# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** NDA 50-781

## MICROBIOLOGY REVIEW(S)

NDA#: 50-781
OraPharma, Inc.

OCT 23 2000

Division of Anti-Infective Drug Products
Clinical Microbiology Review # 1

Dental Consult HFD-540

**NDA#: 50-781**
**Date Completed:** 10/6/00

**Applicant:**

OraPharma, Inc.
732 Louis Drive
Warminster, PA 18974

**Contact Person:**

Markus F. Herzig
Executive Director, RA
205-956-2207

**Therapeutic Type:** Antibacterial

**Providing for:** Adjunctive therapy to scaling and root planing procedures in patients with adult periodontitis.

**Product Name:**
Proprietary: Not finalized
Established Name: Minocycline periodontal therapeutic system (MPTS)
Code Name/Number: None
Chemical Name: 7-dimethylamino-6-demethyl-6-deoxytetracycline hydrochloride
Chemical Formula (empiric): $C_{23}H_{27}N_3O_7 \bullet HCL$
Molecular Weight: 493.94

**Dosage Form:** Topical (powder)
**Strength:** 1 mg/unit dose [Each unit dose delivers 1 mg of minocycline encapsulated in approximately — ] of poly(glycolide-co-di-lactide) (PGLA)]
**Route of Administration:** Subgingivally into periodontal pockets
**Dosage/Duration:** Three treatments in pockets with PD of 5 mm or greater (Note: During the clinical studies the three treatments were done at baseline, 3 months, and 6 months).
**Dispensed:**

**Initial Submission Dates:**
Applicant submission date: 2/16/00
Received by CDER: 2/17/00
Received by reviewer: 2/29/00

NDA#: 50-781
OraPharma, Inc.

Division of Anti-Infective Drug Products
Clinical Microbiology Review # 1

**Supplements/Amendments:** None

**Related Documents:** IND [redacted] NDA [redacted]

**Remarks:** This is a reviewer of a system consisting of minocycline incorporated into a bioresorable matrix for the treatment of adult periodontitis.

Division of Anti-Infective Drug Products
Clinical Microbiology Review # 1

## TABLE OF CONTENTS

NDA#: 50-781
OraPharma, Inc.

Division of Anti-Infective Drug Products
Clinical Microbiology Review # 1

**INTRODUCTION:**

This review is of the application for the product "Minocycline Periodontal Therapeutic System (MPTS)" which is a subgingival sustained-release product for the treatment of adult periodontitis. The system is meant to be used in conjunction with root planning and scaling. The MPTS is a tetracycline derivative (minocycline) microencapsulated in a bioresorable polymer, poly(glycolide-co-di-lactide) (PGLA). It is supplied in a unit dose dispenser. Each unit dose delivers 1 mg of minocycline encapsulated in approximately — — of PGLA subgingivally into the periodontal pocket. The dispenser is a barrel with a narrow hollow delivery tip designed to fit into the periodontal pocket. The drug product resides in the barrel in powder form. Exposure to moisture in the periodontal pocket triggers release of the active ingredient and hydrolysis of the PGLA. The active ingredient in the MPTS is minocycline HCL.

Adult periodontitis has been shown to be associated with the presence of specific bacterial types. The bacteria most commonly associated with the disease are: *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans*, *Bacteroides forsythus, Campylobacter rectus, Eikenella corrodens, Prevotella intermedia* and *Fusobacterium nucleatum* (1). Doxycycline and/or tetracycline in concentrations from 1 to 6 µg/mL have been shown to inhibit the growth of these organisms (2). The MPTS is intended to deliver an amount of minocycline capable of inhibiting the bacteria associated with adult periodontitis.

**PRE-CLINICAL INFORMATION**

Spectrum of activity minocycline:

The tetracycline class of antibiotics has a broad spectrum of activity against microorganisms including facultative, aerobic, and anaerobic bacteria (3). The tetracyclines are bacteriostatic with their main mechanism of action being inhibition of protein synthesis (3).

The applicant provided literature references on the activity of tetracyclines and other antimicrobials against the microorganisms associated with periodontal disease as well as well as a table with this type of information. The references were reviewed and found to contain information showing that minocycline was active against microorganisms associated with periodontitis in the concentrations that are achievable with MPTS. The tabular information for minocycline provided by the applicant is shown in Table 1 (vol1.1 pg. 109 –110).

Table 1. In vitro activity of minocycline against various organisms associated with adult periodontitis

| Organism | Number of Isolates | $MIC_{50}$ (µg/mL) | MIC Range (µg/mL) |
|---|---|---|---|
| *Bacteroides gingivalis* | 30 | 0.05 | 0.025 - 25 |
| *Bacteroides intermedius* | 16 | 0.05 | 0.26 - 6.25 |
| *Fusobacterium nucleatum* | 11 | 0.78 | 0.78 |
| *Eikenella corrodens* | 12 | 0.39 | 0.025 - 0.78 |
| *Actinobaccillus actinomycetemcomitans* | 25 | 1.56 | 1.56 - >25 |
| *Capnocytophaga sp.* | 27 | 0.2 | 0.2 - 0.78 |

Mechanisms of tetracycline resistance:

Tetracycline resistance is widespread among bacteria (4). This resistance may be due to: 1) limiting access of tetracycline to the ribosome the major site of action of tetracyclines, 2) altering the ribosome to prevent effective binding of the tetracycline, or 3) producing tetracycline-inactivating enzymes (5). More than one mechanism of resistance to tetracycline occurring at the same time in bacteria has been described (5).

Fourteen genes coding for tetracycline resistance are currently known. Some of these determinants encode proteins that mediate an efflux mechanism for tetracycline, some mediate resistance by preventing tetracylclines from attaching to ribosomes and a third class mediates the degradation of tetracycline (6). Many of the tetracycline genes from Gram-negative bacilli are located on plasmids and readily transmissible within and between species (6). Other transmissible-resistance genes particularly those found in Gram-positive organisms are located on transposable chromosomal elements that can be transferred between organisms by conjugation (7).

Epidemiology of tetracycline resistance in relation to periodontal disease:

Development of resistance to tetracycline among organisms in the periodontal pocket of patients treated with tetracycline is frequently seen (8). It has been demonstrated that the level of tetracycline–resistant organisms decreases usually to previous levels beginning by 10 week's (9). The presence of tetracycline-resistant bacteria has been described in the oral microflora of individuals with no periodontitis and not receiving

tetracycline (10). In these cases the tetracycline-resistant bacteria have been shown to constitute between 2 to 6% of the viable count in the subgingival samples (10).

**IN VIVO**

Pharmacokinetics and bioavailability (vol. 1.1 pg. 119-131):

Therapeutic devices for the treatment of periodontal disease must accomplish 3 objectives. The medication must reach the intended site of action; remain at an adequate concentration; and last for a sufficient duration of time (11). The duration of exposure required is dependent upon the mechanism by which the antimicrobial agent inhibits or destroys target bacteria. For example chlorhexidine, a bactericidal agent, kills microorganisms by compromising the integrity of the cell membrane and requires a shorter exposure time than a bacteriostatic agent such as tetracycline, which inhibits protein synthesis.

It has been estimated that the fluid present in a 5 mm periodontal pocket is replaced about 40 times an hour (11). Thus, if an antimicrobial agent is placed subgingivally, its local concentration is rapidly reduced (12). The expected half-life (i.e., the time necessary for the concentration to become half the original) of a pharmacological agent in the gingival crevice is about 1 minute (11). This high rate of clearance represents the major obstacle to maintaining effective concentrations of an antimicrobial agent within the pocket. Longer therapeutic duration requires the use of a subgingival drug reservoir such as presented by the applicant.

Pharmacokinetic information provided by the applicant (vol. 1.17 pg. 152) shows that the mean crevicular fluid level of minocycline after deposition of MPTS (1 mg/dose) in 16 subjects ranged from — µg/mL at 1 hour following administration to — µg/mL at 14 days. There were large variations in the concentrations of the minocycline within and between subjects. This information provided by the applicant suggests that the concentrations of minocycline delivered by MPTS and the amount of time the minocycline is present is sufficient to inhibit the growth of the majority of bacteria associated with adult periodontitis.

Animal models

The applicant (vol. 1.1 pg. 112) makes reference to the results of minocycline administered to dogs with periodontitis. The data suggests that there is a statistically significant decline in the counts of *Porphyromonas* sp., *Fusobaterium* sp. and a decline in *Streptococcus* sp. by the fourth week following administration of minocycline into the periodontal pockets.

The applicant has also provided information (vol. 1.1 pg. 118) from a dog study used to evaluate four formulations for MPTS and identify one with the minocycline release characteristics that would yield minocycline concentrations exceeding the MICs (0.05 –

1.56 µg/mL) for organisms associated with periodontal disease for a period of 7 to 10 days. The formulation chosen was one that yielded minocycline concentrations of at least 10 µg/mL for 14 days.

Organism identification:

Microorganisms isolated during this study were identified using DNA probes. The applicant had previous to instituting the studies in this application provided information on these methods to this reviewer. This previous material was reviewed and found acceptable (Microbiology Review of IND# ——— dated ———). In this submission the applicant has provided additional information that adequately supports the correlation between conventional culture results and DNA probe results (vol. 1.17 Appendix 7.8.2.1) and probe validation data (vol. 1.17 pg. 185). The applicant has provided data to show that the detection limit of the probes is at a level of $10^4$ bacteria/mL. The DNA probe method identifies the presence of a bacterium in the same samples as cultural data 62–73% of the time. Similarly DNA probes recognize the absence of a bacterium in the same samples as cultural data 57-60% of the time. The specificity of the probes was shown to meet the requirement of >1000. This means that in order for there to be a cross reaction between a probe and another organism the other organisms must be in a concentration that is 1000 times more than the target organism. The applicant has shown that 92.6% of probe-heterologous species hybridization provided no detectable signals. Probes to species thought to be important periodontal pathogens; *B. forsythus*, *P. gingivalis*, and *T. denticola* showed no cross-reaction with any heterologous species tested. This information is comparable to what has been reported in the literature (12, 13).

Changes in the proportion of plaque microorganisms:

The applicant has provided the results of a phase 3 study (OPI – 103A/B). These studies looked at the change in the proportion of plaque organisms in three study groups (Arm A – S/RP plus subgingival application of MPTS, Arm B – S/RP plus subgingival application of the vehicle, and Arm C – S/RP alone) (vol. 1.1 pg. 132 – 134). Subgingival plaque samples were collected at baseline, and at days 30, 90, 180, and 270. The proportion of plaque microorganisms was determined by analysis of the percentage of total DNA detected by each of 40 probes (Table 2).

Table 2. List of whole genome DNA probes

| No. | Organism | No. | Organism | No. | Organism |
|---|---|---|---|---|---|
| | | 16 | *Streptococcus oralis* | 28 | Capnocytophaga gingivalis |
| 1 | *Actinomyces nasleundii* genospecies 1 & 2 | 17 | *Capnocytophaga ochracea* | 29 | *Streptococcus gordonii* |

| | | | | | |
|---|---|---|---|---|---|
| 2 | *Streptococcus constellatus* | 18 | *Actinomyces israelii* | 30 | *Bacteriodes forsythus* |
| 3 | *Eubacterium nodatum* | 19 | *Streptococcus intermedius* | 31 | *Selenomomas noxia* |
| 4 | *Porphyromonas gingivalis* | | | 32 | *Propionibacterium acnes serotypes* I & II |
| 5 | *Actinobacillus actinomycecomitans* serotypes a & b | 20 | *Treponema dentocola* | | |
| | | 21 | *Prevotella nigescens* | 33 | *Prevotella melanogenica* |
| | | 22 | *Actinomyces* | | |
| 6 | *Fusobacterium nucleatum* ss *vincentii* | | *Odontolyticus* Serotype 1 | 34 | *Streptococcus mitis* |
| | | | | 35 | *Eikenella corrodens* |
| 7 | *Campylobacter rectus* | 23 | *Fusobacterium nucleatum* ss *polymorphum* | 37 | *Capnocytophaga sputigena* |
| 8 | *Treponema socranskii* | | | 38 | *Leptotrichia buccalis* |
| 9 | *Eubacterium saburreum* | | | | |
| 10 | *Peptostreptococcus micros* | 24 | *Campylobacter showae* | 39 | *Campylobacter gracilis* |
| 11 | *Veillonella parvula* | | | | |
| 12 | *Actinomyces viscosus* | 25 | *Fusobacterium periodonticum* | 40 | *Prevotella intermedia* |
| 13 | *Streptococcus anginosus* | | | | |
| 14 | *Streptococcus sanguis* | 26 | *Neisseria mucosa* | | |
| 15 | *Actinomyces gerencseriae* | 27 | *Fusobacterium nucleatum ss nucleatum* | | |

An analysis of the DNA probe data from the subjects was done by placing the organisms into specific groups. This was done because there was no between treatment differences seen for any individual probe. The use of such complexes is not an established method of analysis of microbial changes in periodontal disease. However, because there were no between treatment differences for any individual probe establishing groups of organisms provides a way to analysis the data. The organisms were grouped in the following way (Number in parenthesis refers to numbers on Table 2): Actinos (1. 12, 15, 18); Streps (2, 13, 14, 16, 19, 29,34); Green (17, 28, 35, 37); New (9, 26, 31, 32, 33, 36, 38); Purple (11, 22); Orange (3, 6, 7, 10, 21, 23, 24, 25, 27, 39, 40); and Pathogens (4, 5, 8, 20, 30).

The data show that the most predominant organisms were those in the *Actinomyces* group and those in the Orange group.

Interestingly there were very similar increases and decreases in the plaque microorganisms between scaling and root planing with MPTS and the scaling and root planing alone beginning at baseline and for the 3, 6 and 9 month sampling times (vol.

1.17 pg. 16). The following information refers to both groups (percentages are approximate). Considered together, the DNA percent for the *Actinomyces* decreased over the nine-month course of the study from 35% of all bacteria to 16%. A small increase from 12% to 15% was seen for the "New" group after nine months. The DNA percent for the "Pathogens" decreased from 11% prior to treatment to 4% after 1 month. The DNA percent for the "Pathogens" increased over the next 8 months, but at study end was 2% less than at the start. For the "Strep" group there was basically no change over the course of the study. For the "Purple" group there was an increase of 8% from the start of the study and for the "Orange" group there was an increase of 10% from the start of the study. For the "Green" group there was an increase of 4% after ninth months. The "Actino" group and the "Pathogens" groups were the only groups to show a decline in the total percentage at the nine months. The "Actino" group showed the greatest change. This data when analyzed by distribution of plaque microorganisms shows that there is virtually no difference between the treatment arms of MPTS with scaling and root planing and scaling and root planing alone. This suggests that there is little if any benefit to the use of minocycline for reducing plaque associated microorganisms and that scaling and root planing alone can accomplish reduction in plaque microorganisms. The clinical significance of the shifts in the total numbers of these organisms is not known.

Minocycline resistance of plaque microorganisms (vol. 1.17 pg. 17 - 20):

Treatment emergent antimicrobial resistance (minocycline-resistance defined as >4 µg/mL) was determined using a serial agar dilution culture technique. Samples were collected from a total of 35 subjects from two of the phase 3 investigational sites (San Antonio, TX and Buffalo, NY). Descriptive statistics for percent resistant colonies were calculated for the combined analysis and for each of the two investigation sites (San Antonio, TX and Buffalo, NY). Percent resistant organisms was calculated as 100 times colony forming units (CFU) from minocycline-treated plates divided by CFUs from untreated anaerobic plates. In the combined analysis, percent resistant organisms was low at baseline and increased slightly over the course of the study for both the MPTS wit S/RP (0.2% to 1.7%) and the S/RP alone (0.2% to 0.3%) treatment groups. There was a decrease in percent resistant organisms (0.8% to 0.4%) for the vehicle treatment group. In the San Antonio study the percent of minocycline-resistant organisms was elevated over baseline for 9 months. However, the resistance declined from approximately 2.5% at the end of the first month to 0.5% by the ninth month. In the Buffalo study the percent minocycline-resistant organisms was elevated approximately 2% at the end of the first month and 1% by the end of the third month. At the end of the sixth month the percent of minocycline-resistant organisms increased by 8.5% from baseline. However, there was also an increase in both control groups of approximately 5% at the end of the sixth month. By the end of month 9 the percent of minocycline-resistant organisms was 2.5% above the baseline value and the values for the control groups returned to near baseline values. This spike at the end of the sixth month in all study groups at the Buffalo site has no explanation. Even though at the end of the 9 months there was a higher percentage of minocycline-resistant organisms in the

minocycline-treated group than at baseline (0.3% versus 3%) in the Buffalo group this reviewer does not consider this to be of any major consequence. Overall, for both the San Antonio and Buffalo studies there were no unexpected results in the minocycline-treated groups. As has been reported in the literature (9) there can be an expected increase in tetracycline-resistant bacteria after treatment with the number of resistant bacteria decreasing over time after cessation of treatment.

Proportion of gastrointestinal microorganisms (vol. 1.17 pg. 21 - 24):

The applicant has provided the results of a study (OPI-105) of 18 subjects designed to monitor changes in the (a) total anaerobic flora, (b) the proportion of the flora resistant to minocycline, and (c) the levels of opportunistic pathogens present. The study showed no differences in the total counts for anaerobes, *Candida*, enterics or *Staphylococcus aureus* between baseline counts and counts done at day 56. This finding agrees with published findings with locally applied tetracyclines for periodontal disease, which indicate that local application of tetracycline has little if any impact on changing the flora of the gastrointestinal tract (10).

Resistance of gastrointestinal microorganisms (vol. 1.17 pg. 21 - 23):

Study (OPI-105), which involved 18 subjects, was also used to monitor the development of minocycline-resistant organisms in subjects receiving treatment, with MPTS. The MPTS treated patients did not exhibit an increase in minocycline-resistant organisms or in the resistance to doxycycline, tetracycline, amoxicillin, clindamycin, or erythromycin over baseline values after 56 days. This is consistent with what has been reported in the literature (10). Local application of tetracycline into periodontal pockets has minimal impact on the development of tetracycline-resistant bacteria in the gastrointestinal tract and on the overgrowth of resistant organisms in the intestinal tract (10).

CONCLUSION:

The microbiology data provided by the applicant suggests that root planing and scaling along with MPTS and root planing and scaling alone essentially are equivalent in their effect on the microorganism content of the plaque samples taken from adults with periodontitis. Therefore, any correlation between the clinical outcome in the patients treated with MPTS and the microbiology results will not be possible.

The data provided on the presence of minocycline-resistant organisms in the plaque samples from treated patients is consistent with published data. The data for the presence of minocycline-resistant microorganisms in the intestine of treated subjects and the lack of any major change in the microbiota of the gastrointestinal tract of treated patients is consistent with published information. In fact the local application of antimicrobials versus systemic antimicrobials for the treatment of adult periodontitis may provide a way to reduce the numbers of antimicrobial-resistant organisms in the

gastrointestinal tract and the potential for clinical significant shifts in the microbiota of the gastrointestinal tract.

The MPTS provides a method for the use of an antimicrobial, which because of its direct application to the site to be treated reduces the overall exposure of the patient's system to an antimicrobial.

From a microbiology perspective this product is approvable with the recommended labeling changes.

## REFERENCES

1. Okuda K. 1994. Bacteriological diagnosis of periodontal disease. The Bull Tokyo Dental College 35: 107-119.
2. Slots J, TE Rams. 1990. Antibiotics in periodontal therapy; advantages and disadvantages. J Clin Periodontol 17: 479-493.
3. Standiford HC. 1995. Tetracycline and chloramphenicol, p. 306-310. In GL Mandell, JE Bennett, R Dolin (ed.), Principles and Practice of Infectious Diseases, 4th ed, Churchill Livingstone, NY.
4. Levy, SB. 1988. Tetracycline resistance determinants are widespread. Amer Soc Microbiol News 54: 418-421.
5. Speer B, NB Shoemaker, and AA Slayer. 1992. Bacterial resistance to tetracycline; mechanism, transfer, and clinical significance. Clin Microbiol Rev 5: 387-399.
6. Olsvik B, I Olsen, F Tenover. 1994. The tet (Q) gene in bacteria isolated from patients with refractory periodontal disease. Oral Microbiol and Immunol 9: 251-255.
7. Clewell DB, SE Flannagan, and DD Jaworski. 1995. Unconstrained bacterial promiscuity: The TN 916 – Tn 1545 family of conjugative transposons. Trends in Microbiol 3: 229 – 236.
8. Magnusson I, RG Mark, WB Clark, et al. 1991. Clinical, microbiologic and immunological characteristics of subjects with "refractory" periodontal disease. J Clin Periodontol 61: 686-691.
9. Larsen, T. 1991. Occurrence of doxycycline resistant bacteria in the oral cavity after local administration of doxycycline in patients with periodontal disease. Scand J Infect Dis 23: 89-95.
10. Fiehn NE, and J Westergard. 1990. Doxycyline-resistant bacteria in periodically diseased individuals after systemic doxycycline therapy and in healthy individuals. Oral Microbiol and Immunol 5: 219-222.
11. Goodson J. 1989. Pharmacokinetic principles controlling efficacy of oral therapy J Dent Res 68: 1625-1632.
12. Benet L, D Kroetz, and L Sheiner. Pharmacokinetics: The dynamics of drug Absorption, distribution, and elimination. In: Hardman JG, AG Goodman, L Limbird, eds. The Pharmacological Basis of Therapeutics, 9th ed., New York: The McGraw-Hill Companies; 1996; 3-27.

13. Ali RW, AC Johannessen, G Dahlen, et al. 1997. Comparison of the subgingival microbiota of peridontally healthy and diseased adults in Northern Cameroon. J Clin Periodontol 24: 830-835.
14. Loesche WJ, DE Lopatin, J Stoll, et al. 1992. Comparison of various detection methods for periodontopathic bacteria: Can culture be considered the primary reference standard. J Clin Microbiol 30: 418-426.

## PROPOSED MICROBIOLOGY PORTION OF PACKAGE LABELING

**Microbiology**

Minocycline is a member of the tetracycline class of antibiotics.[1] Minocycline is bacteriostatic and exerts its antimicrobial activity by inhibiting protein synthesis.[1] In vitro susceptibility testing has shown that the organisms *Porphyromonas gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum, Eikenella corrodens, and Actinobacillus actinomycetemcomitans*, which are associated with periodontal disease, are susceptible to minocycline at concentrations of ≤8 μg/mL.[2]

[

]

[

]

[

]

[ ]

**Precautions**

[ ]

REFERENCES

1. Stratton CW, Lorian. Mechanisms of action of antimicrobial agents: general principles and mechanisms for selected classes of antibiotics. Antibiotics in Laboratory Medicine, 4th edition, Williams and Wilkins, Baltimore, MD, 1996.
2. Slots J, Rams TE. 1990. Antibiotics in periodontal therapy: advantages and disadvantages. J Clin Periodontol 17:479-493.

/S/ 10/19/00

Fred Marsik, Ph.D.
Review Microbiologist
Cc: Original 50-781
HFD-520 Divisional File
HFD-520/Micro/F. Marsik
HFD-540/DO/J. Kelsey
HFD-540/DO/C. Gilkes
HFD-540/CSO/K. Bhatt

Concurrence Only

/S/ 10/23/00
HFD-520/DepDir/L. Gavrilovich

/S/ 10/19/00
HFD-520/TLMicro/A. T. Sheldon, Jr.

RD & Final Initiated 10/10 & 19/00 ATS

540/Bhatt

AUG 7 2000

# REVIEW TO HFD-540
# OFFICE OF NEW DRUG CHEMISTRY
# MICROBIOLOGY STAFF/HFD-805
# MICROBIOLOGY REVIEW #1 OF NDA

**7 August 2000**

A. 1. NDA: 50-781/BC

2. TYPE OF SUPPLEMENT: NA

3. SUPPLEMENT PROVIDES FOR: NA

4. APPLICANT/SPONSOR: OraPharma, Inc
732 Louis Drive
Warminster, PA 18974

5. MANUFACTURING SITE:

6. DRUG PRODUCT NAME:
Proprietary: NA
Nonproprietary: Minocycline PTS
Drug Priority Classification: Standard

7. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: 1 mg, subgingival administration

8. METHOD(S) OF STERILIZATION: NA

9. PHARMACOLOGICAL CATEGORY: Antibiotic

B. 1. DOCUMENT/LETTER DATE: February 16, 2000
2. RECEIPT DATE: February 17, 2000
3. CONSULT DATE: June 6, 2000
4. DATE OF AMENDMENT: June 5, 2000
5. ASSIGNED FOR REVIEW: June 12, 2000
6. SUPPORTING/RELATED DOCUMENTS:

C. REMARKS: This amendment is in response to a teleconference between the sponsor, the chemistry reviewer, the project manager and the microbiology reviewer.

D. CONCLUSIONS: This submission is approvable pending resolution of microbiological deficiencies. Please see "Microbiologist's List of Deficiencies and Comments" at the end of this review.

/S/ 8-7-00

Bryan S. Riley, Ph.D.
Microbiology Reviewer

PAC 8/7/00

cc.: Original NDA 50-781
HFD 540/Division File
HFD 540/K. Bhatt
HFD 540/M. Gautam-Basak
HFD 805/Consult File
HFD 805/ B. Riley

Drafted by: Bryan Riley, Ph.D.
R/D initialed by: Peter Cooney, Ph.D.

filename: C:\data\data\word\nda\50781

WITHHOLD 2 PAGE (S)