

Date of Approval: April 28, 2022

**FREEDOM OF INFORMATION SUMMARY**  
**SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION**

NADA 141-137

Pennitracin MD 50G<sup>®</sup>

bacitracin Type A medicated article

Type A medicated article to be used in the manufacture of Type B  
and Type C medicated feeds

Broiler and replacement chickens

This supplement provides for the addition of a therapeutic indication, "for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler and replacement chickens."

Sponsored by:

Pharmgate Inc.

## Executive Summary

Pennitracin MD 50G<sup>®</sup> (bacitracin Type A medicated article) is approved for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler and replacement chickens. A Type A medicated article is used to make Type B and Type C medicated feeds. Only a Type C medicated feed can be fed directly to animals. The Type C medicated feed made from Pennitracin MD 50G<sup>®</sup> contains 50 grams of bacitracin per ton of feed and should be fed to chickens as the sole ration for 28 to 35 days, starting from the time they are placed for brooding. Brooding is the early growing period, and in commercial poultry production, begins when newly hatched chickens are placed in a barn to receive feed, water, and supplemental heat and care.

Pennitracin MD 50G<sup>®</sup> is already approved for increased rate of weight gain and improved feed efficiency in quail, chickens, growing turkeys, and growing pheasants; and for reduction in the number of liver condemnations due to abscesses in beef steers and heifers fed in confinement for slaughter.

Proprietary Name	Established Name	Application Type and Number	Sponsor
Pennitracin MD 50G <sup>®</sup>	bacitracin Type A medicated article	New Animal Drug Application (NADA) 141-137	Pharmgate Inc.

Bacitracin is a polypeptide antibiotic with activity against Gram-positive bacteria. It is bactericidal and inhibits bacterial growth by preventing the formation of peptidoglycan chains needed for cell wall synthesis and by altering membrane permeability. Bacitracin is minimally absorbed from the gastrointestinal tract.

FDA approved Pennitracin MD 50G<sup>®</sup> as an over-the-counter drug because the Agency determined that adequate "directions for use" can be written on the labeling in such a way that non-veterinarians can use the drug safely and effectively. Bacitracin is not considered a medically important antimicrobial for people.

## Safety and Effectiveness

The sponsor conducted two single-site, experimentally induced infection model studies to show that Pennitracin MD 50G<sup>®</sup> prevents mortality caused by necrotic enteritis associated with *C. perfringens* in chickens. On Day 0, day-of-hatch chickens were enrolled in the studies. Chickens in the treatment group were given Pennitracin MD 50G<sup>®</sup> medicated feed for 28 consecutive days. Chickens in the control group were given non-medicated feed for the same period. On Day 14 or 18, all chickens in both the treatment and control groups were challenged with a *C. perfringens* isolate administered in feed. In both studies, there were far fewer mortalities in the treatment group compared to the control group. No adverse reactions were seen in either study.

The sponsor used publicly available literature to justify that the labeled duration range is appropriately targeted to the typical risk period for necrotic enteritis in broiler and replacement chickens. Therefore, Pennitracin MD 50G<sup>®</sup> is labeled to feed as the sole ration for 28 to 35 days, starting from the time the chickens are placed for brooding.

FDA did not require new studies to evaluate the safety of the drug in chickens for this supplemental approval.

### **Human Food Safety**

For microbial food safety, FDA evaluated a hazard characterization that described 1) the intended use of Pennitracin MD 50G<sup>®</sup> in broiler and replacement chickens; and 2) the potential for the drug to promote the emergence or selection of antimicrobial-resistant bacteria of public health concern originating from treated chickens. FDA does not currently consider bacitracin to be "medically important" for people, and the drug is currently approved for both treatment and production uses in food-producing animals. The Agency determined that the intended therapeutic use of Pennitracin MD 50G<sup>®</sup> in broiler and replacement chickens for a defined duration (no more than 35 days) should not result in an increased level of bacitracin-resistant bacteria originating from treated chickens over the current level.

FDA did not require new toxicology studies for this supplemental approval. The Agency determined that it was not necessary to reassess the acceptable daily intake (ADI) for bacitracin. (The ADI is the largest amount of the drug that will not harm people even if they consume that amount every day.) The ADI for total residue of bacitracin remains 0.05 mg/kg body weight per day.

FDA did not require new residue chemistry studies for this supplemental approval. The tolerance for bacitracin in the edible tissues of chickens remains 0.5 parts per million and the withdrawal period remains 0 days. (The tolerance is the highest concentration of drug residues legally allowed to be in or on food products made from treated animals. The withdrawal period allows for drug residues in the animal's body to get to levels that are at or below the tolerance.)

FDA previously evaluated the validated analytical method for detecting bacitracin residues in edible tissues and found its use acceptable.

### **Conclusions**

Based on the data submitted by the sponsor for the approval of Pennitracin MD 50G<sup>®</sup> (bacitracin Type A medicated article), FDA determined that the drug is safe and effective when used according to the labeling.

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**I. GENERAL INFORMATION**

**A. File Number**

NADA 141-137

**B. Sponsor**

Pharmgate Inc.  
1800 Sir Tyler Dr.  
Wilmington, NC 28405

Drug Labeler Code: 069254

**C. Proprietary Name**

Pennitracin MD 50G®

**D. Drug Product Established Name**

bacitracin Type A medicated article

**E. Pharmacological Category**

Antimicrobial

**F. Dosage Form**

Type A medicated article to be used in the manufacture of Type B and Type C medicated feeds

**G. Amount of Active Ingredient**

Each pound contains feed grade bacitracin methylenedisalicylate equivalent to 50 grams bacitracin

**H. How Supplied**

50 lb bag

**I. Dispensing Status**

Over-the-counter (OTC)

**J. Dosage Regimen**

50 grams of bacitracin per ton in Type C medicated feed. Feed as the sole ration for 28 to 35 days, starting from the time chicks are placed for brooding.

**K. Route of Administration**

Oral

**L. Species/Class**

Broiler and replacement chickens

**M. Indication**

For the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler and replacement chickens.

**N. Effect of Supplement**

This supplement provides for the addition of a therapeutic indication, "for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler and replacement chickens."

**II. EFFECTIVENESS**

**A. Dosage Characterization**

Pharmgate Inc. chose to investigate the use of 50 g bacitracin/ton in feed for the prevention of necrotic enteritis in broiler and replacement chickens because Pennitracin MD 50G<sup>®</sup> is approved for use at this level for other indications in chickens, and because various articles in the literature<sup>1,2,3</sup> suggest that this level may be effective against necrotic enteritis.

Two pilot challenge model studies (Studies XB019-18-04xx and XB020-19-04xx) were conducted using a similar protocol to evaluate the effectiveness of bacitracin Type A medicated article fed as a Type C medicated feed to broiler chickens at 0 g/ton or 50 g/ton for 28 days, beginning on the day of hatch, for necrotic enteritis.

In Study XB019-18-04xx, 420 day-of-hatch male, commercial broiler chicks were randomly allocated to one of seven treatment groups in a total of 42 pens (10 chicks per pen). The experimental unit was the pen of birds. Experimental feeds (bacitracin-treated and non-medicated) were administered beginning on day of hatch (Day 0). Chicks were fed starter crumbles from Day 0 through Day 17 and grower pellets from Day 17 through Day 28.

The treatment groups included: Group 1: non-medicated, unchallenged; Group 2: non-medicated (0 g/ton), challenged with a *C. perfringens* inoculum strain ("strain A"); Group 3: bacitracin-treated (50 g/ton), challenged with *C. perfringens* inoculum strain A; Group 4: non-medicated (0 g/ton), challenged with a different *C. perfringens* inoculum strain ("strain B"); Group 5: bacitracin-treated (50 g/ton), challenged with *C. perfringens* inoculum strain B; Group 6: non-medicated (0 g/ton), challenged with a third *C. perfringens* inoculum strain ("strain C"); and Group 7: bacitracin-treated (50 g/ton), challenged with *C. perfringens* inoculum strain C.

All inoculums were administered as 2 to 3 mL of broth culture (approximately  $1.0$  to  $9.0 \times 10^8$  cfu/mL) mixed with a fixed amount of feed to equal approximately 25 g/bird. On Day 17, starter feed was removed for 4 to 8 hours. *C. perfringens* challenge inoculum was administered in grower pellets to birds in Groups 2 through 7 for approximately 1 to 2 hours. On Day 17, the challenge feed was removed and grower pellets were fed through Day 28. Birds were observed twice daily for general health and mortality.

*C. perfringens* inoculum strain A successfully induced representative necrotic enteritis lesions and mortality. Between Day 17 and Day 28 mortality caused by necrotic enteritis was significantly different ( $p < 0.05$ ) and higher in the non-medicated, challenged group (Group 2) compared with the bacitracin-treated, challenged group (Group 3). Group 1 had no necrotic enteritis mortality. There was 21.67% mortality in Group 2 compared with 0.00% mortality in Group 3. The results of Groups 4, 5, 6, and 7 were not used for dosage characterization because the challenge was unsuccessful.

In Study XB020-19-04xx, 2,000 day-of-hatch male, commercial broiler chicks were randomly assigned to one of five treatment groups in a total of 40 pens (50 chicks per pen). The experimental unit was the pen of birds. Experimental feeds (bacitracin-treated and non-medicated) were administered beginning on day of hatch (Day 0). Chicks were fed starter mash from Day 0 through Day 14 and grower pellets from Day 14 through Day 28.

The treatment groups included: Group 1: non-medicated, unchallenged; Group 2: non-medicated (0 g/ton), challenged with a *C. perfringens* inoculum strain mixed at 1 liter bacterial broth per kg of feed (normal level); Group 3: bacitracin-treated (50 g/ton), challenged with the same *C. perfringens* inoculum strain at the normal level; Group 4: non-medicated (0 g/ton), challenged with the same *C. perfringens* inoculum strain mixed at 1.5 liter bacterial broth per kg of feed (high level); and Group 5: bacitracin-treated (50 g/ton), challenged with the same *C. perfringens* inoculum strain at the high level.

On Day 14, starter feed was removed for 8 hours. *C. perfringens* challenge inoculum was administered to birds in grower pellets for approximately 16 hours. On Day 15, challenge feed was removed and grower pellets were fed through Day 28. Birds were observed twice daily for general health and mortality.

Between Day 14 and Day 28 mortality caused by necrotic enteritis was significantly different ( $p < 0.05$ ) and higher in the non-medicated, challenged groups (Groups 2 and 4) compared with the bacitracin-treated, challenged groups (Groups 3 and 5, respectively) without regard to the administration of the normal or high challenge inoculum. Group 1 had no necrotic enteritis mortality. There was 22.75% mortality in Group 2 compared with 0.75% mortality in Group 3. There was 17.25% mortality in Group 4 compared with 1.00% mortality in Group 5.

Based on the results of Studies XB019-18-04xx and XB020-19-04xx, Pharmgate Inc. chose to evaluate administration of 50 g bacitracin/ton in the studies conducted to demonstrate substantial evidence of effectiveness.

References:

1. Prescott, J. F., R. Sivendra, and D. A. Barnum. 1978. The use of bacitracin in the prevention and treatment of experimentally-induced necrotic enteritis in the chicken. *Canadian Veterinary Journal* 19:181-183.
2. Brennan, J., J. Skinner, D. A. Barnum, and J. Wilson. 2003. The efficacy of bacitracin methylene disalicylate when fed in combination with narasin in the management of necrotic enteritis in broiler chickens. *Poultry Science* 82:360-363.
3. Brennan, J. J., J. Radu, D. A. Barnum, D. Carrier, J. Kelly, and B. Kilmer. 1996. Efficacy of zinc bacitracin and bacitracin methylene disalicylate for prevention of necrotic enteritis in broiler chickens. *Poultry Science* 75 (Suppl. 1):283.

**B. Substantial Evidence**

Two single-site experimentally induced infection model studies were conducted and independently analyzed. To demonstrate effectiveness, the results from each study had to show a statistically significant difference in mortality caused by necrotic enteritis between the bacitracin-treated group and the non-medicated group, in favor of the bacitracin-treated group ( $p < 0.05$ ) and show a clinically relevant improvement in mortality caused by necrotic enteritis between the bacitracin-treated group and the non-medicated group. In addition, a sufficient preventive fraction was required to be observed in each study to demonstrate prevention was achieved. Together, the studies demonstrate that Pennitracin MD 50G<sup>®</sup> (bacitracin Type A medicated article) administered at 50 g bacitracin/ton in Type C medicated feed for 28 consecutive days is effective for prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler and replacement chickens. Pharmgate Inc. referred to publicly available literature to justify that a duration range of 28 to 35 days starting from the time chicks are placed for brooding is appropriately targeted to the risk periods for necrotic enteritis that may be experienced by broiler and replacement chickens.

1. Experimentally Induced Infection Model Study

**Title:** Evaluation of the Effectiveness of Dietary Bacitracin Methylendisalicylate from Pennitracin MD 50G<sup>®</sup> Type A Medicated Article for the Prevention and Reduction of Necrotic Enteritis Mortality in Broiler Chickens Challenged with *Clostridium Perfringens* on Study Day 14. (Study No. CB002-19-04xx)

**Study Dates:** July 30, 2020 to August 27, 2021

**Study Location:** Tulare, California

**Study Design:**

Objective: To demonstrate that 50 g bacitracin/ton administered in medicated feed from the time of chick placement for 28 consecutive days prevents mortality caused by necrotic enteritis associated with *C. perfringens* in chickens.



**Study Animals:** The study enrolled 1,600 healthy, day-of-hatch, straight run, commercial strain (Cobb 500) broiler chicks. Chicks were weighed by pen and were representative of industry norms.

**Experimental Design:** This study was a randomized, masked, block design with two treatment groups. The study was conducted in accordance with Good Clinical Practice (GCP) VICH GL9.

A total of 1,600 day-of-hatch chicks were randomly sorted into 16 blocks of 32 pens. Each pen contained 50 chicks. Each block included one bacitracin-treated feed group and one non-medicated feed group.

**Table II.1. Treatment Groups.**

<b>Treatment Group</b>	<b>Number of Pens</b>	<b>Number of Chicks</b>
Non-medicated feed	16	800
Bacitracin-treated feed	16	800

**Drug Administration:** The test article was Pennitracin MD 50G® (bacitracin Type A medicated article) administered in Type C medicated feed at 50 g bacitracin/ton. Non-medicated feed was used as the control article. Treatment began when day-of-hatch chicks were placed in the test facility (Day 0) through Day 28.

**Challenge Administration:** On Day 14, both study groups were challenged with a *C. perfringens* isolate to induce representative disease in challenged chicks. The isolate was initially collected in July 2007 from a broiler chicken that died during a spontaneous necrotic enteritis outbreak in North America. Following an approximately 8-hour period of feed withdrawal, the *C. perfringens* challenge was administered to birds in non-medicated grower feed for approximately 16 hours.

**Measurements and Observations:** Chicks were observed twice daily from Day 0 to Day 28 for abnormal health and mortality. Chicks were weighed by pen on Days 0, 14, and 28. Chicks found dead or euthanized were weighed individually and necropsied to evaluate for the presence or absence of necrotic enteritis lesions. Starter feed was weighed prior to placement in each pen on Day 0, and when feed was removed from each pen on Day 14. Grower feed was weighed prior to placement in each pen on Days 14 and 21, and when removed from each pen on Day 28.

**Statistical Methods:** The primary variable for determining effectiveness was the percentage of mortality caused by necrotic enteritis, confirmed by necropsy, for Days 0 to 28. The experimental unit was the pen of birds. A generalized linear mixed model analysis was performed on the primary effectiveness variable where treatment was a fixed effect and block was a random effect. The analysis was performed using the binomial distribution with the logit link.

**Results:** A statistically significant difference in mortality caused by necrotic enteritis between the bacitracin-treated group and the non-medicated control group was detected, in favor of the bacitracin-treated group ( $p < 0.0001$ ). The least squares means calculated mortality was 0.73% for the bacitracin-treated group and 16.28% for the non-medicated group. The preventive fraction was 0.95, which was considered sufficient to demonstrate prevention was achieved.

**Adverse Reactions:** There were no test article-related adverse reactions reported in this study.

**Conclusion:** This study demonstrates that Pennitracin MD 50G<sup>®</sup> (bacitracin Type A medicated article) administered at 50 g bacitracin/ton in Type C medicated feed for 28 consecutive days is effective for prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler and replacement chickens.

## 2. Experimentally Induced Infection Model Study

**Title:** Evaluation of the Effectiveness of Dietary Bacitracin Methylenedisalicylate from Pennitracin MD 50G<sup>®</sup> Type A Medicated Article for the Prevention and Reduction of Necrotic Enteritis Mortality in Broiler Chickens Challenged with *Clostridium Perfringens* on Study Day 17. (Study No. CB003-19-04xx)

**Study Dates:** August 28, 2020 to May 4, 2021

**Study Location:** Wellington, Colorado

### **Study Design:**

**Objective:** To demonstrate that 50 g bacitracin/ton administered in medicated feed from the time of chick placement for 28 consecutive days prevents mortality caused by necrotic enteritis associated with *C. perfringens* in chickens.

**Study Animals:** The study enrolled 1,280 healthy, day-of-hatch, straight run, commercial strain (Cobb 500) broiler chicks. Chicks were weighed by pen and were representative of industry norms.

**Experimental Design:** This study was a randomized, masked, block design with two treatment groups. The study was conducted in accordance with GCP VICH GL9.

A total of 1,280 day-of-hatch chicks were randomly sorted into 16 blocks of 32 pens. Each pen contained 40 chicks. Each block included one bacitracin-treated feed group and one non-medicated feed group.

**Table II.2. Treatment Groups.**

<b>Treatment Group</b>	<b>Number of Pens</b>	<b>Number of Chicks</b>
Non-medicated control feed	16	640
Bacitracin medicated feed	16	640

**Drug Administration:** The test article was Pennitracin MD 50G<sup>®</sup> (bacitracin Type A medicated article) administered in Type C medicated feed at 50 g bacitracin/ton. Non-medicated feed was used as the control article. Treatment began when day-of-hatch chicks were placed in the test facility (Day 0) through Day 28.

**Challenge Administration:** On Day 18, both study groups were challenged with a *C. perfringens* isolate to induce representative disease in challenged chicks. The isolate was initially collected in July 2007 from a North American broiler facility experiencing necrotic enteritis-induced death loss. Following an approximately 5.5 hour period of feed withdrawal, the *C. perfringens* challenge was administered to birds in non-medicated grower feed for approximately 2 hours.

**Measurements and Observations:** Chicks were observed twice daily from Day 0 to Day 28 for abnormal health and mortality. Chicks were weighed by pen on Days 0, 14, and 28. Chicks found dead or euthanized were weighed individually and necropsied to evaluate for the presence or absence of necrotic enteritis lesions. Starter feed was weighed prior to placement in each pen on Day 0, and when feed was removed from each pen on Day 14. Grower feed was weighed prior to placement in each pen on Days 14 and 21, and when removed from each pen on Day 28.

**Statistical Methods:** The primary variable for determining effectiveness was the percentage of mortality caused by necrotic enteritis, confirmed by necropsy, for Days 0 to 28. The experimental unit was the pen of birds. A generalized linear mixed model analysis was performed on the primary effectiveness variable where treatment was a fixed effect and block was a random effect. The analysis was performed using the binomial distribution with the logit link.

**Results:** The generalized linear mixed model for the primary effectiveness variable failed to converge due to 0.00% mortality in the treated group. Wilcoxon Rank Sum test at pen level was performed instead. A statistically significant difference in mortality caused by necrotic enteritis between the bacitracin-treated group and the non-medicated control group was detected, in favor of the bacitracin-treated group ( $p < 0.0001$ ). The average mortality per pen was 0.00% for the treated group and 6.41% (median 5.00%; range 0.00%-15.00%) for the control group. The preventive fraction was 1, which was considered sufficient to demonstrate prevention was achieved.

**Adverse Reactions:** There were no test article-related adverse reactions reported in this study.

**Conclusion:** This study demonstrates that Pennitracin MD 50G<sup>®</sup> (bacitracin Type A medicated article) administered at 50 g bacitracin/ton in Type C medicated feed for 28 consecutive days is effective for prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler and replacement chickens.

### **III. TARGET ANIMAL SAFETY**

CVM did not require target animal safety studies for this supplemental approval. NADA 141-137, approved October 6, 2015, as published in the FEDERAL REGISTER (80 FR 79474) on December 22, 2015, addressed target animal safety in chickens.

### **IV. HUMAN FOOD SAFETY**

#### **A. Microbial Food Safety**

The Agency evaluated microbial food safety information for the use of Pennitracin MD 50G<sup>®</sup> in broiler and replacement chickens for prevention of necrotic enteritis at a dose of 50 g bacitracin/ton. The microbial food safety assessment submitted for Agency review included a hazard characterization describing the use of Pennitracin MD 50G<sup>®</sup>, and the potential for Pennitracin MD 50G<sup>®</sup> to select for the emergence or dissemination of antimicrobial resistance among organisms of public health concern originating from Pennitracin MD 50G<sup>®</sup>-treated animals. Bacitracin currently is not considered "medically important" per Agency criteria, and bacitracin currently is approved for both treatment and production uses in food-producing animals. Thus, the proposed therapeutic uses of Pennitracin MD 50G<sup>®</sup> in chickens for a defined duration should not provide an increased risk to public health from an increase in the level of bacitracin-resistant organisms originating from treated chickens beyond any level currently originating from ongoing therapeutic and production uses of this drug in treated chicken flocks.

#### **B. Toxicology**

CVM determined that reassessment of the codified ADI was not needed for this supplemental approval. The codified ADI of 0.05 mg/kg body weight per day for total residue of bacitracin is listed under 21 CFR § 556.70. Refer to the FEDERAL REGISTER (80 FR 79474) published on December 22, 2015.

#### **C. Residue Chemistry**

CVM did not require residue chemistry studies for this supplemental approval. This supplement does not result in any changes to the previously established tolerance or withdrawal period. The tolerance for bacitracin in edible chicken tissues is 0.5 ppm. The withdrawal period remains 0 days. Refer to the FEDERAL REGISTER (80 FR 79474) published on December 22, 2015.

#### **D. Analytical Methods for Residues**

##### 1. Description of Analytical Methods

A microbiological method, "Modified Microbiological Method for Determination of Bacitracin in Tissues," is used to assay tissues for bacitracin residues.

## 2. Availability of the Methods

The validated analytical method for analysis of residues of bacitracin methylenedisalicylate Type A medicated article is on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, please submit a Freedom of Information request to:

<https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm>.

## V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Pennitracin MD 50G®:

### User Safety Warnings:

Not for use in humans. Keep out of reach of children.

## 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 (FD&C Act) and 21 CFR part 514. The data demonstrate that Pennitracin MD 50G®, when used according to the label, is safe and effective for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler and replacement chickens. Additionally, data demonstrate that residues in food products derived from species treated with Pennitracin MD 50G® will not represent a public health concern when the product is used according to the label.

### A. Marketing Status

This product can be marketed OTC because the approved labeling contains adequate directions for 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 Pennitracin MD 50G® qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler and replacement chickens.

### 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 Green Book Reports in the Animal Drugs @ FDA database.