Date of Approval: August 19, 2011

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-064

PULMOTIL 90

Tilmicosin
Type A Medicated Article
Beef and Non-Lactating Dairy Cattle

"For the control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in groups of beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group."

Sponsored by:

Elanco Animal Health

TABLE OF CONTENTS

I. GENERAL INFORMATION:

A. File Number:	NADA 141-064
B. Sponsor:	Elanco Animal Health A Division of Eli Lilly & Co. Lilly Corporate Center Indianapolis, IN 46285 Drug Labeler Code: 000986
C. Proprietary Name:	PULMOTIL 90
D. Established Name:	Tilmicosin
E. Pharmacological Category:	Antimicrobial
F. Dosage Form:	Type A medicated article
G. Amount of Active Ingredient:	90.7 g/lb (20%)
H. How Supplied:	22 pound bags
I. How Dispensed:	Veterinary Feed Directive (VFD)
J. Dosage:	568 to 757 g/ton to provide 12.5 mg/kg body weight (BW) for 14 days
K. Route of Administration:	Orally, via complete feed
L. Species/Class:	Cattle/beef and non-lactating dairy
M. Indication:	For the control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in groups of beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group.
N. Effect of Supplement:	This supplement provides for use in a new species/class and a new indication "for the control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in groups of beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group."

II. EFFECTIVENESS:

A. Dosage Characterization:

Four dose determination studies were performed in the United States, using target doses of 6.25, 12.5, and 25 mg tilmicosin/kg BW/day, administered in the feed for 7 or 14 days. Study animals were commercial English or Continental crossbred ruminating beef steers, six to ten months of age, weighing approximately 175 to 230 kg at the beginning of the studies. During the studies, animals were evaluated for clinical signs of BRD. A pooled analysis of the studies was conducted, with success rate determined on Study Day 28. Based on the results of these pilot studies, a target dose of 12.5 mg/kg BW/day administered in the feed for 14 days was selected as an effective dose.

B.Substantial Evidence:

A multi-site, natural infection field study was conducted to demonstrate the effectiveness of tilmicosin Type A Medicated Article for the control of BRD in cattle.

1. Title

"Clinical Study (GCP): Efficacy of Oral Tilmicosin (PULMOTIL 90) Fed for the Control of Bovine Respiratory Disease in Cattle." Study Numbers T5C060805, T5C160806, T5C310729, T5CCA0728, and T5C480804 (safety evaluation only; not included in the effectiveness analysis). September 2007 to March 2009.

2. Investigators and Study Locations

Study Number T5C060805 – Terry TerHune, DVM, PhD;
HMS Veterinary Development, Inc., Tulare, CA

Study Number T5C160806 – Matt Edmonds, DVM, PhD;
Johnson Research, Parma, ID

Study Number T5C310729 – Kelly Lechtenberg, DVM, PhD;
Midwest Veterinary Services, Oakland, NE

Study Number T5CCA0728 – Calvin Booker, DVM, M.Vet.Sc;
Thorlakson Feedyards, Airdrie, Alberta, Canada

Study Number T5C480804 – David Bechtol, DVM;
Agri Research Center, Inc., Canyon, TX
(safety evaluation only, not included in effectiveness analysis)

3. Study Design

a. Objective: To demonstrate the effectiveness of oral tilmicosin for control of BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in groups of cattle, where active BRD has been diagnosed in at least 10% of the animals in the group.

b. Animals: A total of 1,151 commercial English or Continental crossbred ruminating beef calves, five to eleven months of age, weighing a minimum of 400 pounds were enrolled in the four sites used in the effectiveness analysis.

Steers were included at all sites. Heifers and steers were included at Sites T5C060805 and T5C310729. At arrival, animals were processed and evaluated for study eligibility. Severely ill (respiratory or depression score of 3) or moribund animals or animals requiring injectable therapy were excluded from the study.

c. Test Article: PULMOTIL 90 Type A Medicated Article was used to manufacture a Type C medicated feed that was fed to target a dose of 12.5 mg/kg BW per head per day for 14 consecutive days. Non-medicated feed was used as the control article and was fed to both treatment groups during the 14 day post-treatment observation period (Study Days 14-27).

d. Treatment Groups: Across four sites, there were 575 animals enrolled in the test article-treated group and 576 animals enrolled in the control group.

e. Experimental Design: This study was conducted at four sites. The study was originally designed as a five-site study, but Site T5C480804 was excluded from the effectiveness analysis due to a significant protocol deviation. The study used a randomized complete block design at each site, with blocks based on the physical location pens within each site. There were six blocks per site, with four pens per block and 12 animals per pen. The individual animal was the observational unit and the pen was the experimental unit. Study personnel were masked to treatment groups.

f. Measurements and Observations: From arrival, animals were observed daily for signs of BRD. The following depression and respiratory scoring criteria were used to identify clinically ill animals.

Depression Scoring Criteria

0 = Normal: Bright, alert, and responsive.

1 = Mild Depression: May stand isolated with its head down or ears drooping, but will quickly respond to minimal stimulation.

2 = Moderate Depression: May stand isolated with its head down and may show signs of muscle weakness (standing cross-legged or knuckling when walking). Shows a delayed response to minimal stimulation or requires greater stimulation before showing a response.

3 = Severe Depression: May be recumbent and reluctant to rise, or if standing isolated, may be reluctant to move. Ataxia, knuckling, or swaying may be evident when moving. Head carried low with eyes dull and ears drooping. Possible excess salivation and/or lacrimation.

Respiratory Scoring Criteria

0 = Normal: No abnormal respiratory symptoms. Respiratory rate and effort are appropriate for the environment.

1 = Mild Respiratory Distress: Serous nasal or ocular discharge and/or cough.

2 = Moderate Respiratory Distress: Mucous or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort.

3 = Severe Respiratory Distress: Marked increase in respiratory rate or effort, with one or more of the following - open mouth breathing, abdominal breathing, and/or extended head.

Day 0 was defined as the day when greater than or equal to 10% of the animals in the holding pens at a site were classified as clinically ill according to the following criteria:

- Depression score = 1 or 2, AND a rectal temperature ≥ 104.0 °F, OR
- Respiratory score = 2, AND a rectal temperature ≥ 104.0 °F, OR
- Depression or respiratory score = 3, regardless of rectal temperature

Animals with a depression score or respiratory score = 3 were included in the calculation to achieve the minimum 10% clinically ill threshold required to initiate treatment; however they were not enrolled in the study.

On Day 0, animals considered clinically ill were enrolled in the study first, and then the remaining eligible animals from the holding pens were enrolled until all pens were filled.

Animals were fed the test article in complete feed for 14 consecutive days. They were then observed for clinical signs for an additional 14 days. Day 1 through Day 27, animals with a respiratory or depression score of 3 were withdrawn from the study as treatment failures, regardless of rectal temperature.

The primary variable was the treatment success rate on Day 28. A treatment success was defined as an animal that remained in the study through Day 28 and had a depression score = 0 AND respiratory score = 0 or 1 AND a rectal temperature < 104 °F. Animals removed from the study for non-BRD related reasons were excluded from the effectiveness analysis and not considered to be treatment successes or failures. Data for failure rate, BRD-related morbidity rate, BRD-related mortality rate, depression score, respiratory score, rectal temperature, average daily gain, gain efficiency, and feed efficiency were also collected.

Cultures were performed on nasopharyngeal swabs and lung samples. Other supportive variables recorded were individual scores for respiration and depression, rectal temperature, and body weight. During the study, 553 isolates of *Mannheimia haemolytica*, 501 isolates of *Pasteurella multocida*, and 105 isolates of *Histophilus somni* were isolated from Day 0 nasopharyngeal swabs and post-treatment lung samples from both the experimental and control groups across all sites.

g. Statistical Analysis: Statistical analysis of success rate on Day 28 (the primary effectiveness variable) was conducted using a generalized linear mixed effects model. The statistical model contained treatment as a fixed effect and site, site by treatment, and block within site as random effects.

4. Results

Animals administered oral tilmicosin demonstrated significantly higher ($p = 0.032$) Day 28 success rates across all four study sites when compared to animals administered non-medicated control feed. The least squares mean for Day 28 success rate for tilmicosin-treated animals was 67.29% compared to 49.21% for the control group.

5. Adverse Events

There were no test article-related adverse events observed during the study.

6. Conclusion

This study demonstrates that PULMOTIL 90 (tilmicosin) Type A Medicated Article is effective for the control of BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in groups of beef and non-lactating dairy cattle where active BRD has been diagnosed in at least 10% of the animals in the group, when administered in complete feed to target a dose of 12.5 mg/kg BW/day for 14 days.

III. TARGET ANIMAL SAFETY:

A. Toxicity Study:

1. Title

"Non-Clinical Laboratory Study (GLP): Safety Evaluation of Tilmicosin When Administered in the Feed to Cattle." Study Number T5C060731. October 2007 to December 2007.

2. Study Director

Terry TerHune, DVM, PhD, HMS Veterinary Development, Inc.
Tulare, CA

3. Study Design

a. Objective: To determine the margin of safety for tilmicosin when administered orally as a Type C medicated feed top dress to ruminating cattle at 0X, 1X, 2X and 3X the proposed inclusion rate of approximately 12,078 g/ton (to target a dose of 12.5 mg/kg BW per day) for three times the proposed duration of use of 14 consecutive days (42 days).

b. Animals: Forty-eight healthy commercial crossbred feeder calves (24 bulls and 24 heifers), approximately six to ten months of age, weighing between 135 to 243 kg at study initiation. Study animals were acclimated for 13 days.

c. Test and Control Articles: The primary test article was PULMOTIL 90 (tilmicosin) Type A Medicated Article, administered orally in the feed as a pelleted Type C medicated feed top dress for 42 consecutive days. MICOTIL 300 (tilmicosin) Injectable was a secondary test article. However, because the current approval is for PULMOTIL 90 as a Type A Medicated

Article for use in feed, only the results from the Group 2 animals are reported here. The control article for the medicated feed and basal diet was a non-medicated cattle grower ration. Saline was the control article for MICOTIL 300 Injectable.

d. Treatment Groups: Study animals were randomized to one of six treatment groups on Study Day -1. The treatment groups are summarized in Table 1 below.

Table 1: Treatment Groups

Treatment Group	Treatment Description	Treatment Duration	Number of Animals
TG01 (0X)	Non-medicated pelleted top dress feed	42 days	8 (4 males, 4 females)
TG02 (1X)	Tilmicosin at 12,078 g/ton (to target a dose of 12.5 mg/kg BW)	42 days	8 (4 males, 4 females)
TG03 (2X)	Tilmicosin at 24,157 g/ton (to target a dose of 25.0 mg/kg BW)	42 days	8 (4 males, 4 females)
TG04 (3X)	Tilmicosin at 36,235 g/ton (to target a dose of 37.5 mg/kg BW)	42 days	8 (4 males, 4 females)
TG05 (1X PULMOTIL in feed + Tilmicosin injection)	Tilmicosin at 12,078 g/ton (to target a dose of 12.5 mg/kg BW) + 20 mg tilmicosin/kg BW injection (MICOTIL 300 Injectable)	21 days of basal ration followed by 14 days of tilmicosin in the feed + A single subcutaneous injection of tilmicosin (MICOTIL 300 Injectable) on the last day tilmicosin was administered in the feed	8 (4 males, 4 females)

Treatment Group	Treatment Description	Treatment Duration	Number of Animals
TG06 (1X PULMOTIL in feed + saline injection)	Tilmicosin at 12,078 g/ton (to target a dose of 12.5 mg/kg BW) + Saline injection (volume equivalent to that of MICOTIL 300 Injectable)	21 days of basal ration followed by 14 days of tilmicosin in the feed + A single subcutaneous injection of saline on the last day tilmicosin was administered in the feed.	8 (4 males, 4 females)

Each animal was dosed based on its individual body weight starting on Day 0.

e. Measurements and Observations: The following measurements and observations were made on Study Days -1, 15, 29, and 43: physical examinations, animal health observations, body weights, feed consumption, water consumption, hematology, serum chemistry, coagulation analysis, urinalysis, and fecal analysis. Organ weights (liver, kidney, and heart), gross pathology, and histopathology data were obtained from tissues collected at necropsy on the final day of the study (Day 43).

f. Statistical Methods: For all analyses the experimental unit for treatment effect was the individual animal. For variables measured at more than one time point, such as body weight, blood serum variables, and urinalysis variables, a repeated measures analysis of variance was used to test the effects of treatment, treatment by time, treatment by gender, and treatment by gender by time. For variables measured once, such as organ weights, an analysis of variance model was used to test the effects of treatment and treatment by gender. When present, pre-treatment measures were used as covariates. Follow-up pair-wise mean comparisons between the control group and the treated groups were performed, as necessary, using linear contrasts at a significance level of 0.10.

4. Results

a. Clinical Observations: No drug-related findings were observed.

b. Body Weights: No drug-related findings were observed.

c. Food and Water Consumption: No drug-related findings were observed.

d. Hematology: Statistically significant test article-related effects were detected for the total white blood cell count (1X and 3X treatment groups), platelet count (3X treatment group), neutrophil count (1X PULMOTIL in feed + tilmicosin injection treatment group), basophil count (2X treatment group), and monocyte count (3X treatment group). These findings were not considered clinically significant because the effects were small, did not

consistently persist over time, did not indicate a dose-dependent trend, and were typically within the normal reference range.

e. Coagulation Analysis: One animal in the 3X treatment group had a significantly increased prothrombin time and activated partial thromboplastin time on the last sampling day. This animal had normal coagulation values for the preceding sampling times and had no other abnormal clinical or analytical findings on the final sampling day.

f. Serum Chemistry: Statistically significant test article-related effects were seen for amylase (1X, 2X, and 3X treatment groups), potassium (1X PULMOTIL in feed + tilmicosin injection treatment group), and triglycerides (females in the 1X, 2X, and 3X treatment groups). These findings were not considered clinically significant because the effects were small, did not consistently persist over time, did not indicate a dose-dependent trend, and were typically within the normal reference range.

g. Urinalysis: No drug-related findings were observed.

h. Fecal Analysis: No drug-related findings were observed.

i. Gross and Microscopic Pathology: One animal in the 1X group had a 12 mm by 2 mm hemorrhage on the left ventricular papillary muscle. One animal in the 1X PULMOTIL in feed + tilmicosin injection treatment group had a 10 mm by 8 mm by 1 mm hemorrhage on the epicardium. The cardiac lesions were not considered clinically significant because no other abnormalities were seen and the affected animals were clinically normal.

5. Conclusions

This study demonstrates that tilmicosin as PULMOTIL 90 Type A Medicated Article, is safe in cattle when administered as a top dress in feed to target a dose of 12.5 mg/kg BW per day for 14 days.

B.Pharmacokinetics Study:

The relative bioavailability of the tilmicosin in Type C medicated feed (administered daily) as a top dress and as a complete feed was evaluated after a single dose and at steady state in a blood level relative bioavailability study. Because of tilmicosin's long terminal elimination half life, relative bioavailability (based upon AUC values) was assessed for the area under the concentration versus time curve (AUC) from hours 12 – 24 after dose 1 (AUC12 – 24) and over the interval of hrs 324 – 336 at steady state (AUC324-336). The study was designed such that the animals had 12 hours to consume their complete feed or top dress, with the second half of the day dedicated to capturing the necessary blood samples. In so doing, the typical concerns associated with blood sampling decreasing feed consumption were avoided. Because the first 12 hours were not captured, the initial portion of the profile for the top dress could not be described. Therefore, the criteria for confirming equivalence of the magnitude of drug exposure resulting from administration of the top dress and complete feed was that the lower 90% confidence bound for the ratio of treatment (geometric) mean AUC values (complete feed/top dress) should be no less than 0.7.

Since the top dress dose was expected to be consumed much more rapidly than the dose in complete feed, it was determined that administration of the Type C medicated feed as a top dress would result in the higher peak exposures as compared to administration as a complete feed. Accordingly, it was determined that if the AUC values were comparable, the top dress would be the method of administration used to evaluate target animal safety of tilmicosin administered by either method. Likewise, if the AUC values were comparable, the complete feed could be the method of administration used to evaluate effectiveness of tilmicosin administered by either method.

Due to analytical problems, the data from a portion of the animals enrolled in the blood level relative bioavailability study could not be included in the data analysis. As a result, the study lacked the statistical power needed to achieve the targeted confidence limits. Consequently, equivalent drug exposure for the top dress and complete feed could not be confirmed. However, an examination of the individual subject data succeeded in demonstrating that the data were consistent with similar exposure, regardless of the method of tilmicosin administration. These data, in conjunction with the results of the target animal safety study, showing no clinically significant safety concerns across all dose groups, indicated that the target animal safety study conducted using the top dress formulation adequately supported the safety of tilmicosin when administered at the labeled dose either as the top dress or complete feed to cattle. Despite this conclusion, because of the specific problems encountered during the bioavailability study, the relative bioavailability data could not be used in conjunction with the effectiveness study (which was conducted using complete feed) to demonstrate the effectiveness of tilmicosin in cattle when given as a top dress at the labeled dose to cattle.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summaries for the original approval of NADA 140-929 dated, March 3, 1992, and a supplemental approval dated March 2, 2010, contain a summary of all toxicology studies.

B.Residue Chemistry:

1. Summary of Residue Chemistry Studies

a. Total Residue Depletion Study

The total residue depletion and metabolism in the target species and comparative metabolism for MICOTIL 300 (tilmicosin) Injectable are summarized in the FOI Summary for NADA 140-929 dated March 3, 1992. An additional total residue study in the target species is summarized below.

Study title and number: "Non-clinical Laboratory Study (GLP): Total Residues of Tilmicosin in Liver and Feces following Oral Administration to Feedlot Cattle." Study 006-00889.

1) Study Director and Laboratory: John Byrd, Southwest Bio-Labs, Inc., Las Cruces, NM

2) Test Material: [14C]-tilmicosin with a radiochemical purity > 99%

3) Test Animals: Eight (4 castrated males, 4 females) mixed breed beef cattle, weighing 180-237 kg, were divided into 4 groups of 2 animals each, with one male and one female in each group.

4) Dose: 12.5 mg/kg body weight via oral gavage each day for 7 days.

5) Sample Collection and Analysis: Animals were slaughtered on Study Day -1 (Group 1 – control), 7 (Group 2), 14 (Group 3), and 28 (Group 4). Total radioactive tilmicosin residues in liver were measured by combustion and scintillation counting. Parent tilmicosin concentrations in liver samples were assayed using the regulatory method.

6) Results:

Tilmicosin residues in cattle liver at the withdrawal times indicated are summarized in Table 2 below.

Table 2. Concentrations of Parent Tilmicosin and Total Tilmicosin Residues in Liver of Cattle Treated with [14C]-Tilmicosin via Oral Gavage

Days Post Last Dose	**Parent Tilmicosin (ppm)**	**Total Tilmicosin Residues (ppm)**	**Ratio of Parent Tilmicosin to Total Residues (%)**
7	2.28	4.98	45.75
7	2.24	5.76	38.97
14	0.63	1.90	33.03
14	0.43	1.28	33.73
28	<0.06	0.14	42.86
28	0.27	1.15	23.35

7) Conclusions:

The study results are consistent with maintaining the codified tolerance of 1.2 ppm for parent tilmicosin in liver.

b. **Residue Depletion Study**

The following pivotal study was conducted to permit decisions on withdrawal period assignment.

Residue depletion study title and number: "Non-clinical Laboratory Study (GLP): Marker Residues of Tilmicosin in Liver and Muscle following Fourteen Days of Oral Administration with or without Concurrent Use of Micotil in Feedlot Cattle." Study 007-00993.

1) Study Director and Laboratory: Erin Weich, Southwest Bio-Labs, Inc., Las Cruces, NM

2) Test Material: PULMOTIL 90 Type A Medicated Article and MICOTIL 300 (tilmicosin) Injectable

3) Test Animals: Thirty-six (18 males and 18 females) mixed breed beef cattle, weighing 169 to 240 kg, were divided into the following treatment groups:

Table 3. Treatment Groups for Residue Depletion Study

Treatment Group	Number of Animals	Treatment	Euthanization
0	2M + 2F	None	Not unless assigned to other group
1	1M + 1F	Control	Prior to dosing
2	5M + 5F	Oral tilmicosin for a target dose of 12.5 mg/kg for 14 days	10 animals at 28 days post last dose
3	10M+10F	Oral tilmicosin for a target dose of 12.5 mg/kg for 14 days + 20 mg/kg MICOTIL 300 single injection on day 14 of oral dosing	10 animals (5M+5F) at 28 days post injection of tilmicosin AND 10 animals (5M+5F) at 35 days post injection of tilmicosin

4) Dose: Animals in Groups 2 and 3 received tilmicosin in feed at a target dose of 12.5 mg/kg body weight for 14 days. Group 3 animals also received a single injection of MICOTIL 300 (tilmicosin) Injectable at a dose of 20 mg/kg body weight on day 14, immediately after being fed with tilmicosin for 14 days. However, because the current approval is for PULMOTIL 90 as a Type A Medicated Article for use in feed, only the results from the Group 2 animals are reported here.

5) Sample Collection and Analysis: Liver, muscle, and injection site samples were collected and analyzed by validated analytical methods.

6) Results: The residue concentration range in the liver and muscle of cattle treated with tilmicosin in feed alone (Group 2) are summarized in Table 4.

Table 4. Tilmicosin Residue Concentrations in Liver and Muscle of Cattle Treated with Tilmicosin in Feed

Treatment Group	28 Days	
	Liver (ppm)	Muscle (ppm)
2	<0.060 to 0.489	<0.025

7) Conclusions:

At 28 days post treatment with tilmicosin in feed, the upper tolerance limit for parent tilmicosin in liver for 99% of the population at 95% confidence is below 1.2 ppm, supporting a 28-day withdrawal assignment.

2. Target Tissue and Marker Residue Assignment

The target tissue for residue monitoring is liver and the marker residue is parent tilmicosin.

3. Tolerances

The tolerance for parent tilmicosin in liver of cattle is 1.2 ppm (21 CFR 556.735).

The tolerance for parent tilmicosin in muscle of cattle is 0.1 ppm (21 CFR 556.735).

4. Withdrawal Period

A 28-day withdrawal is assigned for cattle treated with tilmicosin in feed for 14 days at a target dose of 12.5 mg/kg body weight.

C. Microbial Food Safety:

The Agency evaluated microbial food safety data for tilmicosin for the control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group. The microbial food safety assessment submitted for Agency review included a release assessment to describe the probability that tilmicosin and its use at a single dose of 12.5 mg/kg BW in feed for cattle, for 14 consecutive days will result in the emergence of resistant bacteria or resistance determinants in treated cattle under the proposed conditions of use; an exposure assessment to describe the likelihood of human exposure to resistant bacteria or resistance determinants through consumption of edible products from treated cattle; and a consequence assessment to describe potential human health consequences arising from exposure to defined resistant bacteria or resistance determinants by considering the human medical importance of antimicrobials (e.g., macrolides) used in the treatment of human infectious diseases.

The risk assessment included information on tilmicosin, specifically its spectrum of antibacterial activity, the mechanisms of macrolide resistance in *Campylobacter*, and the current prevalence of macrolide-resistant *Campylobacter* in cattle and retail beef. In addition, data from studies assessing the potential of tilmicosin phosphate to select for macrolide-resistant *Campylobacter* and *Enterococcus* in cattle when administered at the proposed use was provided.

Based upon the Agency's evaluation of the information submitted by the firm, and in consideration of current macrolide susceptibility profiles of *Campylobacter* spp., including their prevalence in the food commodity of concern (ground beef) and

target animal (beef and non-lactating dairy cattle), and taking into considerations the following conditions of use for tilmicosin in cattle feed…

> *For the control of bovine respiratory disease (BRD) associated with* Mannheimia haemolytica, Pasteurella multocida, *and* Histophilus somni *in groups of beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group.*
>
> *To assure both food safety and responsible use in cattle, administration of feed containing tilmicosin to cattle experiencing an outbreak of BRD:*
>
> *1. must be initiated during the first 45 days of the production period;*
> *2. shall not exceed a single 14-consecutive-day treatment;*
> *3. should not occur concurrent with or following administration of an injectable macrolide; and*
> *4. should not occur within 3 days following administration of a non-macrolide injectable BRD therapy.*
>
> *Tilmicosin medicated feed treatment has not been evaluated in cattle with severe clinical disease. Cattle with severe clinical illness should be evaluated for individual treatment with an alternative non-macrolide therapy.*

…the Agency concludes that use of tilmicosin in cattle feed will not result in a significant risk to the development of macrolide resistance in foodborne *Campylobacter* originating from treated cattle. The overall risk estimation associated with the use of tilmicosin in feed for cattle under the proposed conditions of use is high, based on individual rankings of high for the release assessment, medium for the exposure assessment and high for the consequence assessment. The latter ranking of high for the consequence assessment is based on macrolides being critically important in human medicine, because they are the drug of choice to treat confirmed cases of campylobacteriosis, especially in children where there are safety concerns about the use of fluoroquinolones. However, the Agency thinks that the use of tilmicosin under a veterinary feed directive (VFD), limited to a single 14-day treatment in animals that have not been previously treated for BRD with an injectable macrolide, and the restriction from use of an injectable macrolide for individual animal therapy during tilmicosin feed administration should ensure that approval of this product appropriately limits overall extent of use of additional macrolide therapies in animals receiving treatment with tilmicosin. The Agency therefore concludes that the proposed conditions of use and appropriate label restrictions outlined above are adequate to support the use of tilmicosin in feed for cattle, and help to ensure that risks to public health from macrolide-resistant *Campylobacter* originating from treated cattle are minimal.

D. Analytical Method for Residues:

Information regarding regulatory analytical method has been provided (see the FOI Summary for the original approval of NADA 140-929, dated March 3, 1992).

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PULMOTIL 90:

Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling PULMOTIL 90 should use protective clothing, impervious gloves, goggles, and a NIOSH-approved dusk mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention. Not for human consumption. Keep out of reach of children. The Material Safety Data Sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information, or to obtain a Material Safety Data Sheet, call 1-800-428-4441.

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 PULMOTIL 90 Type A Medicated Article, when used according to the label, is safe and effective for the control of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in groups of beef and non-lactating dairy cattle, where active BRD has been diagnosed in at least 10% of the animals in the group. Additionally, data demonstrate that residues in food products derived from cattle treated with PULMOTIL 90 Type A Medicated Article will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

A valid veterinary feed directive (VFD) is required to dispense this drug. Any animal feed bearing or containing this drug will be fed to animals only by or on a lawful veterinary feed directive issued by a licensed veterinarian in the course of their professional practice. In addition, the veterinary feed directives issued for this drug are not refillable.

Labeling restricts this drug to use by or on the order of a licensed veterinarian. The decision to restrict this drug to use by or on the order of a licensed veterinarian was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product and (b) restricting this drug to use by or on the order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues. Because the drug will be administered in feed, the drug will be marketed as a VFD drug.

B.Exclusivity:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the new claim and the new species for which this supplement is approved.

C. Supplemental Applications:

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.