CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-788

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

NDA#	50-788 [redacted]
PRODUCT	Mupirocin
FORMULATION	Ointment, 2%
SUBMISSION DATE	February 7, 2002
SUBMISSION TYPE	NDA Supplement, 505(b)(2)
SPONSOR	Clay-Park Labs, Inc., Bronx, NY 10457
REVIEWER	Charles R. Bonapace, Pharm.D.
ACTING TEAM LEADER	Phillip M. Colangelo, Pharm.D., Ph.D.
STUDY PERIOD	November 5, 2001 to December 10, 2001
PROTOCOL	FARMOVS 125/2001

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

A Randomized, Crossover Study in Healthy, Normal Subjects to Compare Systemic Exposure To Mupirocin After Multiple, Once Daily Doses of Two Topical Mupirocin Ointment 2% Products

BACKGROUND:

Mupirocin is a topical antibiotic used for the treatment of impetigo, a superficial infection of the skin caused primarily by *Staphylococcus aureus* and *Streptococcus pyogenes*. Mupirocin is the major metabolite (pseudomonic acid) produced from a strain of *Pseudomonas fluorescens* grown in a submerged culture. The antimicrobial activity of mupirocin is due to the reversible inhibition of isoleucyl-tRNA synthetase, which results in the inhibition of protein synthesis and RNA synthesis. Mupirocin competes for bacterial isoleucine binding sites on the isoleucyl t-RNA synthetase enzyme. The reversible inhibition of the formation of the enzyme complex prevents further isoleucine incorporation, which depletes the cellular concentration of isoleucine charged t-RNA and leads to a cessation of protein and RNA synthesis in susceptible bacteria.

Clay-Park Labs, Inc. (CPL) submitted an NDA to obtain approval to market its Mupirocin Ointment, 2% formulation for the treatment of impetigo. CPL's Mupirocin Ointment, 2% was developed as a therapeutic equivalent to GlaxoSmithKline's currently approved product, Bactroban® Ointment, 2%. CPL's Mupirocin Ointment, 2% has the same active ingredient and same indication as Bactroban® Ointment, 2%. To avoid patent issues, CPL developed a formulation that utilizes a lipophilic based vehicle, as compared to GlaxoSmithKline's polyethylene glycol (PEG) based hydrophilic vehicle. As a result of this vehicle difference, CPL is pursuing a 505(b)(2) NDA since it "contains a different quality or quantity of an excipient(s) than the listed drug where the studies required for approval are beyond those considered limited confirmatory studies appropriate to a 505(j) application". Clay-Park Labs intends to [redacted] or its Mupirocin Ointment, 2% in order to market this product as equivalent to GlaxoSmithKline's Bactroban® Ointment, 2%.

CPL's Mupirocin Ointment, 2% formulation consists of the following ingredients:

Ingredient	% w/w
Mupirocin	2.0
Castor oil	
Oleyl alcohol	
Softisan® 378 (hard fat)	
Propylene glycol monstearate, pure	

CPL conducted a single independent, adequate and well-controlled clinical study (Study No. CPL-002) to evaluate the safety and clinical efficacy of Bactroban® Ointment, 2% vs. Mupirocin Ointment, 2%. This multi-center, double-blind, parallel-group, active-control study included a total of 602 subjects (302 randomized to Bactroban® Ointment, 2% and 300 randomized to Mupirocin Ointment, 2%). A majority of subjects were in the age group most vulnerable to this disease (less than 10 years of age) as well as subjects in older age groups. Each product was administered three times daily for 7 days to affected skin areas.

The Division of Anti-Infective Drug Products originally requested CPL to evaluate the systemic availability of Mupirocin Ointment, 2% from 10-12 patients in a clinical efficacy study. However, CPL recommended performing a separate well-controlled clinical study to assess systemic absorption. The results of the study are presented in this review.

OBJECTIVE:
The objective of this study was to evaluate the systemic exposure to mupirocin after multiple daily applications of Bactroban® Ointment, 2% and Mupirocin Ointment, 2%.

FORMULATIONS:
Bactroban® Ointment, 2% (Lot No. 82 1B25, SmithKline Beecham)
Mupirocin Ointment, 2% (Lot No. VA077, Clay-Park Labs, Inc.)

STUDY DESIGN:
This study was an open-label, randomized, multiple application, two-period crossover study involving 24 healthy Caucasian subjects (14 males, 10 females). In Phase 1, 2 grams of either Bactroban® Ointment, 2% or CPL's Mupirocin Ointment, 2% was topically applied to a 20 × 20 cm^2 area on the back of each subject and occluded with a plastic film for 12 hrs. Study drug was administered once daily at least one hr after a bath or shower was taken for Days 1 through Day 7. The same area per subject was used for all applications and was marked by a ' ——— marker. The alternate product was applied in a similar fashion in Phase 2. An eight-day washout period separated Phase 1 and Phase 2.

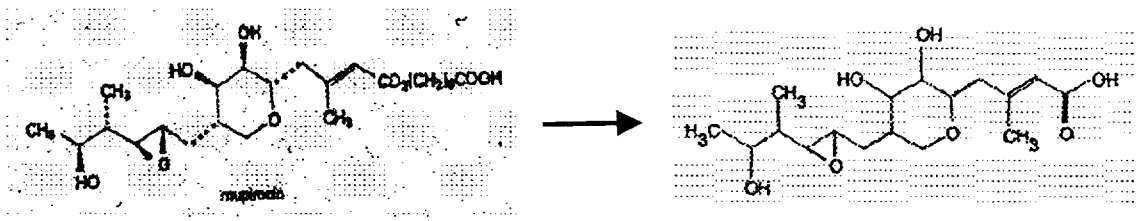
On Days 1-6, subjects received 240 mL water at -1 hrs before administration of study drug. On Day 7, subjects received 240 mL water at -1, 0, 1, 1.5, 2, 4, 6, and 18 hrs after administration of study drug, 200 mL of a caffeine-free warm beverage 8 and 13 hrs after administration of study drug, and 240 mL of orange juice with meals.

Urine samples for mupirocin concentration were collected prior to administration of study drug on Day 1 (pre-dose) and on Day 7 during the following intervals: 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-18, 18-24 hrs after administration of study drug.

MONIC ACID ASSAY METHODOLOGY:

Mupirocin is rapidly metabolized to monic acid following absorption of mupirocin after topical administration. Since monic acid is excreted almost exclusively by the kidneys, the concentration of monic acid in urine was used as a surrogate to quantitate the absorption of mupirocin through the skin after topical application.

The molecular formula of mupirocin is $C_{26}H_{44}O_9$ and the molecular weight is 500.63. The molecular formula of monic acid is $C_{17}H_{28}O_7$ and the molecular weight is 344.40. The chemical structures of both compounds are shown below.



Mupirocin (MW 500.63) **Monic Acid (MW 344.40)**

Criterion	Urine	Comments
Concentration-range	50.1 to 1,001 ng/mL	Satisfactory
LLOQ	———	Satisfactory
Linearity	Not stated	Unsatisfactory
Accuracy	93.7% to 97.4%	Satisfactory
Precision (% CV)	5.5% to 9.1%	Satisfactory
Specificity	Satisfactory	Satisfactory
Stability	Freeze-thaw, standard solutions, and on-instrument stability.	Satisfactory

DATA ANALYSIS:
Systemic exposure to mupirocin was determined by measuring each subject's cumulative urinary monic acid excretion (Ae) over 24 hrs on Day 7 in Phases 1 and 2. In addition, the fractional urinary monic acid excretion, monic acid excretion rate, and monic acid excretion as a percentage of the dose were also calculated for each subject.

STATISTICAL ANALYSIS:
The test product was compared to the reference product with respect to the pharmacokinetic variable (Ae0-24) using an analysis of variance with sequence, subject (sequence), product, and period effects after log-transformation of the data. The parametric point estimate and 95% confidence interval for the test/reference ratio of this variable was calculated.

It was not anticipated that the 95% confidence interval of the "test/reference" mean ratio of the primary variable would necessarily meet the conventional equivalence range of 80% to 125%. It was anticipated that the confidence interval would demonstrate statistical comparability for the test and reference products by either containing the value 100% or showing a high degree of overlap with the bioequivalence interval.

RESULTS:
One subject was withdrawn after the run-in period of Phase 1 due to work-related obligations. No other subjects were withdrawn from the study. The mean (SD) demographics of the 23 male and female subjects who completed the study are shown in the table below. In general, male subjects were heavier and taller than female subjects.

Mean (SD) demographic data of subjects who completed the study

	Age (yrs)	Weight (kg)	Height (cm)	BMI (kg/m^2)
All (n=23)	21.2 (2.1)	70.8 (10.4)	175.9 (9.1)	22.8 (2.4)
Male (n=13)	21.0 (2.3)	77.0 (7.9)	182.2 (6.3)	23.2 (1.9)
Female (n=10)	21.4 (2.0)	62.8 (7.2)	167.6 (3.7)	22.4 (2.9)

The range of urine monic acid concentrations for Bactroban® Ointment, 2% and Mupirocin Ointment, 2% from each urine collection interval is shown in Table 1. The urine monic acid concentration was below the LLOQ (——— for all urine samples in 19/23 subjects receiving Bactroban® Ointment, 2% and 1/23 subjects (Subject #4) receiving Mupirocin Ointment, 2%.

Table 1. Comparison of the range in urine monic acid concentration from each collection interval for Bactroban® Ointment, 2% and Mupirocin Ointment, 2%

	Monic Acid Urine Concentration (ng/mL)							
Product	**0 to 1**	**1 to 2**	**2 to 4**	**4 to 6**	**6 to 8**	**8 to 12**	**12 to 18**	**18 to 24**
Bactroban® Ointment, 2%	<50.1*	<50.1 to 76.3	<50.1 to 55.0	<50.1 to 54.5	<50.1*	<50.1 to 97.8	<50.1 to 62.7	<50.1*
Mupirocin Ointment, 2%	<50.1 to 282.5	<50.1 to 160.5	<50.1 to 158.2	<50.1 to 354.6	<50.1 to 316.9	<50.1 to 637.1	<50.1 to 618.0	<50.1 to 423.4

*** The concentration of monic acid was below the LLOQ for all subjects during this collection interval**

In order to calculate the urinary excretion of monic acid during each interval, the sponsor used one-half of the LLOQ ———). The reviewer also calculated the urinary excretion of monic acid using only data from subjects with monic acid concentrations above the LLOQ. A comparison of the cumulative urinary excretion of monic acid estimated from the sponsor and the reviewer is shown in Table 2.

Table 2. Comparison of the mean ± SD (Range) cumulative monic acid excretion and cumulative monic acid excretion (% of dose) calculated by the sponsor and the reviewer

	Cumulative urinary monic acid excretion (ng)		Cumulative urinary monic acid excretion (% of dose)	
Product	**Sponsor[1]**	**Reviewer[2]**	**Sponsor[1]**	**Reviewer[2]**
Bactroban® Ointment, 2%	**N=23** 80,941 ± 14,752	**N=4** 29,835 ± 19,263	**N=23** 0.29 ± 0.05	**N=4** 0.11 ± 0.07
Mupirocin Ointment, 2%	**N=23** 355,881± 189,024	**N=22** 344,798 ± 202,340	**N=23** 1.29 ± 0.69	**N=22** 1.25 ± 0.73

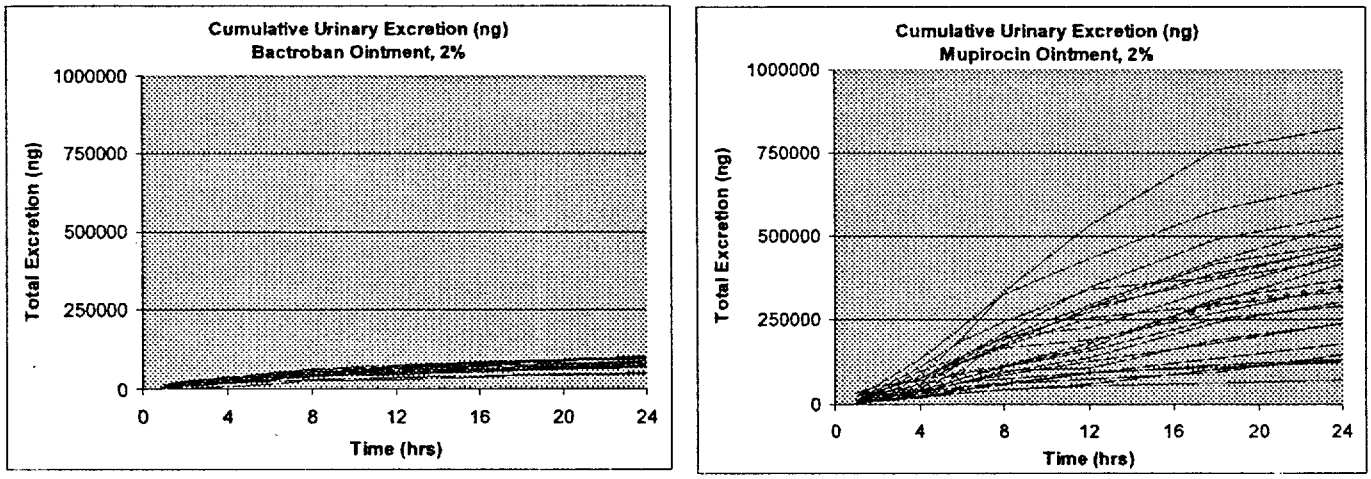
1 - Monic acid urine concentrations below the LLOQ were set to 1/2 LLOQ (———
2 - Subjects with all monic acid concentrations in urine below the LLOQ were excluded

Based on the sponsor's analysis, the mean 24 hr cumulative urinary excretion of monic acid was 0.081 mg following the application of Bactroban® Ointment, 2% and 0.356 mg following the application of Mupirocin Ointment, 2%. Although the systemic absorption of mupirocin was ≤1.29% following the administration of both products, the systemic absorption of mupirocin following the application of Mupirocin Ointment, 2% was approximately 3.4-fold greater than the absorption of mupirocin following the application of Bactroban® Ointment, 2%.

Based on the reviewer's analysis, the mean 24 hr cumulative urinary excretion of monic acid was 0.030 mg following the application of Bactroban® Ointment, 2% and 0.345 mg following the application of Mupirocin Ointment, 2%. Based on this analysis, the systemic absorption of mupirocin following the application of Mupirocin Ointment, 2% was approximately 10.4-fold greater than the absorption of mupirocin following the application of Bactroban® Ointment, 2%.

The relationship between cumulative urinary monic acid excretion vs. urine collection time for Bactroban® Ointment, 2% and Mupirocin Ointment, 2% are shown in Figure 1 (based on the cumulative urinary monic acid excretion calculated by the sponsor). The median cumulative urinary monic acid excretion following application of Bactroban® Ointment, 2% and Mupirocin Ointment, 2% were 0.083 mg and 0.347 mg, respectively.

Figure 1. Individual* cumulative urinary monic acid excretion following administration of Bactroban® Ointment 2% (n=23) and Mupirocin Ointment, 2% (n=23) calculated by the sponsor

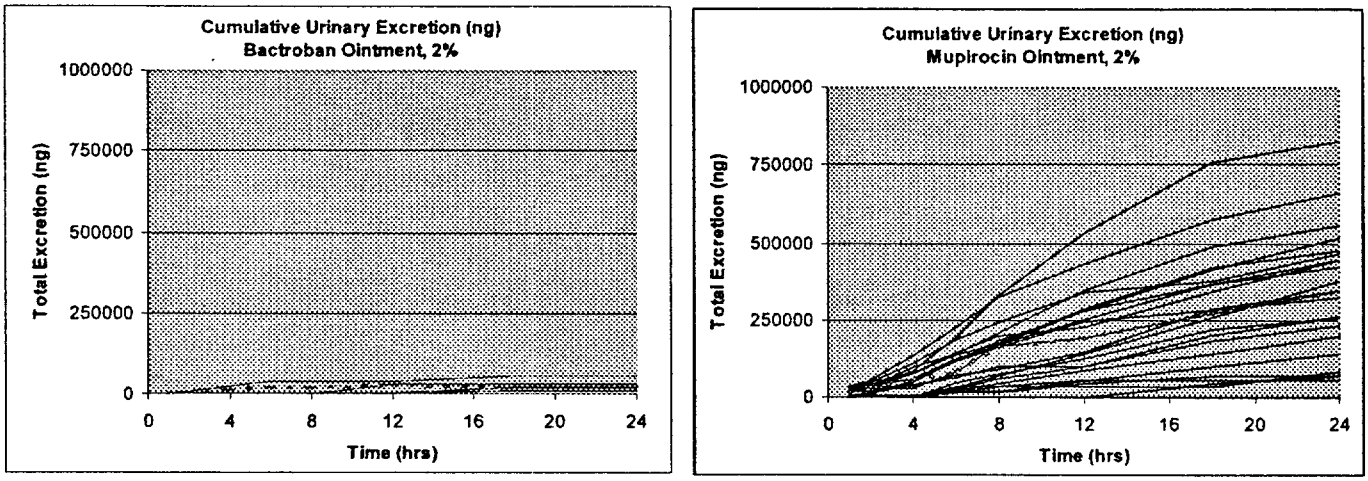


***The solid lines represent individual cumulative urine monic acid excretion (ng); the dashed line represents the median cumulative urine monic acid excretion (ng).**

In contrast, the relationship between cumulative urinary monic acid excretion vs. urine collection time for Bactroban® Ointment, 2% and Mupirocin Ointment, 2% are shown in Figure 2 (based on the cumulative urinary monic acid excretion calculated by the reviewer). The median cumulative urinary monic acid excretion following application of Bactroban® Ointment, 2% and Mupirocin Ointment, 2% were 0.025 mg and 0.347 mg, respectively.

The reviewer assessed the cumulative urinary monic acid excretion (% of dose) for the four subjects with urine monic acid concentration above the LLOQ. The mean (range) cumulative urinary excretion of monic acid was 0.11% ( ) and 1.72% ( ) of the administered dose for Bactroban® Ointment, 2% and Mupirocin Ointment, 2%, respectively. Based on monic acid urinary excretion from four subjects, the mean systemic absorption (for each individual subjects) of Mupirocin Ointment, 2% was 20.4-fold greater than for Bactroban® Ointment, 2%.

Figure 2. Individual* cumulative urinary monic acid excretion following administration of Bactroban® Ointment 2% (n=4) and Mupirocin Ointment, 2% (n=22) calculated by the reviewer



***The solid lines represent individual cumulative urine monic acid excretion (ng); the dashed line represents the median cumulative urine monic acid excretion (ng).**

The reviewer also compared the absorption of mupirocin from Bactroban® Ointment, 2%, Bactroban® Cream, 2%, and Mupirocin Ointment, 2%. The results of studies assessing these formulations are summarized below.

Bactroban® Ointment, 2% (NDA 50-591)

Approximately 500 mg of ^{14}C-mupirocin ointment (Bactroban® Ointment, 2%) (144.9 µCi per gram of ointment) was applied to the forearm (15 cm × 15 cm) of six healthy male subjects. The application area was covered with an occlusive dressing for 24 hrs. Blood, urine, and feces were collected for 120 hrs. No measurable ^{14}C activity was detected in plasma, whole blood, urine, or feces at any time period following the application of Bactroban® Ointment, 2%. The mupirocin concentration in whole blood was less than 1.1 ng/mL. Based on the radioassay detection limit (0.6 ng/sample), the total amount of pseudomonic acid-related material excreted in the urine and feces did not exceed means of 0.20% (0.16% to 0.29%) and 0.04% (0.03% to 0.05%) of the applied dose, respectively. The mean maximum extent of systemic absorption of pseudomonic acid-related material from the applied ^{14}C-mupirocin ointment was calculated to be <0.24% (<0.19% to <0.32%) of the applied dose.

Bactroban® Cream, 2% (NDA 50-746)

The study design did not allow for a definitive assessment of the extent of absorption of mupirocin from Bactroban® Cream, 2%. Sixteen adults and ten children applied Bactroban® Cream, 2% to skin lesions (laceration or suture wound, abrasion, atopic dermatitis, eczematous dermatitis, or stasis dermatitis) three times daily for 5 days. Concentrations of mupirocin and monic acid were determined in spot urine samples collected on Day 3 and Day 6 using [redacted]). Urine samples were collected approximately 2 hrs after dosing. Mupirocin was not detected in any of the spot urine samples collected. From children, monic acid was quantifiable in 7/10 urine samples on Day 3 (<0.05 to 1.295 µg/mL) and 8/10 samples on Day 6 (<0.05 to 0.696 µg/mL). From adults, monic acid was quantifiable in 6/16 samples on Day 3 (<0.05 to 10.034 µg/mL) and in 5/15 urine samples on Day 6 (<0.05 to 0.731 µg/mL). The median monic acid concentration was 0.17 µg/mL on Day 3 and 0.20 µg/mL on Day 6.

Mupirocin Ointment, 2% (Current study, NDA 50-788)
The median (range) urine concentration of monic acid from the 1-2 and 2-4 hr collection intervals on Day 7 were 0.066 µg/mL (<0.050 to 0.076 µg/mL) and 0.055 µg/mL (<0.050 to 0.055 µg/mL), respectively following application of Bactroban® Ointment, 2%. Following the application of Mupirocin Ointment, 2%, the median (range) urine concentration of monic acid from the 1-2 and 2-4 hr collection intervals on Day 7 were 0.090 µg/mL (<0.050 to 0.161 µg/mL) and 0.079 µg/mL (<0.050 to 0.158 µg/mL), respectively.

SAFETY:
There were 55/300 (18.3%) of patients in the Mupirocin Ointment, 2% patient group who experienced adverse events during the pivotal clinical study (Study No. CPL-002) vs. 40/302 (13.2%) of patients in the Bactroban® Ointment, 2% group. The sponsor divided these reactions into two groups: those which were skin related and those which were not. The numbers of patients with skin related reactions were nearly identical between the groups (12 for Mupirocin Ointment, 2% and 13 for Bactroban® Ointment, 2%), while there were 43 patients with non skin related events in the Mupirocin Ointment, 2% group vs. 27 in the Bactroban Ointment, 2% group. The non skin related adverse events were not classified as being associated with the study drug (they include occurrences such as accidents, fever, pharyngitis, etc.). Discontinuances due to adverse events totaled four for the Mupirocin Ointment, 2% group and two for the Bactroban® Ointment, 2% group. The medical officer's review should be consulted for additional information.

CONCLUSIONS:
Based on urine concentrations of monic acid, the absorption of mupirocin was more than 10-fold greater following the application of Mupirocin Ointment, 2% compared to Bactroban® Ointment, 2%. However, ≤1.25% of the administered dose of mupirocin from either formulation was absorbed systemically based on urine monic acid excretion.

Based on data reported in the current label for Bactroban® Cream, 2%, the median urine monic acid concentration was greater at approximately 2 hrs following application of Bactroban® Cream, 2% than Mupirocin Ointment, 2%. However, the systemic absorption of mupirocin from Bactroban® Cream, 2% was not assessed in this study.

The greater absorption of mupirocin from Mupirocin Ointment, 2% compared to Bactroban® Ointment, 2% is unlikely to be clinically relevant based on the adverse events of mupirocin reported in Study No. CPL-002 (see SAFETY above).

LABELING COMMENTS:
Clinical Pharmacology:
The proposed clinical pharmacology section should be deleted and replaced with the following:
"Following the application of Mupirocin Ointment, 2% to a 400 cm^2 area on the back of 23 healthy volunteers once daily for 7 days, the mean (range) cumulative urinary excretion of monic acid over 24 hrs following the last administration was 1.25% (0.2% to 3.0%) of the administered dose of mupirocin. The monic acid concentration in urine collected at specified intervals for 24 hrs on Day 7 ranged from <0.050 to 0.637 µg/mL."

Drug Interactions:
Since it is unknown if studies have been performed assessing the possible interaction between Mupirocin Ointment, 2% and other topical medications, the Drug Interactions section should be replaced with the following: "The effect of the concurrent application of Mupirocin Ointment, 2% and other drug products is unknown."

COMMENTS:

1. The sponsor has not provided data supporting the linearity and long-term stability at -20°C of the urine monic acid [redacted] assay validation. The sponsor is encouraged to submit the requested assay validation data to the Agency when it becomes available.

RECOMMENDATIONS:

This application was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation III and found to be acceptable from a clinical pharmacology point of view.

Please forward comment #1 above to the reviewing medical officer and the sponsor.

Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Phillip M. Colangelo, Pharm.D., Ph.D.
Acting Team Leader

cc:
Division File: NDA 50-788
HFD-520 (CSO/Dillon-Parker)
HFD-520 (MO/Bostwick)
HFD-880 (Division File, Lazor, Selen, Colangelo, Bonapace)
CDR (Clin. Pharm./Biopharm.)

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