Parameters Measured:
    a) Health Examinations/observations – Prior to the onset of each period, each horse received a veterinarian-conducted physical examination in accordance with protocol specifications. Animals were monitored for about 45 minutes after each dosing for adverse reactions.

    b) Grain ration consumption – The amount of grain ration consumed within 30 minutes was recorded as 0%, 25%, 50%, 75% or 100% with "100%" indicating the entire grain ration was consumed. If animals did not consume 100% of the allotment of treated grain within the allowed time interval, the remainder was removed completely from the feed trough and measured in graduated measuring device.

    c) Data analysis – A&G Pharmaceuticals, Inc.'s phenylbutazone oral powder was to be considered palatable when mixed in a grain ration if at least 75% of the treated feedings were consumed 100% by the participating animals in the 30-minute feeding period allowed.

**Results:** The horses completely consumed the medicated grain ration 80.4 percent of the times it was offered, fulfilling the criterion of the study that at least 75% of the treated feedings were consumed 100% by the participating animals in the 30-minute feeding period allowed.

**Adverse Reactions:** No adverse reactions to the test product were noted during this study.

**Conclusions:** Based on a criterion that the 90% confidence interval for the difference between product means be within ±80-125% of the reference product mean (for log transformed data), A & G Pharmaceuticals, Inc.'s phenylbutazone oral powder was found to be bioequivalent to the reference product.

The results from the palatability study indicate that A&G Pharmaceuticals, Inc.'s phenylbutazone oral powder is palatable when fed with a grain ration at the 2 grams per 500 pounds of body weight per day dosage.

### *3. HUMAN SAFETY:*

This drug is intended for use in horses, which are non-food producing animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

Human warnings are provided on the product label as follows: "Keep this and all medications out of the reach of children. Dispense in tight, child resistant containers."

## *4. AGENCY CONCLUSIONS:*

This Abbreviated New Animal Drug Application (ANADA) filed under section 512(b)(2) of the Federal, Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that EQUIZONE 100, when used under its proposed conditions of use, is safe and effective for its labeled indications.

Safety and effectiveness for this generic animal drug, EQUIZONE 100, were established by the demonstration of blood-level bioequivalence to the pioneer product, Phenylbutazone Tablets, USP, sponsored by Phoenix Scientific, Inc. under NADA 091-818. Palatability was also tested and found to be acceptable.

## *5. ATTACHMENTS:*

Facsimile generic labeling and currently approved pioneer labeling are attached as follows:

Generic Labeling for ANADA 200-334:
EQUIZONE 100 (phenylbutazone)
Jar label – 2.2 lb (1 kg)
Outsert labeling

Pioneer Labeling for NADA 091-818:
Phenylbutazone Tablets, USP
Container label – 100 tablets
Package insert