Date of Approval: February 11, 2016

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-449

SAFE-GUARD AquaSol

Fenbendazole oral suspension

Swine, except for nursing piglets

For the treatment and control of Lungworms: Adult *Metastrongylus apri,* adult *Metastrongylus pudendotectus*; Gastrointestinal worms: Adult and larvae (L3, L4 stages, liver, lung, intestinal forms) large roundworms (*Ascaris suum*), nodular worms (*Oesophagostomum dentatum, O. quadrispinulatum*), small stomach worms (*Hyostrongylus rubidus*), Adult and larvae (L2, L3, L4 stages – intestinal mucosal forms) whipworms (*Trichuris suis*); and Kidney worms: Adult and larvae *Stephanurus dentatus*.

Sponsored by:

Intervet Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-449

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

SAFE-GUARD AquaSol

D. Established Name

Fenbendazole oral suspension

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Suspension

G. Amount of Active Ingredient

200 mg/mL

H. How Supplied

1 Liter and 1 Gallon high density polyethylene plastic containers

I. Dispensing Status

OTC

J. Dosage Regimen

2.2 mg fenbendazole/kg body weight (BW) (1 mg/lb) daily for 3 consecutive days

K. Route of Administration

Oral, in drinking water

L. Species/Class

Swine, except for nursing piglets

M. Indications

For the treatment and control of Lungworms: Adult *Metastrongylus apri,* adult *Metastrongylus pudendotectus*; Gastrointestinal worms: Adult and larvae (L3, L4 stages, liver, lung, intestinal forms) large roundworms (*Ascaris suum*); nodular worms (*Oesophagostomum dentatum, O. quadrispinulatum*); small stomach worms (*Hyostrongylus rubidus*); Adult and larvae (L2, L3, L4 stages – intestinal mucosal forms) whipworms (*Trichuris suis*); and Kidney worms: Adult and larvae *Stephanurus dentatus.*

N. Effect of Supplement

This supplement provides for the addition of swine, except for nursing piglets, for the above indications.

II. EFFECTIVENESS

A. Dosage Characterization

Several non-pivotal pharmacokinetic studies were conducted to identify a dose of fenbendazole 20% oral suspension that would result in comparative rate and extent of exposure to the approved dose of SAFE-GUARD (fenbendazole) 20% Type A medicated article (NADA 131-675) in swine. In one study SAFE-GUARD (fenbendazole) 20% Type A medicated article was administered as a single dose (9 mg fenbendazole/kg body weight [BW]) via voluntary uptake of a 500 g feed bolus; fenbendazole oral suspension was drenched at 3 different dosages (3, 5, and 6 mg fenbendazole/kg BW) in a volume of 20 mL. In the second phase of this study, the dose of 6 mg fenbendazole/kg BW administered as fenbendazole oral suspension in drinking water resulted in similar rate and extent of absorption to the approved total dose of 9 mg fenbendazole/kg BW in feed. Another study showed that the results from the bioequivalence analysis between the dose 2.5 mg/kg (approximately one-third of the total 3 day dose) of fenbendazole 20% oral suspension and SAFE-GUARD (fenbendazole) 20% Type A medicated article (administered at 3 mg fenbendazole/kg, i.e., one-third of the total labeled dose) approached bioequivalence (0.70, 1.25). Because the total drug exposure after the 2.5 mg/kg dose administration in pigs was still outside of the upper confidence interval limits initially set for the study, a single dose of 2.2 mg fenbendazole/kg BW was selected for the pivotal comparative bioavailability study. The dosing regimen chosen for the fenbendazole oral suspension in swine is 2.2 mg/kg BW per day administered on 3 consecutive days.

B. Substantial Evidence

Substantial evidence of effectiveness is based on a pharmacologic bridge between SAFE-GUARD (fenbendazole) 20% Type A medicated article (NADA 131-675) and SAFE-GUARD AquaSol (fenbendazole oral suspension) in swine and a dose-confirmation study using the dose-limiting parasite for fenbendazole in swine (adult *Trichuris suis*).

PHARMACOLOGIC BRIDGE TO SUPPORT EFFECTIVENESS:

Two studies (comparative bioavailability and palatability) and information on comparative water versus feed intake patterns in healthy pigs were used for the

pharmacologic bridge between SAFE-GUARD (fenbendazole) 20% Type A medicated article (NADA 131-675) and SAFE-GUARD AquaSol (fenbendazole oral suspension) in swine.

1. Comparative Bioavailability Study in Swine

a. Title: "Comparative evaluation of the pharmacokinetic profiles of fenbendazole in pigs following oral administration of 20% fenbendazole suspension at a dose of 2.2 mg/kg of SAFE-GUARD Type A medicated article at a dose of 3 mg/kg" (Study Number V-0079-1781).

b. Study Director: Silke Sczesny, Ph.D.
Intervet Innovation GmbH
Schwabenheim, Germany

c. Study Design:

i. Objective: To determine whether fenbendazole oral suspension administered to pigs at a dose of 2.2 mg fenbendazole/kg BW would result in comparable rate and extent of exposure to the pioneer product, SAFE-GUARD 20% (fenbendazole) Type A medicated article administered at a dose of 3 mg/kg BW.

ii. Study Animals: A total of 52 German Landrace x Pietrain pigs, females and castrated males, approximately 3 months of age, and weighing between 55 and 66 kg were included in the treatment phase of the study. Pigs were housed individually.

iii. Treatment Groups: The study was performed using a parallel study design with two segments containing 13 pigs per group per segment: fenbendazole oral suspension (test product) group and SAFE-GUARD (fenbendazole) 20% Type A medicated article (reference product) group. A total of 26 pigs were in each group.

iv. Drug Administration: SAFE-GUARD AquaSol (fenbendazole oral suspension) was administered via a stomach tube at a dose of 2.2 mg fenbendazole/kg BW; SAFE-GUARD (fenbendazole) 20% Type A medicated article was administered in feed at a dose of 3 mg fenbendazole/kg BW.

v. Measurements and Observations: Pigs were observed for health abnormalities daily during and after the morning feeding throughout the study. Additional general health observations were performed directly before treatment, and approximately 30 minutes, 6 hours, 12 hours, 24 hours, and 32 hours after treatment. Plasma samples for fenbendazole analysis were collected before treatment and approximately

30 minutes, 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, and 32 hours after treatment. A blood sample was collected before treatment and approximately 32 hours after treatment for hematological and clinical chemistry analysis. Analysis of fenbendazole in plasma samples of pigs was performed using a validated HPLC-MS-MS method (with the lower limit of quantification of 10 ng/mL).

d. Statistical Methodology: Comparability of the two treatments was assessed by evaluating the C_{max} (maximum plasma concentration) and the $AUC_{0\text{-}LOQ}$ (area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration) between the two treatment groups. Products were considered to have comparable rate and extent of exposure if the 90% confidence intervals (CI) for the ratio (oral suspension/Type A medicated article) of their respective log-transformed C_{max} (lnC_{max}) and $AUC_{0\text{-}LOQ}$ ($lnAUC_{0\text{-}LOQ}$) values were contained within the limits [0.70, 1.25]. The wider lower limit was allowed because of additional effectiveness data collected in the pivotal dose confirmation study. The wider lower confidence limit did not have a negative impact on the evaluation of the study.

e. Results: Adverse events were reported for animals in both treatment groups and were considered unrelated to treatment. Results of the blood chemistry and hematology analyses before treatment revealed no clinically relevant findings and there were no treatment related changes in the hematology parameters after treatment.

   Three pigs from the fenbendazole oral suspension treated group had some product spillage during drug administration and were likely under-dosed. Because this under-dosing was expected to influence plasma fenbendazole concentrations and the evaluation of bioavailability, the statistical evaluation was performed with and without the under-dosed pigs.

   In order to evaluate the effect of spillage on comparative exposure assessment, statistical analysis was initially conducted with the 3 under-dosed pigs excluded (Table II.B.2.1) and with all pigs included in the analysis (Table II.B.2.2).

Table II.B.2.1: Comparison of fenbendazole rate and extent of exposure in swine when administered as a bolus dose of 2.2 mg/kg fenbendazole oral suspension or in feed as SAFE-GUARD (fenbendazole) 20% Type A medicated article at a dose of 3 mg/kg BW (with three under-dosed pigs excluded)

PK Parameter	**Oral suspension[1]**	**Type A medicated article[1]**	**Coefficient of Variation %**	**Means Ratio**	**Lower limit[2]**	**Upper limit[2]**
lnC_{max} (ng/mL)	75	68.5	23.40	109	98.1	122
$lnAUC_{0\text{-}LOQ}$ (ng*hr/mL)	729	877	24.96	83.1	73.9	93.5

[1]Back-transformed means
[2]Lower and upper limit of the 90% confidence interval for the ratio

Table II.B.2.2: Comparison of fenbendazole rate and extent of exposure in swine when administered as a bolus dose of 2.2 mg/kg fenbendazole oral suspension or in feed as SAFE-GUARD (fenbendazole) 20% Type A medicated article at a dose of 3 mg/kg BW (all pigs included)

PK Parameter	**Oral suspension[1]**	**Type A medicated article[1]**	**Coefficient of Variation %**	**Means Ratio**	**Lower limit[2]**	**Upper limit[2]**
lnC_{max} (ng/mL)	70.95	68.5	25.72	104	92.1	117
$lnAUC_{0\text{-}LOQ}$ (ng*hr/mL)	694	877	27.45	79.1	69.8	89.6

[1]Back-transformed means
[2]Lower and upper limit of the 90% confidence interval for the ratio

Although the result for the lower limit of the 90% confidence interval for the mean $AUC_{0\text{-}LOQ}$ was barely at the acceptable limit of 70 in the analysis that included all study pigs, the additional statistical analysis excluding the under-dosed animals (Table II.B.2.1), provided further confirmation that the two products had statistically comparable rate and extent of exposure in swine.

f. Conclusions: The systemic exposure of fenbendazole oral suspension after administration to swine at a bolus dose of 2.2 mg/kg is similar to the exposure after administration of SAFE-GUARD (fenbendazole) 20% Type A Medicated article in feed at a dose of 3 mg/kg.

2. Palatability of 20% Fenbendazole Oral Suspension in Swine

a. Title: "Evaluation of the palatability of 20% fenbendazole suspension in pigs through voluntary consumption when offered as medicated water over 5 hours on each of 3 consecutive days at a dose of 2.2 mg fenbendazole/kg BW/day" (Study Number V-0079-3620).

b. Study Design:

i. Objective: To evaluate the palatability of 20% fenbendazole oral suspension in pigs through voluntary consumption of medicated water when offered for approximately 5 hours a day over 3 consecutive days at a dose of 2.2 mg fenbendazole/kg BW per day.

ii. Materials and Methods: Seventy-two pigs weighing between 90.0 and 117.0 kg were divided into 36 pens and assigned to one of two groups (A or B), resulting in 18 pens per treatment group. Each pen was equipped with a separate water container connected to a drinking bowl. The study was performed in three phases to account for possible inter-day variations in individual water intake of the pigs. In Phase 1, the average amount of non-medicated water consumed per pen in approximately 5 hours on each of three consecutive days was determined. In Phase 2, Group A received SAFE-GUARD AquaSol (fenbendazole oral suspension) in drinking water and Group B received non-medicated water; in Phase 3, Group A received non-medicated water and Group B received SAFE-GUARD AquaSol (fenbendazole oral suspension) in drinking water. During Phase 2 and 3, each pen was offered its average amount of water consumed in Phase 1 for approximately 5 hours on each of three consecutive days and the amount consumed per pen was assessed each day.

c. Results: The average percent of fenbendazole medicated water consumed by Group A for Phase 2 was 96.86% of the offered amount and the average percent of medicated water consumed by Group B for Phase 3 was 99.50% of the offered amount. The average percent of medicated water consumed for Phase 2 (Group A) and Phase 3 (Group B) was 98.18% of the offered amount.

d. Conclusion: The average percent of fenbendazole medicated water consumed was above 90% (98.18%) of the amount of non-medicated water consumed. Therefore, the study demonstrated that 20% fenbendazole suspension has acceptable palatability.

3. Feed versus Water Intake Patterns in Healthy Pigs

Pigs have a biphasic circadian rhythm with an extended rest phase at night. Within this biphasic rhythm, two-thirds of the total amount of feed

consumed in 24 hours is eaten during the day and the remaining third of the feed is consumed at night (Bigelow and Houpt, 1988[1]). Pigs also show a clear prandial drinking behavior. Pigs consume most of the total daily water directly before, during, or directly after their meal (Bigelow and Houpt, 1988; Haugse et al. 1965[2]). The authors demonstrated that 75% of the total daily water intake is closely associated with eating, with 27% of water being consumed preprandially, 32% intraprandially, and 16% postprandially.

The literature above provided evidence that physiologic feeding and water intake patterns in pigs are closely related under normal conditions. In addition, it is unlikely that water intake in pigs will be more negatively affected by environmental factors, stress, health status, etc. than feed intake under similar conditions. Therefore, it was concluded that the bioavailability comparison of fenbendazole administered in water versus feed is valid.

Conclusions from the Pharmacologic Evidence of Effectiveness

Based on the bioavailability study of fenbendazole oral suspension and SAFE-GUARD (fenbendazole) 20% Type A medicated article, high palatability of fenbendazole oral suspension, and closely related feed versus water intake patterns in healthy pigs, it was concluded that the exposure of fenbendazole in drinking water is comparable to SAFE-GUARD (fenbendazole) 20% Type A medicated article. Comparable exposure provides a basis for demonstrating effectiveness of fenbendazole oral suspension in swine. Effectiveness was confirmed in a pivotal dose confirmation study with the dose-limiting parasite, *Trichuris suis*.

<u>DEMONSTRATION OF EFFECTIVENESS IN A MULTI-SITE DOSE CONFIRMATION STUDY:</u>

Multi-site Dose Confirmation Field Study

1. Type of Study: Multi-site dose confirmation study in swine with artificially-induced infections of adult *Trichuris suis* (*T. suis*). (Study Numbers C09-102-0 and C09-102-02). The studies were conducted between July 26, 2010, and November 19, 2010.

2. Investigators:

Nathan L. Winkelman, D.V.M. Swine Services Unlimited, Inc. Rice, MN C09-102-01	Terry N. TerHune, D.V.M. HMS Veterinary Development, Inc. Tulare, CA C09-102-02

[1] Bigelow JA. and Houpt TR. Feeding and drinking patterns in young pigs. Physiol Behav 43: 99-109. 1988.
[2] Haugse CN, Dinusson WE, Erickson DO, Johnson JN, Buchanan ML. A day in the life of a pig. N Dakota Farm Res 23: 18-23. 1965.

3. Study Design:

   a. Objective: To evaluate the efficacy of fenbendazole oral suspension administered daily in drinking water at 2.2 mg/kg BW for 3 consecutive days against adult *Trichuris suis* (*T. suis*) in experimentally infected pigs. The study was performed in accordance with Good Clinical Practice (GCP) guidelines.

   b. Study Animals: A total of 48 (24 pigs per site) pigs of approximately 6 weeks of age at receipt were used. Body weights ranged from 28.0 to 35.0 lbs (12.7 to 15.9 kg) at the C09-102-01 facility and 15.4 to 27.6 lbs (7 to 12.5 kg) at the C09-102-02 facility. Swine breeds were representative of U.S. commercial production. Both barrows (castrated males) and gilts (females) were used.

   c. Treatment Groups: In each study, 24 healthy pigs were randomly assigned to one of two treatment groups (fenbendazole-treated and non-medicated). Six pens of 2 pigs each were used per treatment group.

   d. Infection: Fifty-six days prior to treatment administration, all suitable study candidates were orally dosed with approximately 4000 embryonated *T. suis* eggs. A natural field isolate of *T. suis* collected in April, 2010, from a sow located on a commercial farrow-to-wean operation in the U.S. was used. Individual fecal samples were obtained from each candidate animal 46, 47, and 48 days after *T. suis* inoculation and analyzed for the presence of *T. suis* eggs. Animals with at least two fecal examinations positive for *T. suis* eggs were eligible for inclusion in the study.

   e. Drug Administration: Non-medicated water consumption of the pigs in each treatment pen was measured prior to treatment administration to estimate the amount of water required for dosing on each day of the treatment period. The amount of 20% fenbendazole suspension administered in drinking water to the study pigs was calculated from pre-treatment body weights. Medicated water was prepared on each treatment day by diluting fenbendazole oral suspension in drinking water to provide a daily dose of 2.2 mg/kg body weight to the fenbendazole treated group. The fenbendazole medicated water was provided for 3 consecutive days. Fenbendazole treated animals were dosed once per day, with each dosing period lasting 4 to 6 hours.

      The control group received non-medicated drinking water.

   f. Study Duration: The study animals were necropsied after either 8 or 9 days following the last fenbendazole administration and the large intestine was removed for worm counts.

g. Pertinent Measurements/Observations: Adult *T. suis* worms attached to the large intestinal tract and in the contents of the tract were counted.

4. Statistical Methodology: The parasite counts for each study site were analyzed separately. Parasite counts for each animal were transformed to the natural logarithm of (count + 1) for analysis and calculation of geometric means. Percent efficacy was calculated using Abbott's formula: 100[(NM-M)/NM], where NM is the geometric mean for the non-medicated (control) group and M is the geometric mean for the fenbendazole-medicated group. The null hypothesis that the two treatments share the same mean worm count versus the alternative that the mean worm count of the two groups are different was tested using an $\alpha = 0.05$ (two-sided) significance level.

5. Results:

   There were 24 (C09-102-01) and 23 (C09-102-02) pigs included in the analyses. One C09-102-02 control animal died on Day 3 of causes unrelated to the test article and was not included in the statistical analyses.

   At the C09-102-01 site, 11 out of 12 control animals showed adequate *T. suis* worm counts of 100 or more. At the C09-102-02 site, 9 of 12 controls showed adequate *T. suis* worm counts of 100 or more.

   At the C09-102-01 site, there was a statistically significant difference between the mean worm counts of the two treatment groups ($p = 0.0006$) and the percent efficacy was 98.5%. At the C09-102-02 site, there was a statistically significant difference between the mean worm counts of the two treatment groups ($p = 0.0003$) and the percent efficacy was 98.6%.

   No drug related health problems were observed during the study.

6. Conclusion

   Fenbendazole oral suspension is effective against the dose-limiting parasite *T. suis* in swine when administered at 2.2 mg/kg/BW for 3 consecutive days.

III. TARGET ANIMAL SAFETY

Animal safety was established in the original approval for SAFE-GUARD (fenbendazole) 20% Type A medicated article under NADA 131-675 (49 FR 3846, January 31, 1984). A GLP margin of safety study was not required for approval of SAFE-GUARD AquaSol (fenbendazole oral suspension). Safety of SAFE-GUARD AquaSol (fenbendazole oral suspension) in swine was demonstrated through a pharmacologic bridge (described in the Effectiveness summary above) between SAFE-GUARD (fenbendazole) 20% Type A medicated article (NADA 131-675) and SAFE-GUARD AquaSol (fenbendazole oral suspension) in swine. The pharmacologic bridge used to support target animal safety included two studies (comparative bioavailability and palatability) and information on comparative water versus feed intake patterns in healthy pigs.

The comparative bioavailability study (Study Number V-0079-1781) demonstrated that fenbendazole oral suspension administered to swine by gavage at a dose of 2.2 mg fenbendazole/kg BW had statistically comparable rate and extent of exposure as SAFE-GUARD (fenbendazole) 20% Type A medicated article administered at a dose of 3 mg/kg BW. In particular, the log-transformed C_{max} (lnC_{max}) and $AUC_{0\text{-}LOQ}$ ($lnAUC_{0\text{-}LOQ}$) values were below the upper limit for the 90% confidence interval set for the study (1.25). In addition, no drug related adverse events were observed during the course of this study.

The palatability study (Study Number V-0079-3620) demonstrated acceptable palatability of fenbendazole oral suspension in swine for the intended dose and duration of treatment.

Information on comparative water versus feed intake patterns in healthy pigs demonstrated that physiologic feed and water intake patterns in pigs are closely related under normal conditions.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

CVM did not require additional information for microbial food safety (antimicrobial resistance) for this supplemental approval. The FOI Summary for the original approval of NADA 141-449 dated October 2, 2015, contains a summary of all information used to assess the risk to microbial food safety (antimicrobial resistance).

B. Impact of Residues on Human Intestinal Flora

CVM did not require additional information for the impact of residues on human intestinal flora for this supplemental approval. The FOI Summary for the original approval of NADA 141-449 dated October 2, 2015, contains a summary of all information used to assess the impact of residues on human intestinal flora.

C. Toxicology

Reassessment of the toxicological acceptable daily intake (ADI) was not needed for this supplemental approval. The FOI summaries for the original approval of NADA 128-620, dated September 20, 1983, and the original approval of NADA 141-449, dated October 2, 2015, contain relevant toxicology information.

D. Establishment of the Final ADI

The final ADI is the toxicological ADI of 40 µg/kg BW/day derived from a 6 month repeated dose oral toxicity study in dogs. The codified ADI is listed under 21 CFR 556.275.

E. Safe Concentrations for Total Residues in Edible Tissues

The safe concentrations of total residues of fenbendazole in each edible tissue of swine are 4.0 ppm for muscle, 12 ppm for liver, 24 ppm for kidney, and 24 ppm for fat or skin/fat.

F. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

      A total residue and metabolism study was not required for this supplemental approval. A summary of the total residue and metabolism study in swine is provided in the original approval of NADA 131-675 (48 FR 3846, approval dated January 31, 1984).

   b. Comparative Metabolism Study

      CVM did not require comparative metabolism studies for this supplemental approval. Results from the comparative metabolism studies for fenbendazole have been summarized in the original approval of NADA 128-620 (48 FR 42809, dated September 20, 1983).

   c. Study to Establish Withdrawal Period and/or Milk Discard Time

      (i) Tissue Residue Depletion Study

      Title: "Residue Depletion Study of Fenbendazole in Edible Tissues of Pigs (Liver) After Oral Administration of Panacur AquaSol at a Dose of 2.5 mg Fenbendazole/Kg Body Weight/Day Administered For 3 Consecutive Days." Study number S13065-00

      Study Dates: October, 2014 to May, 2015

      Study Director: Terry N. TerHune, D.V.M., Ph.D., HMS Veterinary Development, Inc., Tulare, CA

      In-Life Facility: HMS Veterinary Development, Inc., Tulare, CA

      Analytical Laboratory: Merck Animal Health, Rahway, NJ

      Forty-four cross bred swine (22 castrated males and 22 females) weighing 102-125 kg at Study Day -5 were randomly assigned to one of 6 treatment groups (Table 1). Animals in groups 2-5 received fenbendazole as medicated water at a target dose of 2.5 mg FBZ/kg BW/day for three consecutive days. Swine were slaughtered according to the schedule listed in Table 1 below, and liver samples were collected. Fenbendazole concentrations were determined in swine liver using a validated LC-MS/MS method.

Table 1. Experimental Design.

Study group	Number of Animals	Treatment	Withdrawal time (hours)
1 (control)	2	Unmedicated	12
2	12	Medicated Water	12
3	6	Medicated Water	18
4	6	Medicated Water	24
5	6	Medicated Water	30
6	6	Medicated Water	36

Fenbendazole residue concentrations in liver are presented in Table 2 below.

Table 2. Fenbendazole concentrations (ppm) in liver of swine treated with 2.5 mg FBZ/kg BW/day for three consecutive days.

Withdrawal Period (hours)	Fenbendazole in Liver (ppm)
12	2.75 ± 0.63
18	2.75 ± 1.1
24	2.22 ± 0.25
30	1.50 ± 0.54
36	2.08*

* Only one value above LOQ
LOQ (ppm) 0.729

2. Target Tissue and Marker Residue

   Based on the results of the total residue and metabolism study provided in the original approval of NADA 131-675 (48 FR 3846, approval dated January 31, 1984), the target tissue is liver and the marker residue is parent fenbendazole.

3. Tolerance

   Based on a revised safe concentration of 12 ppm for liver listed in the original approval of NADA 141-449 (FOI Summary dated October 2, 2015), and total residue and metabolism study in swine provided in the original approval of NADA 131-675 (48 FR 3846, approval dated January 31, 1984), a revised tolerance of 3.2 ppm is assigned as the tolerance for parent fenbendazole in swine liver.

4. Withdrawal Period and Milk Discard Time

   Tissue residue data from Study #S13065-00 were analyzed using a statistical tolerance limit algorithm that determines the upper tolerance limit for the 99^{th} percentile of the population with 95% confidence. The data support assignment of a 2-day withdrawal period for Safe-Guard AquaSol in swine when used according to label directions.

G. Analytical Method for Residues

1. Description of Analytical Method

   a. Determinative Procedure

      Homogenized swine liver containing fenbendazole (FBZ) is fortified with the internal standard (FBZ-d3) and extracted twice with methanol. An aliquot of the methanol extract is diluted with aqueous methanol and analyzed by LC-MS/MS. Quantitation is based on the m/z 300 → m/z 268 and m/z 303 → m/z 268 transitions for FBZ and FBZ-d3, respectively.

   b. Confirmatory Procedure

      Sample extraction and LC-MS/MS analysis for the confirmatory procedure are identical to those for the determinative procedure. Fenbendazole-specific ion transitions (m/z 300→m/z 268, m/z 300→m/z 159 and m/z 300→m/z 131) are monitored to obtain ion ratios, signal to noise ratios, and retention times that meet the required acceptability criteria.

2. Availability of the Method

   The method is available from the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to SAFE-GUARD AquaSol:

User Safety Warnings: Not for use in humans. Keep out of reach of children. Protective gloves should be used and care should be taken when handling the product to avoid skin and eye exposure and accidental ingestion. Accidental exposure may result in skin and eye irritation. Accidental ingestion may cause gastrointestinal disturbances and hypersensitivity reactions in humans. For customer service, adverse effects reporting, and/or a copy of the SDS, call 1-800-211-3573. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that SAFE-GUARD AquaSol, when used according to the label, is safe and effective for the treatment and control of Lungworms: Adult *Metastrongylus apri,* adult *Metastrongylus pudendotectus*; Gastrointestinal worms: Adult and larvae (L3, L4 stages, liver, lung, intestinal forms) large roundworms (*Ascaris suum*), nodular worms (*Oesophagostomum dentatum, O. quadrispinulatum*), small stomach worms (*Hyostrongylus rubidus*), Adult and larvae (L2, L3, L4 stages – intestinal mucosal forms) whipworms (*Trichuris suis*); and Kidney worms: Adult and larvae *Stephanurus dentatus* in swine, except for nursing piglets. Additionally, data demonstrate that residues in food products derived from species treated with SAFE-GUARD AquaSol will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for the use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity

This supplemental approval for SAFE-GUARD AquaSol qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included a dose confirmation study to demonstrate effectiveness against the dose-limiting parasite for fenbendazole in swine. This exclusivity begins as of the date of our approval letter and only applies to the addition of swine indications as approved in the supplemental application.

C. Supplemental Application

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.