CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-795

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA #	50-795
PRODUCT	Coated doxycycline hyclate pellets (Doryx®)
FORMULATION	Oral tablets, 75mg and 100mg
SUBMISSION DATES	April 5, 2004; November 23, 2004; December 10, 2004; December 14, 2004; December 17, 2004; December 20, 2004; January 11, 2005; February 18, 2005; March 10, 2005
SUBMISSION TYPE	New Drug Application
SPONSOR	FH Faulding & Co., Ltd. t/a Mayne Pharma International, 1538 Main North Road, Salisbury South, South Australia 5106, Australia
OCPB DIVISION	Division of Pharmaceutical Evaluation III
MEDICAL DIVISION	Division of Anti-Infective Drug Products
REVIEWER	Jeffrey J. Tworzyanski, Pharm.D.
TEAM LEADER	Venkat R. Jarugula, Ph.D.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

1 EXECUTIVE SUMMARY

FH Faulding submitted a New Drug Application to seek approval for a new dosage form (tablet) of their currently marketed product Doryx® capsule. The sponsor currently markets Doryx® (coated doxycycline hyclate pellets) capsules, 75mg and 100mg. In support of their application, the sponsor has submitted data from a single and multiple dose bioequivalence study, and a food effect study. In addition, the sponsor is requesting a biowaiver for the Doryx® 75mg tablet based on dissolution testing results.

The currently marketed product Doryx® (coated doxycycline hyclate pellets) capsules are approved for treatment of a wide spectrum of Gram positive and Gram negative bacteria including Rocky Mountain spotted fever, typhus fever, respiratory tract infections caused by *Mycoplasma pneumoniae*, Inclusion conjunctivitis caused by *Chlamydia trachomatis*, Nongonococcal urethritis caused by *Ureplasma urealyticum*, Plague caused by *Yersinia pestis*, Tularemia caused by *Francisella tularensis*, and Chancroid caused by *Haemophilis ducreyi.*

The bioequivalence study results demonstrated that the currently marketed and the new dosage form of Doryx® are bioequivalent at the 100mg strength. The sponsor's request for a waiver of a bioequivalence study at a lower strength (75mg) is acceptable since the 75mg and 100mg tablet strengths are compositionally proportional and the in vitro dissolution profiles are similar in acid medium and buffer medium (pH of 5.5). The results of the food effect study indicate that food decreased the rate (mean C_{max} is 24% lower), and the extent of doxycycline absorption (mean AUC is 13% lower). The clinical

significance of this decrease in absorption is unknown. However, a similar decrease was noted for the currently approved Doryx capsules. The results of the food-effect study should be stated in the clinical pharmacology section of the label.

1.1 RECOMMENDATIONS:
The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III (OCPB/DPE-III) has reviewed NDA 50-795 and has found the submission acceptable from a Clinical Pharmacology point of view.

The following labeling changes with respect to food effect of Doryx 100mg tablets are recommended to the sponsor:

CLINICAL PHARMACOLOGY

Sponsor proposed:

Change to:

DOSAGE AND ADMINISTRATION

Sponsor proposed:

Change to:

1.2 PHASE IV COMMITMENTS:
No Phase IV commitments are recommended.

Jeffrey J. Tworzyanski, Pharm.D.
Office of ClinicalPharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Venkat R. Jarugula, Ph.D.,
Team Leader

cc:
Division File: NDA 50-795
HFD-520 (CSO/Milstein)
HFD-520 (CMC/Pagay)
HFD-520 (MO/Cooper)
HFD-880 (Division File, Lazor, Selen, Jarugula, Tworzyanski)
CDR (Clin. Pharm./Biopharm.)

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1.3 Summary of Clinical Pharmacology and Biopharmaceutics findings

Doryx tablets and Doryx capsules administered in a single or multiple-dose regimen under fasting conditions were bioequivalent (Study PR-01402-Single and Multiple-Dose Bioavailabilty). The ratio of least square means (and 90% C.I.) for log transformed C_{max} and $AUC_{0-\infty}$ following single dose administration were 103.84% (90% C.I.: 88.04-122.46) and 101.04% (90% C.I.: 89.88-113.60) respectively. The ratio of least square means (and 90% C.I.) for log transformed C_{max} and $AUC_{0-\tau}$ following multiple dose administration were 91.69% (90% C.I.:86.63-97.05) and 89.23% (90% C.I: 84.84-93.85) respectively.

Administration of Doryx with food decreased the rate and extent of doxycycline absorption (Study PR-08302-Administration of Doryx Tablets in the Fed or Fasted State). The mean C_{max} value following the administration of one Doryx tablet in the high-fat fed state was 24% lower (90% C.I.: 69.6-83) than when the tablet was administered in the fasted state. The mean $AUC_{0-\infty}$ following administration of one Doryx tablet in the fed state was 13% lower (90% C.I.: 79.8-95.7) than when the tablet was administered in the fasted state. The clinical significance of the observed decrease in the absorption of Doryx tablets is unknown. However, a similar decrease in the absorption was noted for the currently approved Doryx capsules. The current label for Doryx capsules indicates that if gastric irritation occurs it is recommended that doxycycline be given with food or milk. The results of the food-effect study for Doryx tablets should be stated in the clinical pharmacology section of the label.

FH Faulding is requesting a waiver of the in vivo bioequivalence study requirements for Doryx Tablets 75mg. The biowaiver is acceptable since the composition of both 75mg and 100mg tablets is proportional and they have similar dissolution characteristics.

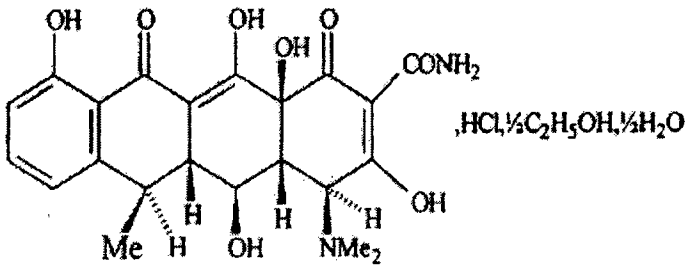
2 QUESTION-BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Doxycycline is a broad spectrum antibiotic synthetically derived from oxytetracycline. The molecular formula is $C_{22}H_{24}N_2O_8$, HCl, $\frac{1}{2}C_2H_6O$, $\frac{1}{2}H_2O$ and the molecular weight is 512.9. The chemical designation of doxycycline hyclate is [4S (4aR, 5S, 5aR, 6R, 12aS)]-4-(dimethylamino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 5, 10, 12, 12a-pentahydroxyl-6-methyl-1, 11-deoxonapthtacene-2-carboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. The chemical structure of doxycycline hyclate is shown below:

Figure 1. Chemical Structure of Doxycycline Hyclate



Doryx (coated doxycycline hyclate pellets) Tablets contain [redacted] of doxycycline hyclate per tablet equivalent to 75mg and 100mg doxycycline base, respectively. Doryx Tablets, 75mg and 100mg are prepared [redacted] The only difference between Doryx Tablets 75mg and Doryx Tablets 100mg is the tablet weight, the target tablet weights are [redacted] and [redacted] for 75mg and 100mg tablets, respectively. The unit dose composition of Doryx Tablets is provided in Table 1.

Table 1. Composition of Doryx Tablets, 75mg and 100mg

Component	100mg Tablet[a] (mg/tablet)	75mg Tablet[a] (mg/tablet)
Doxycycline Hyclate		
Lactulose Monohydrate		
Microcrystalline Cellulose		
Sodium Lauryl Sulfate		
Sodium Chloride		
Talc		
Lactose Anhydrous		
Starch		
Crospovidone		
Magnesium Stearate		
Aim Tablet Weight		

[a] While these figures represent standard quantities calculated on a "dried basis", in practice some variations will occur due to differences in the potency of doxycycline raw material batches, residual moisture levels and slight fluctuations in pellet coat weight.
[b] Based on average potency of
[c] Based on average potency of

The coated doxycycline hyclate pellets have a pH dependent coating designed to delay the release of doxycycline hyclate until the pellets reach the higher pH environment of the small intestine.

Nevertheless, the composition of the delayed-release coating was modified only slightly thereby preserving the delayed release characteristics of the pellets.

The pellet manufacture process uses a

2.1.2 What is the proposed mechanism(s) of action and therapeutic indications?
Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline has activity against a wide range of Gram-positive and Gram-negative organisms. The Gram-negative organisms that doxycycline has pharmacological activity against are Neisseria gonorrhoeae, Calymmatobacterium granulomatis, Haemophilus ducreyi, Haemophilus influenzae, Yersinia pestis, Francisella tularensis, Vibrio cholerae, Bartonella bacillirformis, Brucella species, [redacted]. The Gram-positive orgamisms that doxycycline has pharmacological activity against are [redacted]

2.1.3 What are the proposed dosage(s) and route(s) of administration?
The usual dose of oral doxycycline is 200mg on the first day of treatment (administered 100mg every 12 hours) followed by a maintenance dose of 100mg/day. In the management of more severe infections (particularly chronic infections of the urinary tract), 100mg every 12 hours is recommended. In acute epididymo-orchitis caused by *N. gonorrhoeae* the dose is 100mg by mouth twice a day for ten days. [redacted]. In uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis*, and uncomplicated gonocoocal infections the dose is 100mg orally twice a day for at least seven days. In Nongonococcal urethritis and acute epididymo-orchitis caused by *C. trachomatis* and *U. urealyticum*, the dose is 100mg by mouth, twice a day for at least — days. For inhalation anthrax the adult dose is 100mg orally twice a day for 60 days.

2.2 General Clinical Pharmacology
2.2.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?
The active moiety of doxycycline was quantitated in plasma since the pharmacological activity is directly related to its concentration and metabolites have not been previously identified.

2.3 Intrinsic factors
Not applicable to the current NDA. See package insert for available information.

2.4 Extrinsic factors

Not applicable to the current NDA. See package insert for available information. The food effect on the proposed new formulation will be discussed in the "General Biopharmaceutics" section below.

2.5 General Biopharmaceutics

2.5.2 What is the relative bioavailability of the proposed new formulation compared to the approved formulation?

The sponsor is seeking approval of Doryx® 75mg and 100mg tablet formulation by comparison to the approved 75mg and 100mg capsule formulation. The sponsor conducted a bioequivalence study to determine the bioavailability following oral administration of Doryx® tablets (coated doxycycline hyclate pellets) 100mg relative to that of Doryx® capsules 100mg following single and multiple-dose administration under fasting conditions to healthy volunteers. The study has shown that Doryx tablets and Doryx capsules administered in a single or multiple-dose regimen under fasting conditions were bioequivalent. Tables 2a. and 2b. report the bioequivalence parameters for both formulations.

Table 2a. Summary of Doxycycline Pharmacokinetic Parameter Values Following Oral Administration of Doryx Tablets 100mg and Doryx Capsules 100mg in a Single or Multiple-Dose Regimen; PR-01402.0 (n=20)

Regimen	Parameter	Arithmetic Mean (%CV) Test (Doryx Tablets)	Arithmetic Mean (%CV) Reference (Doryx Capsules)	Ratio of LS Means	90% Confidence Interval
Single Dose	Cmax	1112.64 (30)	1041.60 (17)	103.11	90.93 – 116.93
	AUC 0–t	19569.55 (28)	18594.95 (16)	103.82	93.42 – 113.15
	AUCinf	21318.60 (32)	20327.30 (17)	101.59	91.66 – 112.60
	tmax	2.53 (22)	2.38 (26)	–	–
Multiple Dose	Cmax	1552.05 (23)	1702.35 (24)	91.32	86.62 – 96.28
	AUC 0–t	20063.30 (25)	22074.30 (22)	89.94	85.51 – 94.59
	tmax	2.70 (30)	2.80 (26)	–	–

Cmax = Maximum plasma concentration, ng/mL;
AUC 0–t = Area under plasma concentration-time curve from 0 to time t, the time of last determinable concentration, ng/mL·h;
AUCinf = Area under the plasma concentration-time curve from 0 to infinity (AUCinf is calculated as the sum of AUC 0–t plus the ratio of the last measurable plasma concentration to the elimination rate constant), ng/mL·h;
AUC 0–t = Area under plasma concentration-time curve from 0 to t, the dosing interval (24 hours), ng/mL·h;
tmax = Time of Cmax, h
Source Data: RR-10203; Tables 10 and 11

A Division of Scientific Investigations (DSI) audit of the I
conducted between 12/6/04-12/10/04 revealed a failure to demonstrate the accuracy of the analytical method (LC/MS) at concentrations near mid QC's (1200 ng/ml) for five subjects. DSI recommended that the data from Subjects 5, 11, 15, 18, and 21 be not accepted for review, and be excluded from the bioequivalence determination. The sponsor reanalyzed the data excluding these five subjects and the result showed that the Doryx tablets and Doryx capsules administered in a single or multiple-dose regimen under fasting conditions are bioequivalent. See DSI reports in DFS.

Table 2b. Summary of Doxycycline Pharmacokinetic Parameter Values Following Oral Administration of Doryx Tablets 100mg and Doryx Capsules 100mg in a Single or Multiple-Dose Regimen; PR-01402.0 (n=15)

Regimen	Parameter	Arithmetic Mean (%CV) Test (FP225 Tablets)	Arithmetic Mean (%CV) Reference (Doryx Capsules)	Ratio of LS Means	90% Confidence Interval
Single Dose	Cmax	1110.59 (33)	1017.43 (16)	103.84	88.04–122.46
	AUC 0–t	19182 (25)	18203 (14)	103.37	93.37–114.45
	AUCinf	21036 (32)	20162 (17)	101.04	89.88–113.60
	tmax	2.6 (20)	2.4 (28)	-	-
Multiple Dose	Cmax	1543.64 (25)	1683.17 (24)	91.69	86.63–97.05
	AUC 0–τ	19960 (25)	22031 (22)	89.23	84.84–93.85
	tmax	2.8 (26)	2.8 (26)	-	-

Cmax = Maximum plasma concentration, ng/mL; AUC 0–t = Area under plasma concentration-time curve from 0 to time t, the time of last determinable concentration, ng/mL·h; AUCinf = Area under the plasma concentration-time curve from 0 to infinity (AUCinf is calculated as the sum of AUC 0–t plus the ratio of the last measurable plasma concentration to the elimination rate constant), ng/mL·h; AUC 0–τ = Area under plasma concentration-time curve from 0 to τ, the dosing interval (24 hours), ng/mL·h; tmax = Time of Cmax, h

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

The sponsor is requesting a waiver of the in-vivo bioequivalence study requirements for Doryx tablets 75mg. This request is based upon the fact that the Doryx pellets and tablet ——— for Doryx tablets 75mg are identical to those for Doryx tablets 100mg. The only difference between the two strengths is —, tablet weight. The 75mg tablet weighs ——, which is 75% of the 100mg tablet weight ——). Therefore the two formulations are proportional. In addition, the ——————; of Doryx tablets 100mg (n=12) and Doryx tablets 75mg (n=12) in Buffer ——————— —) are similar (see dissolution data reported in section 2.5.5).

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendations should be made, if any, regarding administration of the product in relation to meals or meal types?

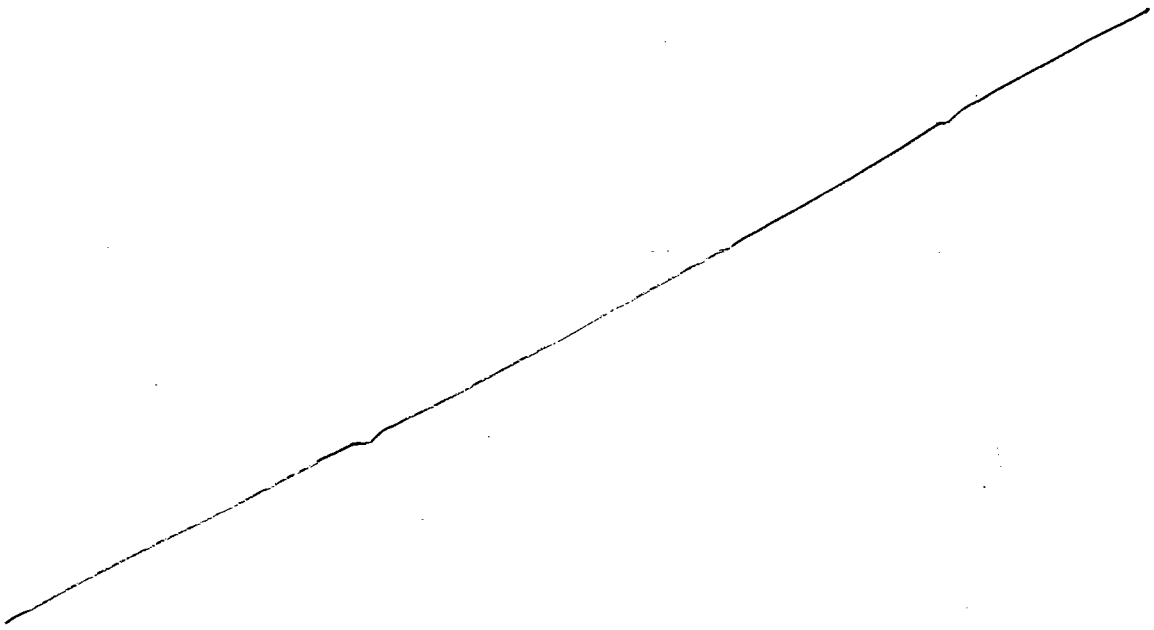
The administration of Doryx 100mg tablet with a high-fat meal resulted in a lower C_{max} (decrease of 24%), and lower $AUC_{0-\infty}$ (decrease of 13%) but the clinical significance of this decrease is unknown.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Doxycycline hyclate is soluble in water and [redacted] The coated doxycycline hyclate pellets in the Doryx tablet formulation have a pH dependent coating designed to delay the release of doxycycline hyclate until the pellets reach the higher pH environment of the small intestine. The delayed release properties are demonstrated *in vitro* in the drug release acid test.

[redacted] *in vitro* release tests were conducted on Doryx tablets. [redacted]

The proposed dissolution methods and specifications



3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Doxycycline was extracted from plasma samples by

2.6.2 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The concentration of doxycycline reported in plasma is based on total drug concentrations. , the use of total doxycycline concentrations is appropriate for assessing the bioequivalence of the standard marketed doxycycline capsules and reformulated doxycycline tablets.

2.6.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

2.6.4 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The lower limit of quantification is and the upper limit of quantification is for Study PR-01402.0. In Study PR-08302.0 the lower limit of quantification was and the upper limit of quantification was

2.6.5 What are the accuracy, precision, and selectivity at these limits?

In Study PR-01402.0 the range for between batch accuracy of QCs was . The range for between batch precision of QCs was). The within batch accuracy range was . The within batch precision range .

In Study PR-08302.0 the range for between batch accuracy of QCs was . The range for between batch precision of QCs was

[redacted]). The within batch accuracy range was [redacted]
The within batch precision range was [redacted]
Selectivity was defined as the ability of the chromatographic method to measure a response from the analyte without influence from the biological matrix. This was accomplished by evaluating [redacted] different lots of plasma without IS. In Study PR-08302.0, no significant baseline interference was detected in [redacted] out of the [redacted] lots at the retention times of Doxycycline or IS. In Study PR-01402.0, no significant baseline interference was detected at the retention times of Doxycycline or IS.

2.6.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

[redacted]

3 Appendices
3.1 Package Insert

14 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

__✓__ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1

3.2 Clinical Pharmacology and Biopharmaceutics Individual Study Review

A Study to Examine Doxycycline Oral Bioavailability Following Administration of FP225 Tablets (Coated Doxycycline Hyclate Pellets) 100mg Relative to that of Doryx® Capsules 100mg (Protocol PR-01402.0)

Date: March 4, 2003 to April 4, 2003
Clinical Site: [redacted]

Analytical Site: Same as above

BACKGROUND:
Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline; it is available as doxycycline hyclate. Doxycycline is active against a wide range of organisms and is indicated for the treatment of infections caused by both gram-negative and gram-positive microorganisms. A new delayed-release formulation (FP225 tablets) has been developed which contains coated doxycycline hyclate pellets in a tablet. Each tablet contains doxycycline hyclate equivalent to 75mg or 100mg doxycycline.

OBJECTIVES:
The objective is to characterize doxycycline oral bioavailability of FP225 tablets (coated doxycycline hyclate pellets) 100mg (Test) relative to that of Doryx Capsules 100mg (Reference) following multiple-dose administration under fasting conditions to healthy volunteers.

FORMULATIONS:
Doryx® [reference] Capsule containing 100mg doxycycline (Batch No. 75907); FP225 [test] tablet (coated doxycycline hyclate pellets) containing 100mg doxycyline (Batch No. 226790A: Pilot scale, [redacted]

STUDY DESIGN:
This was a single-center, multiple-dose, non-blinded, 2-treatment, 2-sequence, 2-period randomized crossover study in 24 healthy male subjects between age 18 and 45 years. All subjects each received six doses of either test or reference treatment in each of the two treatment periods. Treatment was administered with 240ml (8 fluid ounces) of water. The subjects were fasted for ten hours (overnight) before dosing and for four hours following the first dose. During the multiple dosing phase of each treatment subjects were fasted for at least four hours before and for one hour after each dose.

Subjects remained at the clinic for 24 hours after dosing (Day 1). During this time blood samples for determination of plasma doxycycline concentration were collected at predose and 15, 30, 60, 90 minutes, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours post-treatment. Subjects then returned to the clinic for collection of further blood samples at 36, 48, and 72 hours post-treatment. Immediately following collection of the 72-hour (Day 4) blood sample,

administration using log-transformed data. The confidence intervals were expressed as a percentage relative to the LSM of the reference formulation.

RESULTS:

Twenty-four subjects were originally enrolled in the study. Subjects 13, 14, and 23 were withdrawn during Period 1 after failing to return for day six dose administration. Subject 04 was withdrawn from further study participation prior to collection of the day 32 blood sample (Period 2) as he required treatment for bronchitis. The evaluable dataset was therefore 20 subjects. However the results of a DSI inspection conducted at ———) from 12/6/04 to 12/10/04 indicated objectionable observations. There was a failure to demonstrate accuracy of the analytical method (LC/MS) at concentrations near mid QC's (1200 ng/ml) for five subjects (See DSI report in Appendix II). The calibration curve also lacked a standard in the interval between 1000 and 2500 ng/ml. The study mean C_{max} values following single and multiple doses were in the 1000 to 1700 ng/ml concentration range. DSI recommended that the data from Subjects 5, 11, 15, 18, and 21 be not accepted for review and that this data be excluded from bioequivalence determination. Consequently the sponsor conducted a reanalysis of the data excluding the 5 previously mentioned subjects. The results from the remaining 15 subjects show that the confidence intervals for AUC and C_{max} are within the acceptable range of 80.00 to 125.00 % for both single dose and multiple dose administration. The mean pharmacokinetic parameters are listed in Tables 1, 2, and 3. The mean plasma concentration-time plots for single and multiple dose administration are presented on linear and log-linear scales in Figures 1-4.

Table 1. Summary of Doxycycline Pharmacokinetic Parameter Values Following Single-Dose Administration of FP225 Tablets or Doryx Capsules; PR-01402.0 (n=20)

Parameter	Geometric Mean [Median] Test (FP225 Tablet)	Reference (Doryx Capsule)	Ratio	90% Confidence Interval
Cmax	1066.34	1027.10	103.11	90.93 – 116.93
AUC 0-t	18887.39	18361.86	102.82	93.42 – 113.15
AUCinf	20378.57	20034.22	101.59	91.66 – 112.60
tmax	[2.50]	[2.50]	–	–
	Arithmetic Mean (%CV) [Harmonic Mean]			
Cmax	1112.64 (30)	1041.60 (17)		
tmax	2.53 (22)	2.38 (26)		
AUC 0-t	19569.55 (28)	18594.95 (16)		
AUCinf	21318.60 (32)	20327.30 (17)		
kel	0.0403 (23)	0.0369 (20)		
t½	18.20 (27) [17.19]	19.66 (24) [18.78]		

Cmax = Maximum plasma concentration, ng/mL
AUC 0-t = Area under plasma concentration-time curve from 0 to time t, the time of last determinable concentration, ng/mL·h
AUCinf = Area under the plasma concentration-time curve from 0 to infinity, ng/mL·h
tmax = Time of Cmax, h
kel = Apparent terminal elimination rate constant, 1/h
t½ = Apparent terminal elimination half-life [Harmonic mean = 0.693/mean kel], h.
Ratio = Ratio of Test to Reference treatment least squares means (LSM)
90% Confidence Interval = 90% Confidence Intervals for the difference between treatment LSM

The mean C_{max} and AUC_{0-t} values following single-dose administration of Doryx Capsules and FP225 Tablets are presented in Table 1. The 90% confidence intervals for the difference between the test and reference least-squares means for the parameters C_{max} and AUC_{0-t} using ln-transformed data for doxycycline were within 80.00 to 125.00%.

Table 2. Summary of Doxycycline Pharmacokinetic Parameter Values Following Multiple-Dose Administration of FP225 tablets or Doryx capsules; PR-01402.0 (n=20)

Parameter	Geometric Mean [Median]		Ratio	90% Confidence Interval
	Test (FP225 Tablet)	Reference (Doryx Capsule)		
Cmax	1517.11	1661.68	91.32	86.62 – 96.28
AUC 0–τ	19484.38	21609.45	89.94	85.51 – 94.59
tmax	[2.50]	[170.80]	-	-
	Arithmetic Mean (%CV) [Harmonic Mean]			
Cmax	1552.05 (23)	1702.35 (24)		
tmax	2.7 (30)	2.8 (26)		
AUC 0–τ	20063.30 (25)	22074.30 (22)		
Cavg	835.97 (25)	919.76 (22)		
Cmin	456.45 (32)	515.49 (29)		
kel	0.0357 (21)	0.0345 (23)		
t½	20.27 (21) [19.45]	21.79 (39) [20.11]		
Fluctuation	133.51 (15)	129.59 (12)		
R	1.64 (16)	1.89 (18)		

Cmax = Maximum plasma concentration, ng/mL
AUC 0–τ = Area under plasma concentration-time curve from 0 to τ, the dosing interval (24 hours), ng/mL·h
Cavg = Average plasma concentration = AUC 0–τ/τ, ng/mL
tmax = Time of Cmax, h
Cmin = Minimum plasma concentration at steady state, ng/mL
Fluctuation = Percent fluctuation at steady state = 100 × [(Cmax – Cmin)/Cavg]
R = Accumulation index = AUC 0–τ / AUC0–24
kel = Apparent terminal elimination rate constant, 1/h
t½ = Apparent terminal elimination half-life [Harmonic mean = 0.693/mean kel], h.
Ratio = Ratio of Test to Reference treatment least squares means (LSM)
90% Confidence Interval = 90% Confidence Intervals for the difference between treatment LSM

Table 3. Summary of Doxycycline Pharmacokinetic Parameter Values Following Oral Administration of FP225 Tablets and Doryx Capsules in a Single or Multiple-Dose Regimen; PR-01402.0 (n=15)

Regimen	Parameter	Arithmetic Mean (%CV)		Ratio of LS Means	90% Confidence Interval
		Test (FP225 Tablets)	Reference (Doryx Capsules)		
Single Dose	Cmax	1110.59 (33)	1017.43 (16)	103.84	88.04–122.46
	AUC 0–t	19182 (25)	18203 (14)	103.37	93.37–114.45
	AUCinf	21036 (32)	20162 (17)	101.04	89.88–113.60
	tmax	2.6 (20)	2.4 (28)	-	-
Multiple Dose	Cmax	1543.64 (25)	1683.17 (24)	91.69	86.63–97.05
	AUC 0–τ	19960 (25)	22031 (22)	89.23	84.84–93.85
	tmax	2.8 (26)	2.8 (26)	-	-

Cmax = Maximum plasma concentration, ng/mL; AUC 0–t = Area under plasma concentration-time curve from 0 to time t, the time of last determinable concentration, ng/mL·h; AUCinf = Area under the plasma concentration-time curve from 0 to infinity (AUCinf is calculated as the sum of AUC 0–t plus the ratio of the last measurable plasma concentration to the elimination rate constant), ng/mL·h; AUC 0–τ = Area under plasma concentration-time curve from 0 to τ, the dosing interval (24 hours), ng/mL·h; tmax = Time of Cmax, h

The mean C_{max} and $AUC_{0-\tau}$ values following multiple-dose administration of FP225 tablets or Doryx capsules are presented in Tables 2 and 3. The 90% confidence intervals for the difference between FP225 tablets and Doryx capsules least-squares means for the parameters C_{max} and $AUC_{0-\tau}$ using ln-transformed data for doxycycline were within 80.00 to 125.00%.

The mean doxycycline concentration-time profiles following single dose administration are presented in Figure 1. (linear scale) and Figure 2. (log scale). Following single-dose administration of Doryx Capsules or FP225 Tablets, plasma doxycycline concentrations reached peak levels at approximately 2.5 hours for both products and then decreased log-linearly over the remainder of the 72-hour period. The mean plasma doxycycline concentration-time profiles of the two treatment groups were almost superimposable.

Figure 1. Mean Plasma Doxycycline Concentration-Time (Linear Scale) Following Single-Dose Administration of FP225 Tablets and Doryx Capsules to Healthy Male Volunteers; PR-01402.0 (n=20)

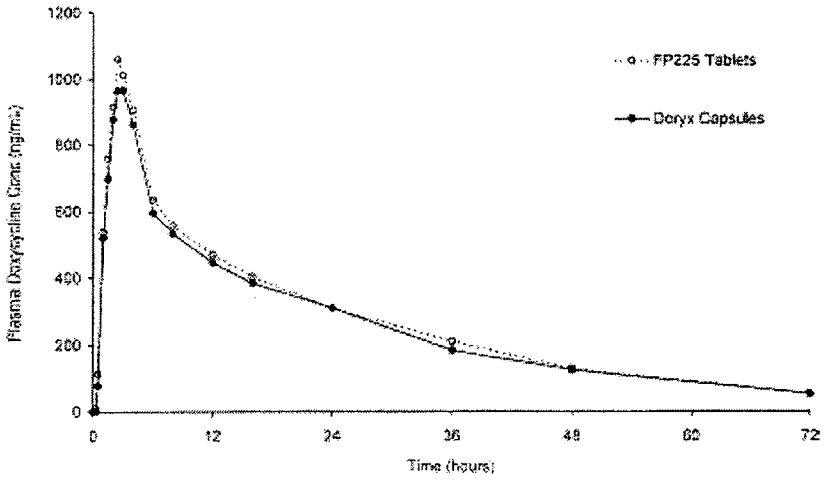


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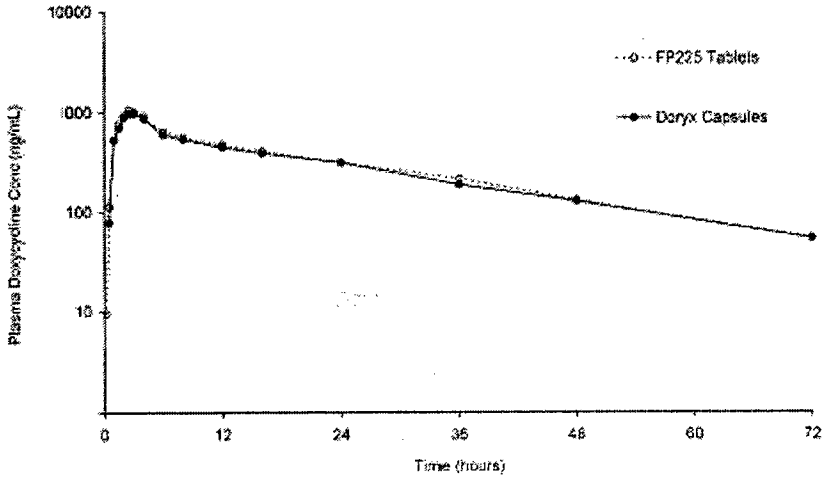
Figure 2. Mean Plasma Doxycycline Concentration-Time Profile (Log Scale) Following Single-Dose Administration of FP225 Tablets and Doryx Capsules to Healthy Male Volunteers; PR-01402.0 (n=20)



The mean doxycycline concentration-time profiles following multiple-dose administration are presented in Figure 3. (linear scale) and Figure 4. (log scale). Following multiple-dose administration of FP225 Tablets or Doryx Capsules, the plasma doxycycline concentrations reached peak levels at approximately 2.5 hours for both products and then decreased log-linearly over the remainder of the 72-hour period. The mean plasma doxycycline concentration-time profiles of the two treatment groups were very similar.

Figure 3. Mean Plasma Doxycycline Concentration-Time Profile (Linear Scale) Following Multiple-Dose Administration of FP225 Tablets and Doryx Capsules to Healthy Male Volunteers; PR-01402.0 (n=20)

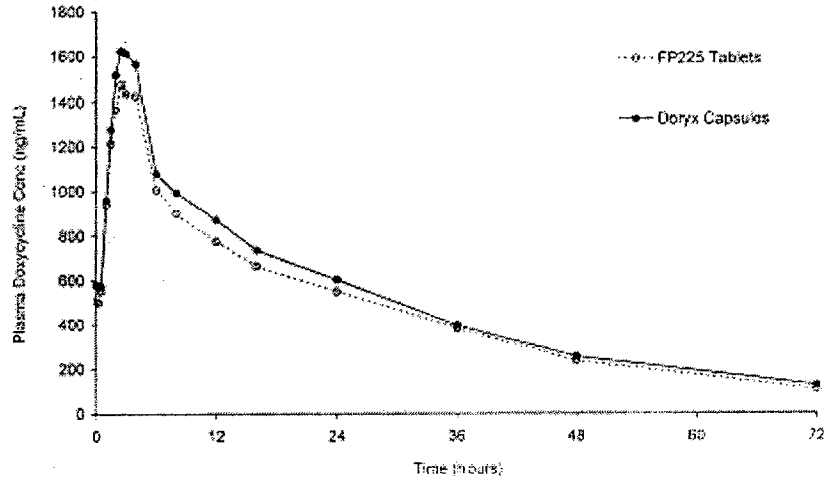
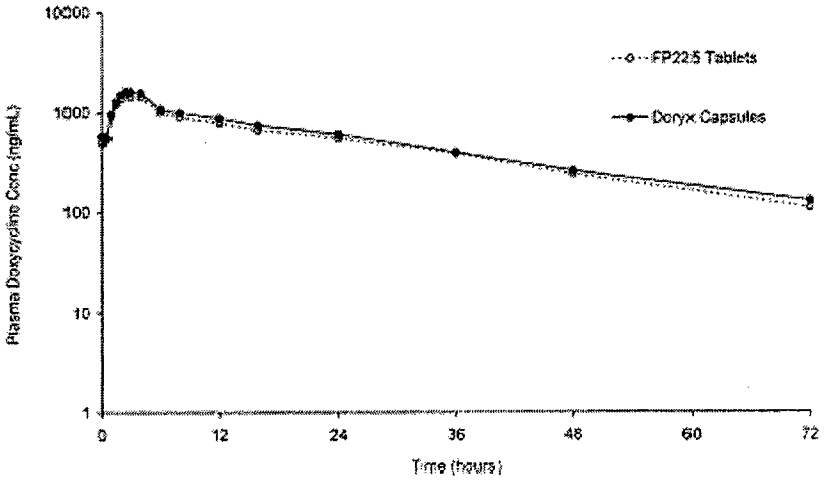


Figure 4. Mean Plasma Doxycycline Concentration-Time Profile (Log Scale) Following Multiple-Dose Administration of FP225 Tablets and Doryx Capsules to Healthy Male Volunteers; PR-01402.0 (n=20)



CONCLUSIONS:

The 90% confidence intervals for the difference between FP225 tablets and Doryx capsules administered in a single or multiple-dose regimen under fasting conditions were within 0.8 to 1.25 and are bioequivalent.

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A Study to Examine the Effect of Food on Doxycyline Bioavailability Following Oral Administration of a Single Dose of FP225 (Coated Doxycycline Hyclate Pellets) Tablets in Healthy Volunteers (Protocol PR-08302.0)

Date: May 18, 2003 to June 5, 2003
Clinical Site: [redacted]

Analytical Site: Same as above

BACKGROUND:
Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline; it is available as a doxycycline hyclate. Doxcycline is active against a wide range of organisms and is indicated for the treatment of infections caused by both gram-negative and gram-positive microorganisms. A new delayed-release formulation (FP225 tablets) has been developed which contain coated doxycycline hyclate pellets in a tablet. Each tablet contains doxycycline hyclate equivalent to 75mg or 100mg doxycycline.

OBJECTIVES:
The objective is to assess the effect of food on doxycycline bioavailability following oral administration of a single FP225 tablet (coated doxycycline hyclate pellets).

FORMULATION:
FP225 tablet (coated doxycycline hyclate pellets) containing 100mg doxycycline (Batch No. 226790A).

STUDY DESIGN:
This was a single-center, single-dose, nonblinded, 2- treatment, 2-sequence, 2-period, randomized crossover study in 18 healthy, non-smoking, male volunteers aged 18-45 years. All subjects received one FP225 tablet with 240ml of water in each of the two treatment periods. In period one, half of the subjects received treatment following an overnight fast of at least ten hours and did not receive food for at least four hours post-dose (fasted treatment). The other half of the subjects received treatment within 5 minutes of consuming a high-fat, high calorie, test meal over a 30-minute period (fed treatment) following an overnight fast of at least ten hours. The high-fat (approximately 50% of total caloric content of the meal), high calorie (800 to 1000 calories) meal consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces (100 g) of hash brown potatoes, and eight fluid ounces (240 ml) of whole milk. After a 14-day washout, each subject received the alternative treatment.

Subjects remained at the clinic for 24 hours after dosing (Day 1). During this time blood samples for determination of plasma doxycycline concentration were collected at predose (0 hour) and 15, 30, 60, 90 minutes, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours post-treatment. Subjects then returned to the clinic for collection of further blood samples at 36, 48, 72, and 96 hours post-treatment. Four days later the second treatment period commenced; subjects again attended the clinic in the evening prior to dosing. The washout period from

Table 1. Summary of Doxycycline Pharmacokinetic Parameter Values Following Administration of FP225 Tablets in the Fed or Fasted State; PR-08302.0 (n=18)

Parameter	Geometric Mean [Median]		Ratio	90% Confidence Interval
	Fed	Fasted		
Cmax	866.01	1137.46	76.14	69.65 – 83.22
AUC 0–t	17223.44	19799.78	86.99	78.92 – 95.87
AUCinf	18374.30	21031.43	87.37	79.78 – 95.67
tmax	[3.00]	[2.50]	–	–
	Arithmetic Mean (%CV) [Harmonic Mean]		–	–
Cmax	893.89 (25)	1170.46 (22)	–	–
tmax	3.14 (39)	2.39 (31)	–	–
AUC 0–t	17615.11 (21)	20572.61 (26)	–	–
AUCinf	18762.28 (21)	21768.00 (25)	–	–
kel	0.0393 (18)	0.0381 (16)	–	–
t½	18.20 (20) [17.62]	18.68 (17) [18.20]	–	–

Cmax = Maximum plasma concentration, ng/mL
AUC 0–t = Area under plasma concentration-time curve from 0 to time t, the time of last determinable concentration, ng/mL·h
AUCinf = Area under the plasma concentration-time curve from 0 to infinity, ng/mL·h
tmax = Time of Cmax, h
kel = Apparent terminal elimination rate constant, 1/h
t½ = Apparent terminal elimination half-life [Harmonic mean = 0.693/mean kel], h.
Ratio = Ratio of Test to Reference treatment least squares means (LSM)
90% Confidence Interval = 90% Confidence Intervals for the difference between treatment LSM

Figure 1. Mean Plasma Doxycycline Concentration-Time Profile (Linear Scale) Following Administration of FP225 tablets in the Fed or Fasted State to Healthy Male Volunteers; PR-08302.0 (n=18)

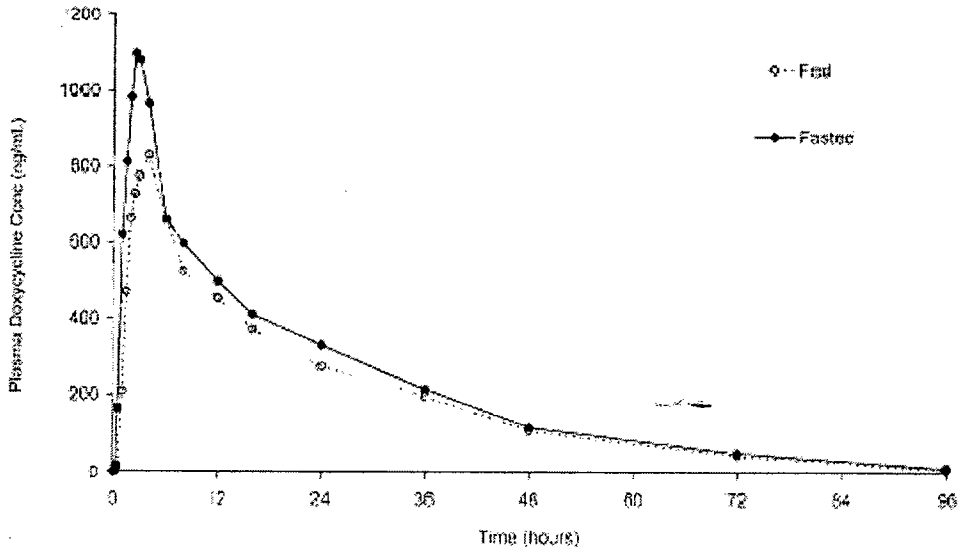
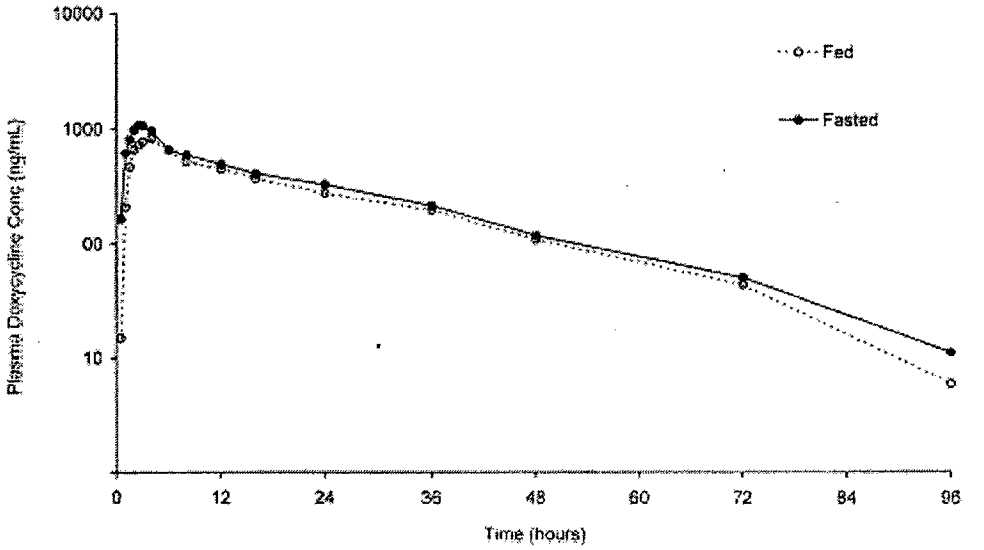


Figure 2. Mean Plasma Doxycycline Concentration-Time Profile (Semi-Log Scale) Following Administration of FP225 Tablets in the Fed or Fasted State to Healthy Male volunteers; PR-08302.0 (n=18)



The mean C_{max} value following administration of one FP225 tablet in the fed state was 24% lower than when one tablet was administered in the fasted state (Range of individual ratios: ———). There were three subjects with slight increase in C_{max} with food. The mean $AUC_{0\text{-}inf}$ following administration of one FP225 tablet in the fed state was 13% lower than when one tablet was administered in the fasted state (Range of individual ratios: ——— . There were five subjects with increases in AUC with food. The plots in figures 3 and 4 represent the graphing of individual subject data for log transformed C_{max} and $AUC_{0\text{-}\infty}$ data points for all 18 subjects in the study.

Figure 3. Stick plots demonstrating C_{max} of FP225 after a single 100mg dose administered under Fasted and Fed Conditions

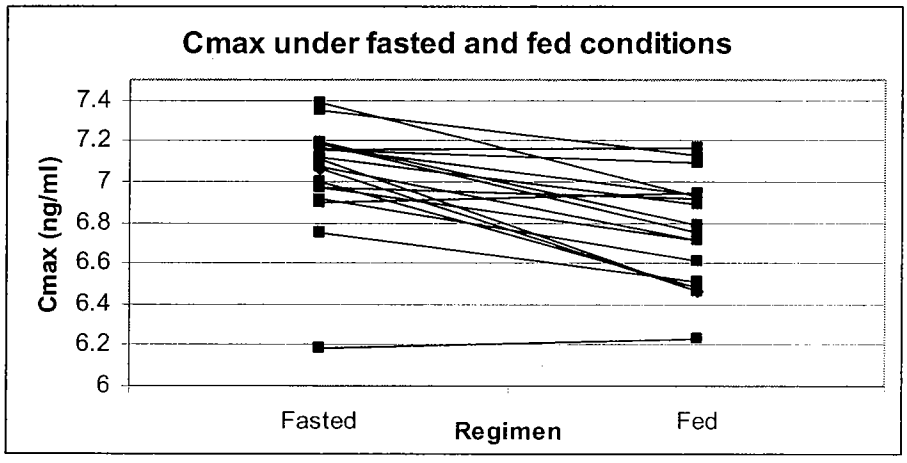
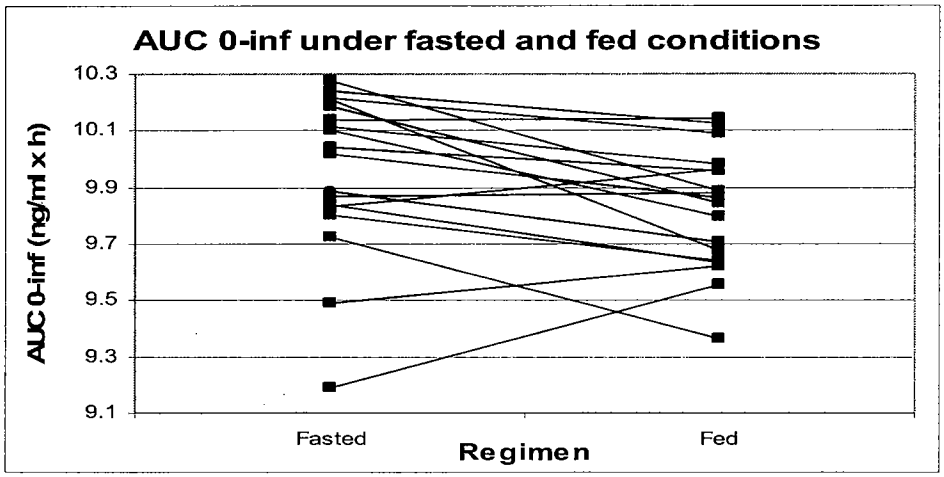


Figure 4. Stick plots demonstrating $AUC_{0\text{-}inf}$ of FP225 after a single 100mg dose administered under Fasted and Fed Conditions



CONCLUSIONS:

Administration of FP225 (coated doxycycline hyclate pellets) 100mg tablets with food decreased the rate of absorption by 24% (C_{max}) and the extent of doxycycline absorption by 13% (AUC). The clinical significance of the decrease in absorption is unknown.

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