Date of Approval: May 23, 2017

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 055-099

CLAVAMOX® CHEWABLE

amoxicillin and clavulanate potassium tablets

Chewable tablets

Dogs and Cats

This supplement provides for the addition of a flavored, chewable tablet.

Sponsored by:

Zoetis, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 055-099

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

CLAVAMOX® CHEWABLE

D. Product Established Name

Amoxicillin and clavulanate potassium tablets

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

62.5 mg tablets, 125 mg tablets, 250 mg tablets, 375 mg tablets

Each 62.5-mg tablet contains amoxicillin trihydrate equivalent to 50 mg of amoxicillin activity and 12.5 mg of clavulanic acid as the potassium salt. For use in dogs and cats.

Each 125-mg tablet contains amoxicillin trihydrate equivalent to 100 mg of amoxicillin activity and 25 mg of clavulanic acid as the potassium salt. For use in dogs only.

Each 250-mg tablet contains amoxicillin trihydrate equivalent to 200 mg of amoxicillin activity and 50 mg of clavulanic acid as the potassium salt. For use in dogs only.

Each 375-mg tablet contains amoxicillin trihydrate equivalent to 300 mg of amoxicillin activity and 75 mg of clavulanic acid as the potassium salt. For use in dogs only.

H. How Supplied

CLAVAMOX® CHEWABLE tablets are supplied in strip packs. Each carton holds 10 strips with 10 tablets per strip (100 tablets per carton).

I. Dispensing Status

Rx

J. Dosage Regimen

Dogs: The recommended dosage is 6.25 mg/lb of body weight twice a day.

Cats: The recommended dosage is 62.5 mg twice a day.

K. Route of Administration

Oral

L. Species/Class

Dog and cats

M. Indications

CLAVAMOX CHEWABLE Tablets are indicated in the treatment of:

Dogs:

Skin and soft tissue infections such as wounds, abscesses, cellulitis, superficial/juvenile and deep pyoderma due to susceptible strains of the following organisms: β-lactamase-producing *Staphylococcus aureus*, non-β-lactamase-producing *Staphylococcus aureus, Staphylococcus* spp*., Streptococcus* spp*.,* and *E. coli.*

Periodontal infections due to susceptible strains of both aerobic and anaerobic bacteria. CLAVAMOX CHEWABLE has been shown to be clinically effective for treating cases of canine periodontal disease.

Cats:

Skin and soft tissue infections such as wounds, abscesses, and cellulitis/dermatitis due to susceptible strains of the following organisms: β-lactamase-producing *Staphylococcus aureus,* non-β-lactamase-producing *Staphylococcus aureus, Staphylococcus* spp*., Streptococcus* spp*., E. coli,* and *Pasteurella* spp*.*

Urinary tract infections (cystitis) due to susceptible strains of *E. coli*.

Therapy may be initiated with CLAVAMOX CHEWABLE prior to obtaining results from bacteriological and susceptibility studies. A culture should be obtained prior to treatment to determine susceptibility of the organisms to CLAVAMOX. Following

determination of susceptibility results and clinical response to medication, therapy may be reevaluated.

N. Effect of Supplement

This supplement provides for the addition of a flavored, chewable tablet.

II. EFFECTIVENESS

For the dog and cat indications, the effectiveness of CLAVAMOX® CHEWABLE tablets was demonstrated via the use of a relative bioavailability approach for bridging to the data generated when using the original film-coated CLAVAMOX® tablets (amoxicillin and clavulanate potassium tablets). The following is a summary of the data used to support this bridge.

A. Dogs

The effectiveness for CLAVAMOX® CHEWABLE tablets has been demonstrated via bioequivalence to the original CLAVAMOX® tablets. Refer to the original Freedom of Information (FOI) Summary for CLAVAMOX® tablets (NADA 055-099) for the effectiveness studies used to support the original approval (September 28, 1984) for the treatment of skin infections such as superficial/juvenile and deep pyoderma of dogs due to susceptible strains of the following organisms: β-lactamase (penicillinase) producing *Staphylococcus aureus*, non-β-lactamase *Staphylococcus aureus* and *Staphylococcus* spp. in dogs. Refer to the FOI summary for the supplemental approval dated December 16, 1985, for the effectiveness studies to support the approval of CLAVAMOX® tablets for the additional indication for soft tissue infections in dogs. Refer to the FOI Summary for the supplemental approval dated December 23, 1997, for the effectiveness data to support the additional indication against canine periodontal infections due to susceptible strains of aerobic and anaerobic bacteria.

The palatability of CLAVAMOX® CHEWABLE tablets in dogs was evaluated in a clinical field study.

1. **Dosage Characterization**

   This supplemental approval does not change the previously approved dosage as presented in the FOI Summary for the original and supplemental approvals of NADA 055-099, dated September 28, 1984, December 16, 1985, and December 23, 1997, respectively.

2. **Substantial Evidence**

   Dog Bioequivalence Study: Comparative Pharmacokinetic Study of CLAVAMOX® Tablet and a Chewable Amoxicillin with Clavulanic Acid Tablet Following Oral Administration in Dogs (Study number A461N-US-14-474).

   Type of Study: Pharmacokinetic study

   Testing Facility: Covance Laboratories Inc.

General Design:

Purpose of Study: This pharmacokinetic study was conducted to demonstrate the bioequivalence of the currently approved CLAVAMOX® tablet and the CLAVAMOX® CHEWABLE tablet in dogs following oral administration.

Study Design: This study was a two treatment three period crossover design. A four day washout separated the period 1 and 2 drug administrations, and a three day washout separated the period 2 and 3 dose administrations. Animals were randomly assigned to sequence and pen.

Table 1: Treatment Groups in the Dog

Sequence	Treatment Group Period 1	Treatment Group Period 2	Treatment Group Period 3	Number of Animals
1	CLAVAMOX® tablets	CLAVAMOX® tablets	CLAVAMOX® CHEWABLE tablets	9
2	CLAVAMOX® tablets	CLAVAMOX® CHEWABLE tablets	CLAVAMOX® tablets	9
3	CLAVAMOX® CHEWABLE tablets	CLAVAMOX® tablets	CLAVAMOX® tablets	9

Description of Test Animals: Twenty-seven (27) healthy, male and female Beagles, over 6 months of age and weighing 7.2 to 13.2 kg, were used in the study.

Dosage Form: CLAVAMOX® tablets and CLAVAMOX® CHEWABLE tablets.

Prandial State: Animals were fasted (>8 hr) prior to each dose with food returned approximately 4 hours post dose.

Route of Administration: All tablets were pilled followed by 5 mL of water.

Dose Rate: For each dosing and both treatments, dogs received one 125 mg tablet containing 100 mg amoxicillin trihydrate and 25 mg potassium clavulanate.

Blood Sampling: Pre-dose, then post-dose at 20 and 40 minutes, and 1, 1.5, 2, 3, 4, 5, 8, 14 and 24 hours.

Assay Methodology: Amoxicillin and clavulanic acid concentrations in plasma were determined using a validated LC-MS/MS method.

Statistical Methods: The data was analyzed with a mixed model procedure (SAS/STAT User's Guide, SAS Institute, Cary, North Carolina). The pharmacokinetic variables area under curve from time zero to the last concentration at or above the analytical limit of quantification (AUClast), µg/mL×hr) and the maximum observed concentration (Cmax, µg/mL) were calculated for each animal, treatment, and period combination. These variables

were transformed to the natural log before analysis and were analyzed with a statistical model appropriate for the study design. Estimates of the treatment means and the difference between the means along with 90% confidence intervals were determined. Treatment Least Square means and their difference were back-transformed to geometric means and geometric mean ratios, respectively.

The arithmetic (untransformed) values of the secondary PK parameters, time to peak concentrations (Tmax) and terminal elimination half-life (Thalf) were also analyzed. The test and reference values for these secondary parameters were qualitatively compared.

Results:

Table 2a. Summary of Bioequivalence Results of Amoxicillin in Dogs Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Product	Ref	Test	Ref	Test	Ref	Test	Ref	Test
Number of Observations	54	27	54	27	54	27	54	27
Variable evaluated	Mean AUClast (hr*µg/mL)	Mean AUClast (hr*µg/mL)	Mean Cmax (µg/mL)	Mean Cmax (µg/mL)	Mean Tmax (hr)	Mean Tmax (hr)	Mean Thalf (hr)	Mean Thalf (hr)
Mean	17.69*	17.68*	5.78*	5.94*	1.48**	1.44**	1.26**	1.24**
Minimum***	7.53	7.17	3.19	2.27	1.00	1.00	0.86	0.93
Maximum***	33.40	31.90	11.89	9.60	3.00	2.00	2.67	1.91

* = geometric Least Square mean
** = arithmetic Least Square mean
*** = minimum and maximum of all observations

Table 2b: Bioequivalence Decision: Amoxicillin in Dogs Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Parameter	AUClast (hr*µg/mL)	Cmax (µg/mL)
GMR	1.00	1.03
Lower Confidence Interval	0.93	0.95
Upper Confidence Interval	1.07	1.11
Bioequivalence Conclusion	Pass	Pass

GMR = geometric mean ratio = exponentiated value of the Least Square mean of the difference between the Ln-transformed AUC or Cmax values.

Table 2c: Summary of Bioequivalence Results of Clavulanic Acid in Dogs Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Product	Ref	Test	Ref	Test	Ref	Test	Ref	Test
Number of Observations	54	27	54	27	54	27	54	27
Variable evaluated	AUClast (hr*µg/mL)	AUClast (hr*µg/mL)	Cmax (µg/mL)	Cmax (µg/mL)	Tmax (hr)	Tmax (hr)	Thalf (hr)	Thalf (hr)
Mean	4.56*	4.75*	3.09*	3.15*	0.93**	1.03**	0.58**	0.59**
Minimum***	0.36	2.66	0.21	1.63	0.33	0.67	0.48	0.50
Maximum***	7.76	7.12	4.93	5.68	2.00	2.00	1.13	0.69

* = geometric Least Square mean
** = arithmetic Least Square mean
*** = minimum and maximum of all observations

Table 2d: Bioequivalence Decision: Clavulanic Acid in Dogs Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Parameter	AUClast (hr*µg/mL)	Cmax (µg/mL)
GMR	1.04	1.02
Lower Confidence Interval	0.90	0.87
Upper Confidence Interval	1.21	1.20
Bioequivalence Conclusion	Pass	Pass

GMR = geometric mean ratio = exponentiated value of the Least Square mean of the difference between the Ln-transformed AUC or Cmax values.

Conclusions: CLAVAMOX® tablets and CLAVAMOX® CHEWABLE tablets were bioequivalent following oral administration to dogs.

3. **Biowaiver of additional tablet strengths.**

Type of Study: *In Vitro* Dissolution

Testing Facility: Zoetis Animal Health

General Design:

The *in vitro* dissolution testing was conducted in 900 mL of water using the paddle at 75 rpm. Temperature was maintained at 37° ± 0.5° C. Peaked vessels were used across all tablet strengths to insure adequate mixing of dissolution fluids and disintegrated drug. Sampling time points included 5, 10, 15, 20, 30, and 45 minutes. A high performance liquid chromatography (HPLC) method was used to quantify the concentrations of amoxicillin and clavulanic acid in the dissolution vessels.

The conditions for granting this waiver of *in vivo* bioequivalence study requirements included proportional equivalence in the amounts of active and inactive ingredients included in each tablet, and a demonstration of equivalent dissolution profiles between the additional strengths of the test formulation versus that of the lot of the test tablet used in the pivotal *in vivo* bioequivalence study. Across strength differences in test product *in vitro* dissolution profiles were observed for the highest strength; therefore, the

profile comparison for that strength was based upon a within-strength comparison between the test and reference products. Justification for this between-product comparison was made by showing that the reference tablets themselves fail to show equivalence to the strength of the reference product that was used in the *in vivo* bioequivalence study.

In vitro tablet dissolution profile comparability was numerically determined through the use of an algorithm termed the "F2" metric. The F2 metric is estimated as follows:

$$F2 = 50 \times log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R-T)^2\right]^{-0.5} \times 100\right\}$$

where F2 equals fifty times the log of the value defined by the following computation: the value of one plus the sum of the squared differences between the average percent dissolved of the reference and test products. The summed value is divided by n, where n is the number of time points included in the summation. The inverse of the square root of that resulting value is generated, and then that resulting value is multiplied by 100.

R is the dissolution mean value of the reference (pre-change) batch at time t, and T is the dissolution mean value of the test (post-change) batch at time t.

F2 is an algorithm that is calculated on the basis of mean percent dissolution at each of the sampling times. The *in vitro* analytical method used to quantify the amount of drug dissolved in the dissolution fluids was shown to be accurate, precise, linear, and stable throughout the range of concentrations to be measured in the *in vitro* dissolution fluids.

For curves to be considered similar, F2 values should be equal to or greater than 50 (50-100).

Results:

The *in vitro* dissolution of all test and reference tablet strengths exhibited greater than 85% of the label amount of amoxicillin and clavulanic acid within 15 minutes of testing. The 62.5 mg and 250 mg strength chewable tablet strengths succeeded in meeting the F2 criterion for the two active pharmaceutical ingredients. However, the 375 mg strength tablet failed to demonstrate comparability to the test lot that was used in the *in vivo* bioequivalence study. Therefore, a comparison was made of the dissolution profiles associated with the chewable (test) and film coated (reference) 375 mg tablets. Both amoxicillin and clavulanic acid met the F2 metric for this comparison. It was also noted that the reference product itself failed to meet the comparability criterion when the 125 mg and 375 mg strengths were compared. The estimates of the F2 metric for each comparison made during this analysis are provided in Tables 3 and 4:

Table 3a: F2 Metric Calculated Across Tablet Strengths for Comparisons of the Test (CLAVAMOX® CHEWABLE) and Reference/Ref (Film Coated CLAVAMOX® Tablet): Clavulanic Acid, Reference Tablet Used in Bio Lot Study vs. Test Tablet

Bio Lot Tablet (as "Reference" strength) (mg)	Test Tablet (strength for biowaiver) (mg)	F2
25	12.5	76.94
25	50	61.19
25	75	41.94

Table 3b: F2 Metric Calculated Across Tablet Strengths for Comparisons of the Test (CLAVAMOX® CHEWABLE) and Reference/Ref (Film Coated CLAVAMOX® Tablet): Clavulanic Acid, Test Tablet vs. Original Film Coated Tablet

Chewable Tablet (test formulation) (mg)	Film Coated Tablet (original formulation) (mg)	F2
25 (bio lot)	25	59.97
75	75	63.38

Table 3c: F2 Metric Calculated Across Tablet Strengths for Comparisons of the Test (CLAVAMOX® CHEWABLE) and Reference/Ref (Film Coated CLAVAMOX® Tablet): Clavulanic Acid, Different Strengths of Original Film Coated Tablet

Ref (film coated) Tablet	Ref (film coated)Tablet	F2
25 mg	75 mg	34.11

Table 4a: F2 Metric Calculated Across Tablet Strengths for Comparisons of the Test (CLAVAMOX® CHEWABLE) and Reference/Ref (Film Coated CLAVAMOX® Tablet): Amoxicillin, Reference Tablet Used in Bio Lot Study vs. Test Tablet

Bio Lot Tablet (as "Reference" strength) (mg)	Test Tablet (strength for biowaiver) (mg)	F2
100	50	54.05
100	200	51.39
100	300	42.62

Table 4b: F2 Metric Calculated Across Tablet Strengths for Comparisons of the Test (CLAVAMOX® CHEWABLE) and Reference/Ref (Film Coated CLAVAMOX® Tablet): Amoxicillin, Test Tablet vs. Original Film Coated Tablet

Chewable Tablet (test formulation) (mg)	Film Coated Tablet (original formulation) (mg)	F2
100	100	46.28
300	300	58.10

Table 4c: F2 Metric Calculated Across Tablet Strengths for Comparisons of the Test (CLAVAMOX® CHEWABLE) and Reference/Ref (Film Coated CLAVAMOX® Tablet): Amoxicillin, Different Strengths of Original Film Coated Tablet

Ref (film coated) Tablet	Ref (film coated)Tablet	F2
100 mg	300 mg	33.75

It should be noted that with the exception of the 375 mg strength tablets, all of the F2 calulations were based upon three timepoints. Comparisons including the 375 mg strength tablets included four sampling timepoints. It should also be noted that the lots of the 125 mg strength test tablets were identical to those used in the pivotal canine *in vivo* bioequivalence study. However, that of the reference formulation was not the same as the lot that was used in the original *in vivo* bioequivalence (BE) study (the lot of the reference product used in the *in vivo* BE study was beyond expiry at the time of this *in vitro* dissolution study). Because the biowaiver depended on comparison to the 125 mg test formulation and because the reference tablet 125 mg versus 375 mg strength tablet dissolution profiles differed to a magnitude that was even greater than that observed with the chewable tablets, this deviation was not considered a critical flaw.

Conclusion: The biowaiver is granted for the 62.5 mg, 250 mg, and 375 mg strength CLAVAMOX® CHEWABLE tablet formulation.

4. Palatability study in dogs

Title: CLAVAMOX® CHEWABLE Tablets Palatability Study in Client-Owned Dogs (STUDY NUMBER: A163C-US-13-170)

Type of Study: Multi-location field study in the United States

Animals: Client owned dogs of any breed, sex, 6 months of age or older, weighing ≥ 5 lbs and ≤ 120 lbs at study start. The dogs were administered an oral antibiotic containing amoxicillin and clavulanic potassium to treat a skin or soft tissue infection such as a wound, abscess, cellulitis or pyoderma.

General Design: A non-randomized, unmasked, multi-centered clinical study.

Table 5: Palatability Study Design in the Dog

Treatment	Minimum Dosage	Regimen	Route of Administration	Days of Voluntary Acceptance Assessment*	Number of Evaluable Animals
CLAVAMOX® CHEWABLE Tablets	6.25 mg/lb (12.5 mg/kg)	twice daily for 7 (+3) Days	Oral	Days 0-6	112

* First 14 doses, Days 0-6 +/-1 day.

Dosage Form: Commercial Amoxicillin and Clavulanate Potassium tablets (CLAVAMOX® CHEWABLE), in the following strengths: 62.5 mg, 125 mg, 250 mg, 375 mg, and 500 mg tablets.

Prandial State: CLAVAMOX® CHEWABLE was administered without respect to when the dog had been fed.

Voluntary Acceptance Assessment: The voluntary acceptance of the CLAVAMOX® CHEWABLE article was assessed by the Owner twice daily through Day 6 (+1, total of 14 doses). Although some dogs continued to receive CLAVAMOX® CHEWABLE article beyond the 14 doses, these additional offerings (i.e. Days 7-9) were not evaluated.

Results: 116 dogs were enrolled in study over nine study sites. Four dogs were removed from the palatability summary due to not being offered a minimum of 12 doses or because of owner lack of compliance. Of the remaining 112 dogs, a total of 1567 doses were offered and 1293 (82.51%) doses were freely accepted within five minutes.

Conclusions: The palatability of CLAVAMOX® CHEWABLE tablets was evaluated in a multi-location field study. One hundred twelve (112) client-owned dogs were dosed with CLAVAMOX® CHEWABLE tablets at 6.25 mg/lb (12.5 mg/kg) twice daily for seven days and evaluated for palatability of the product. Dogs freely consumed 83% of their doses within five minutes of offering from an empty bowl or owner's hand. Of the 17% of doses unconsumed after five minutes, 16% were administered with a treat/food or forced intake and 1% of doses were refused.

B. Cats

The effectiveness for CLAVAMOX® CHEWABLE tablets has been demonstrated via a comparison of the systemic exposure of amoxicillin and clavulanic acid resulting from administration of CLAVAMOX® CHEWABLE tablets and the original CLAVAMOX® tablets. Refer to the original Freedom of Information (FOI) Summary for CLAVAMOX® tablets (NADA 055-102) for the effectiveness studies used to support the original approval (November 20, 1985) for the treatment of feline skin/soft tissue infections such as wounds, abscesses and cellulitis/dermatitis due to susceptible strains of the following organisms: β-lactamase producing *Staphylococcus aureus*, non-β-lactamase *Staphylococcus aureus, Staphylococcus* spp., *Streptococcus* spp., *E. coli* and *Pasteurella* spp. as well as urinary tract infections (cystitis) due to susceptible strains of *E. coli*. NADA 055-102 was

combined into NADA 055-099 with the supplemental approval dated December 16, 1985.

1. **Relative Bioavailability Studies in the Cat:**

Two pharmacokinetic studies were included in this relative bioavailability assessment. Twenty-three out of the twenty-four cats in Study number A481N-US-15-170 were identical to those used in Study number A481N-US-14-142; the design of the two studies was identical.

Title: Comparative Pharmacokinetic Study of CLAVAMOX® tablet and a Chewable Amoxicillin with Clavulanic Acid Tablet Following Oral Administration in of 62.5 mg Tablets to Cats (Study Numbers A481N-US-15-170 and A481N-US-14-142)

Type of Study: Pharmacokinetic study

Testing Facility: Experimur, Chicago IL

General Design:

Purpose of Study: These comparative pharmacokinetic studies were conducted to demonstrate the comparability of the rate and extent of systemic clavulanic acid exposure and of amoxicillin exposure following oral administration of the approved CLAVAMOX® tablets and the proposed CLAVAMOX® CHEWABLE tablets in cats.

Study Design: Both studies were conducted as a two treatment, three period crossover investigation. A 15 day washout separated the period 1 and 2 drug administrations, and a seven day washout separated the period 2 and 3 dose administrations. Animals were randomly assigned to sequence and pen. Administration of the reference product on two separate occasions allowed for the application of reference scaled average bioequivalence.

Table 6: Treatment Groups in Cats

Sequence	Treatment Group Period 1	Treatment Group Period 2	Treatment Group Period 3	Number of Animals
A	CLAVAMOX® tablets	CLAVAMOX® tablets	CLAVAMOX® CHEWABLE tablets	8
B	CLAVAMOX® tablets	CLAVAMOX® CHEWABLE tablets	CLAVAMOX® tablets	8
C	CLAVAMOX® CHEWABLE tablets	CLAVAMOX® tablets	CLAVAMOX® tablets	8

Description of Test Animals: Twenty-four (24) domestic short hair female cats > 6 months of age.

Dosage Form: CLAVAMOX® tablets and CLAVAMOX® CHEWABLE tablets

Prandial State: Animals were fasted (>8 hr) prior to each dose with food returned approximately 4 hours post dose.

Route of Administration: All tablet types were pilled followed by an oral water flush.

Dose Rate: For each dosing and both treatments, animals received one 62.5 mg tablet containing 50 mg amoxicillin trihydrate and 12.5 mg potassium clavulanate.

Assay Methodology: Amoxicillin and clavulanic acid concentration in plasma was determined using a validated LC-MS/MS method.

Statistical Methods: The data were analyzed using a mixed model procedure (SAS/STAT User's Guide, SAS Institute, Cary, North Carolina). The pharmacokinetic variables, area under concentration versus time curve from time zero to the last concentration at or above the limit of quantification of the analytical method (AUClast, µg/mL×hr) and the maximum observed concentration (Cmax, µg/mL) were calculated for each animal-treatment-period combination. These variables were transformed to the natural logarithm before analysis and were analyzed with a statistical model appropriate for the study design. Estimates of the treatment means and the difference between the means along with 90% confidence intervals were determined. Treatment Least Square means and their difference were back-transformed to geometric means and geometric mean ratios, respectively. Due to the large within-individual variability observed for the clavulanic acid AUClast and Cmax values in Study A481N-US-15-170, a reference-scaled average bioequivalence (RSABE) approach was used during the formulation comparison in Study A481N-US-15-170. The RSABE approach could not be employed for Study #A481N-US-14-142.

The following calculations and considerations were incorporated into the bioequivalence determination using the RSABE approach:

RSABE bounds = reference scaled bounds based upon the equation:

$$-\left[\ln(1.25)\frac{S_{WR}}{\sigma_{W0}}\right] \leq \mu_{T-}\mu_R \leq \ln(1.25)\frac{\sigma S_{WR}}{\sigma_{W0}}$$

and σ_{WO} is the US regulatory constant set at 0.25
Swr = the estimated within subject variability of the reference product.

Stating this equation in words: The negative of the value of the natural logarithm of 1.25 multiplied by the ratio of the estimated within subject variability of the reference product divided by the US regulatory constant, which is less than or equal to $\mu_T - \mu_R$ where μ_T is the population average response of the log-transformed measure for the test (T) formulation minus $\mu_{R,}$ the population average response of the log-transformed measure of the reference product (R), which is less than or equal to the natural logarithm of 1.25 multiplied by the ratio of the estimated within subject variability of the reference product divided by the US regulatory constant.

Since Swr ≥0.294 in Study A481N-US-15-170, it was deemed acceptable to use the RSABE bounds when interpreting product comparability based upon the 90% confidence interval (CI) for the treatment geometric mean ratios (GMR). However, the criterion of Swr ≥0.294 was not met for Study #A481N-US-14-142 and therefore the RSABE approach could not be employed.

The arithmetic (untransformed) values of the secondary PK parameters, time to peak concentrations (Tmax) and terminal elimination half-life (Thalf) were also analyzed. The test and reference values for these secondary parameters were qualitatively compared.

Results:

Table 7a: Summary of Study #A481N-US-14-142 Results of Amoxicillin in Cats Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Product	Ref	Test	Ref	Test	Ref	Test	Ref	Test
Number of Observations	48	24	48	24	48	24	48	24
Variable evaluated	Mean AUClast (hr*µg/mL)	Mean AUClast (hr*µg/mL)	Mean Cmax (µg/mL)	Mean Cmax (µg/mL)	Mean Tmax (hr)	Mean Tmax (hr)	Mean Thalf (hr)	Mean Thalf (hr)
Mean	31.10*	38.13*	8.12*	9.70*	1.70**	1.75**	1.39**	1.36**
Minimum***	18.73	11.11	4.75	3.02	1.00	1.50	1.18	1.18
Maximum***	64.39	60.88	17.82	15.05	2.00	2.00	2.37	2.47

* = geometric Least Square mean
** = arithmetic Least Square mean
*** = minimum and maximum of all observations

Table 7b: Bioequivalence Decision: Amoxicillin in Cats Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Parameter	AUClast (hr*µg/mL)	Cmax (µg/mL)
GMR	1.23	1.19
Lower Confidence Interval (not scaled)	1.07	1.05
Upper Confidence Interval (not scaled)	1.40	1.35
Bioequivalence Conclusion	Fail	Fail

GMR = geometric mean ratio = exponentiated value of the Least Square mean of the difference between the Ln-transformed AUC or Cmax values.

Table 7c: Summary of Study #A481N-US-14-142 Results of Clavulanic Acid in Cats Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Product	Ref	Test	Ref	Test	Ref	Test	Ref	Test
Number of Observations	48	24	48	24	48	24	48	24
Variable Evaluated	Mean AUClast (hr*µg/mL)	Mean AUClast (hr*µg/mL)	Mean Cmax (µg/mL)	Mean Cmax (µg/mL)	Mean Tmax (hr)	Mean Tmax (hr)	Mean Thalf (hr)	Mean Thalf (hr)
Mean	8.21*	7.97*	4.98*	4.61*	0.67**	0.83**	0.65**	0.66**
Minimum***	4.87	3.82	2.60	1.39	0.33	0.67	0.51	0.52
Maximum***	13.78	12.39	8.38	8.22	1.00	1.50	1.19	2.13

* = geometric Least Square mean
** = arithmetic Least Square mean
*** = minimum and maximum of all observations

Table 7d: Bioequivalence Decision: Clavulanic Acid in Cats Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Parameter	AUClast (hr*µg/mL)	Cmax (µg/mL)
GMR	0.97	0.93
Lower Confidence Interval (not scaled)	0.90	0.83
Upper Confidence Interval (not scaled)	1.05	1.02
Bioequivalence Conclusion	Pass	Pass

GMR = geometric mean ratio = exponentiated value of the Least Square mean of the difference between the Ln-transformed AUC or Cmax values.

Table 8a: Summary of Study #A481N-US-15-170 Results of Amoxicillin in Cats Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Product	Ref	Test	Ref	Test	Ref	Test	Ref	Test
Number of Observations	48	24	48	24	48	24	48	24
Variable Evaluated	Mean AUClast (hr*µg/mL)	Mean AUClast (hr*µg/mL)	Mean Cmax (µg/mL)	Mean Cmax (µg/mL)	Mean Tmax (hr)	Mean Tmax (hr)	Mean Thalf (hr)	Mean Thalf (hr)
Mean	36.08*	37.85*	8.53*	8.89*	1.83**	1.94**	1.54**	1.52**
Minimum***	19.63	14.09	4.53	3.62	1.00	1.50	1.25	1.26
Maximum***	66.42	65.54	14.32	17.51	3.00	3.00	3.58	3.67

* = = geometric Least Square mean
** = arithmetic Least Square mean
*** = minimum and maximum of all observations

Table 8b: Bioequivalence Decision: Amoxicillin in Cats Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Parameter	AUClast (hr*µg/mL)	Cmax (µg/mL)
GMR	1.05	1.04
Swr	0.32	0.29
Lower Confidence Interval	0.90	0.90
Upper Confidence Interval	1.22	1.20
Bioequivalence Conclusion	Pass	Pass

GMR = geometric mean ratio = exponentiated value of the Least Square mean of the difference between the Ln-transformed AUC or Cmax values.
Swr = estimated within subject variability of the reference product

Table 8c: Summary of Study #A481N-US-15-170 Results of Clavulanic Acid in Cats Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Product	Ref	Test	Ref	Test	Ref	Test	Ref	Test
Number of Observations	48	24	48	24	48	24	48	24
Variable Evaluated	Mean AUClast (hr*µg/mL)	Mean AUClast (hr*µg/mL)	Mean Cmax (µg/mL)	Mean Cmax (µg/mL)	Mean Tmax (hr)	Mean Tmax (hr)	Mean Thalf (hr)	Mean Thalf (hr)
Mean	7.57*	6.51*	4.66*	3.85*	0.77**	0.90**	0.67**	0.72**
Minimum***	2.03	2.77	1.23	1.74	0.67	0.67	0.53	0.51
Maximum***	14.40	10.60	9.30	7.10	1.50	2.00	2.03	2.37

* = = geometric Least Square mean
** = arithmetic Least Square mean
*** = minimum and maximum of all observations

Table 8d: Bioequivalence Decision: Clavulanic Acid in Cats Using CLAVAMOX® CHEWABLE (Test) versus Film Coated CLAVAMOX® Tablets (Ref)

Parameter	AUClast (hr*µg/mL)	Cmax (µg/mL)
GMR	0.86	0.83
Swr	0.36	0.43
Lower Confidence Interval	0.74 (RSABE bound = 0.73)	0.70 (RSABE bound = 0.67)
Upper Confidence Interval	0.99 (RSABE bound = 1.37)	0.98 (RSABE bound = 1.49)
Bioequivalence Conclusion	Pass	Pass

GMR = geometric mean ratio = exponentiated value of the Least Square mean of the difference between the Ln-transformed AUC or Cmax values.
Swr = estimated within subject variability of the reference product

Conclusions: Based upon the results of these two studies, it is concluded that the rate and extent of amoxicillin released and absorbed from the chewable tablets are either the same as or slightly greater than that of the original film coated tablets. With regard to the clavulanic acid component, the *in vivo* dissolution and absorption from the new chewable tablet formulation was

found to be the same or slightly less than that of the original film coated tablet formulation. In this regard, product equivalence was observed for the clavulanic acid AUClast and Cmax comparisons in Study #A481N-US-14-142, but lower chewable versus film coated tablet clavulanic acid AUClast and Cmax values were observed in Study A481N-US-15-170. Nevertheless, the clavulanic acid comparison in Study A481N-US-15-170 succeeded in demonstrating product bioequivalence when evaluated from the perspective of the RSABE bounds. Accordingly, it is concluded that the small difference seen in the clavulanic blood levels following administration of the chewable tablet versus the film coated tablet is not clinically relevant.

Based upon the results obtained from Studies #A481N-US-14-142 and #A481N-US-15-170, it is concluded that the observed blood levels of amoxicillin and clavulanic acid support a bridge to the existing effectiveness and safety data generated with the film coated tablets.

III. TARGET ANIMAL SAFETY

The target animal safety of the CLAVAMOX® CHEWABLE tablets was demonstrated via the use of a relative bioavailability approach to bridge back to the original CLAVAMOX® film coated tablets.

Dog
Refer to the original Freedom of Information (FOI) summary for CLAVAMOX® tablets (NADA 055-099) for the safety studies used to support the original approval on September 28, 1984, for use in dogs. Additional safety studies for dog are presented in the FOI summaries for the supplemental approvals dated December 16, 1985 and December 23, 1997.

Cat
Refer to the original FOI summary for CLAVAMOX® tablets (NADA 055-102) for the safety studies to support the original approval on November 20, 1985, for use in cats. NADA 055-102 was combined into NADA 055-099 with the supplemental approval dated December 16, 1997.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs and cats. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to CLAVAMOX® CHEWABLE:

Not for human use. Keep this and all drugs out of reach of children. Antimicrobial drugs, including penicillins and cephalosporins, can cause allergic reactions in sensitized individuals. To minimize the possibility of allergic reactions, those handling such antimicrobials, including amoxicillin and clavulanate potassium, are advised to avoid direct contact of the product with the skin and mucous membranes.

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 CLAVAMOX® CHEWABLE when used according to the label is safe and effective in dogs and cats.

A. Marketing Status

This drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed in the diagnosis of bacterial infections in dogs and cats, treatment of these conditions, and monitoring for possible adverse effects of the drug.

B. Exclusivity

CLAVAMOX® CHEWABLE, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the Food, Drug, and Cosmetic Act.

C. Supplemental Applications

For the purpose of the relative bioavailability assessment for clavulanic acid in cats, this supplemental NADA required an evaluation of certain safety 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.